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Drotrecogin Alfa (Activated) in Severe Sepsis: a systematic review of observational studies (Update of Report 29)

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by

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TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Foreword

On October 25, 2011, the US Food and Drug Administration announced that Eli Lilly and Company had withdrawn drotrecogin alfa (activated), a decision taken in light of the results of a clinical trial, subsequently published on May 31, 2012, (1) in which the preparation failed to show a survival benefit for patients with severe sepsis and septic shock. Thus, for the purpose of guiding MUHC policy, the present report is no longer necessary. However, since it constitutes a significant contribution to knowledge it is reproduced below.

Background:

In April 2003 and March 2007 reports were developed by the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) on the use of drotrecogin alfa (activated) (DrotAA) for the treatment of severe sepsis. Both concluded that there was no good evidence of a significant reduction in 28-day mortality with DrotAA treatment, even in high-risk patients, and recommended that DrotAA be used only in severe sepsis patients at highest risk of mortality.

Objective:

A review of the main outcomes of studies published on this issue since March 1, 2007.

Findings:

Apart from the report noted in the Foreword above, no RCTs were found. We found 15 uncontrolled observational cohort studies. Hospital mortality rates for patients on DrotAA ranged from 40% to 50.7%, and the 28-day mortality rates ranged from 25.1% to 56%. The hospital mortality rate for patients not taking DrotAA based on one study was 63.5%, and the 28-day mortality rate, based on three studies, varied from 31.8% to 69%. Most studies reported being sponsored by the manufacturer.

Conclusions:

- The mortality rates reported in the observational studies we reviewed, were higher than the rates previously reported in RCTs (PROGRESS and ADDRESS).
- Studies that included a comparison group of patients not treated with DrotAA, generally concluded that there was a beneficial effect of DrotAA treatment.
- The majority of studies reported being supported by the manufacturer.

LIST OF ABBREVIATIONS

APACHE II	Acute Physiology and Chronic Health Evaluation
CI	Confidence Interval
DrotAA	Drotrecogin Alfa (Activated)
FDA	US Food and Drug Agency
HRQoL	Health-related Quality of Life
ICU	Intensive Care Unit
MR	Mortality Rate
MUHC	McGill University Health Centre
OR	Odds Ratio
RCT	Randomized Controlled Trial
RR	Risk Ratio
SIRS	Systemic Inflammatory Response Syndrome
TAU	Technology Assessment Unit

Drotrecogin Alfa (Activated) in Severe Sepsis: A systematic review of observational studies

FOREWORD

On October 25, 2011, the US Food and Drug Administration notified healthcare professionals and the public that Eli Lilly and Company had announced a worldwide voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] (See announcement on FDA website)

This decision had been taken in the light of the results of a new clinical trial (subsequently published, May 31, 2012, (1)) in which Xigris failed to show a survival benefit for patients with severe sepsis and septic shock. In this study 1696 patients were randomly selected into two groups. The 28 day all cause mortality rates were 26.4% and 24.2% for the treatment and placebo groups, respectively. Thus, the present report is no longer necessary for the purpose of guiding MUHC policy on this issue. However, since it constitutes a significant contribution to knowledge it is reproduced below.

1. BACKGROUND

Severe sepsis is a complex syndrome characterized by the presence of infection, which results in the systemic inflammatory response syndrome and leads to end organ dysfunction(2;3). In addition, a wide spectrum of non-infectious agents can also trigger a host's response in a similar manner to the sepsis syndrome. As a result, there is no good case definition, a fact which can lead to inaccurate diagnosis and unsuccessful treatment of severe sepsis(2).

DrotAA (drotrecogin alfa [activated], Xigris [Eli Lilly Co, UK])(4) is a recombinant form of human activated protein C produced by recombinant DNA techniques that intervenes at multiple points in the systemic response to infection(5). DrotAA counteracts the hypercoagulable state, inflammation, and thrombosis associated with severe sepsis and is thought to function by reversing the impairment of endogenous activated protein C production(5). Based on the results of the first phase-three multicenter RCT (PROWESS trial) the drug was approved by the US Food and Drug Administration (FDA) in 2001, the European Union in 2002, and Health Canada in 2003(6). However, these regulatory bodies approved DrotAA for use only in high-risk patients as defined by an APACHE II score ≥25(6).

The PROWESS RCT showed a 6.1% absolute 28-day mortality reduction with DrotAA compared to placebo (7). Hospital mortality rates were 29.7% in the DrotAA group and 34.9% in the placebo group (p=0.03) (7). The ADDRESS RCT, published in 2005, included less severe patients and found a hospital mortality of 20.6% in the placebo group and 20.5% in the DrotAA group (p=0.98), and 28-day mortality rates of 17% in the placebo group and 18.5% in the DrotAA group (p=0.34) (7).

The Technology Assessment Unit (TAU) of the McGill University Health Centre evaluated the use of DrotAA for the treatment of severe sepsis in 2003(7) and again in 2007 (6). On the basis of two major RCTs, the PROWESS (2001), and ADDRESS (2005)(6), the latter report recommended restriction of the use of DrotAA to severe sepsis patients at highest risk (6).

2. OBJECTIVES

To review studies published since February 2007 to determine whether they provide any new evidence to indicate that treatment of adult patients with severe sepsis with DrotAA may favourably influence mortality.

3. METHODS

An updated search for studies carried out in adult patients treated with DrotAA was performed (See appendix 1).

4. LITERATURE REVIEW

No RCTs were found (other than the as yet unpublished RCT cited in the Foreword). Systematic search identified 15 studies(4;8-21) that met our eligibility criteria (See Table 1). All were cohort studies (one third prospective and two thirds retrospective). The number of participants ranged from 23 to 2796. The number of patients that were taking DrotAA ranged from 9 - 3228. The proportion of patients taking DrotAA in each study sample ranged from 4% to 100%. In seven studies(10;11;17-21) 100% of the study sample was taking DrotAA. The mean age of participants ranged, from 51.5±14.2 years to 67±15 years. Ten studies, (66.7%) declared a conflict of interest, with sponsorship by Eli Lilly, two (13.3%) reported no conflict of interest, and three studies(20%) did not report whether or not there was a conflict of interest.

In ten studies(4;8;11;17-19;21) data were collected at one or more hospitals. (See Table 2). The remaining five studies(10;12;14;16;20) (all supported by Eli Lilly) used either the INDEPTH, PROGRESS, or ENHANCE databases. The INDEPTH database represented a large integrated cohort of five clinical trials sponsored by Eli

Lilly between July 1996 and January 2003(16). Likewise, PROGRESS was an international, multi-centre observational study funded by Eli Lilly to document patients with severe sepsis treated in ICUs across 37 countries from December 2002 to December 2005(22). Only one(10) of the aforementioned five studies used the Canadian data from the ENHANCE cohort, which was a multiple-country, open-label, single-arm trial also funded by Eli Lilly.

Overall, the majority (8/10) of studies that reported eligibility criteria included only severe sepsis patients. Five of the 15 included studies did not report on the patient eligibility criteria. Studies differed in their definition of severe sepsis. For instance, the study by Martin(14) and colleagues defined severe sepsis as scoring at least two on the SIRS (Systemic Inflammatory Response Syndrome) criteria, having an infection, and having at least one organ dysfunction. In contrast, the study by Behnes et al.(8) defined severe sepsis as scoring at least three on the SIRS criteria and having more than two organ failures.

The criteria for the comparison groups used in the outcome analysis are summarised in Table 2. The majority of studies (11, 73.3%) either compared risk factors among survivors and non-survivors who received DrotAA or compared outcomes in DrotAA users with a control group of non-users. For instance, the studies by Ferrer et al.(9), Kanji et al.(11), and Spriet et al.(18) compared survivors and non-survivor patients, both groups taking DrotAA. The remaining eight studies (4;8;12-14;19-21) compared DrotAA and nonDrotAA patients, not necessarily from the same study population. Only four studies compared mortality rates between DrotAA and nonDrotAA patients within the same study population (4;12-14). Three(12-14) of the studies concluded that DrotAA lowered the risk of mortality and improved health outcomes in patients with severe sepsis. The study by Longo et al. stated that patients on DrotAA appeared to recover more quickly and had higher health-related quality of life in a 7-month follow-up. The fourth study(4) did not show an effect on mortality with DrotAA treatment.

In summary, the range of hospital mortality rates for patients on DrotAA across all studies was 40% to 50.7% and the 28-day mortality rates ranged from 25.1% to 56%. The propensity adjusted odd ratios (ORs) range for overall hospital mortality ranged from 0.59 and 0.72, and the OR for 28-day mortality was 0.79 in one study (12).

When comparing the 28-day mortality rates from the non-RCT studies in this report to the rates in the PROWESS and ADDRESS RCTs, the non-RCT mortality range is higher than the rate obtained in the RCT.

5. DISCUSSION

This brief report reviewed 15 cohort studies evaluating the effectiveness of DrotAA in severe sepsis patients. Studies were published between 2006 and 2010 and had a wide range of participants, from 23 to 2796. The wide population range was due to the varying sources of data collection. The majority of studies collected data from hospitals and individual ICUs. In contrast, most studies using international databases and registries, such as INDEPTH and PROGRESS, analysed data on a much larger population (4,459 to 12,492 participants). In addition, the majority of studies reported a conflict of interest and few studies reported 28-day mortality rates or generated hospital rates.

Eli Lilly and Company announced in October 2011 the withdrawal of drotrecogin alfa (activated) due to the unfavourable results of the PROWESS-SHOCK RCT.

6. CONCLUSIONS

- The mortality rates reported in the observational studies we reviewed, were higher than the rates previously reported in RCTs (PROGRESS and ADDRESS).
- Studies that included a comparison group of patients not treated with DrotAA, generally concluded that there was a beneficial effect of DrotAA treatment.
- The majority of studies reported being supported by the manufacturer.

TABLES

Table 1 Summary of included observational studies

Study (citation)	Year of publication	Country of origin	Total population	No. patients on DrotAA (%)	Mean age* (yrs) (SD)	Study design	Manufacturer support
Steingrub et al. (19)	2010	United States	548	548 (100%)	58 (17)	Prospective cohort	Yes
Ferrer et al. (9)	2009	Spain	2796	165 (6%)	62.2 (16.3)	Prospective cohort	Yes
Hodder et al. (10)	2009	Canada	305	305 (100%)	56.9 (17.2)	Retrospective cohort	Yes
Behnes et al. (8)	2008	Germany	20	10 (50%)	DrotAA: 51.5 (14.2) NonDrotAA: 61.4 (20.5)	Prospective cohort	None
Van Doorn et al. (4)	2008	Belgium	46	16 (35%)	DrotAA: 66 (15) NonDrotAA: 67 (15)	Prospective cohort	Unspecified
Muller et al. (15)	2008	France	230	9 (4%)	Range: 52-80	Retrospective cohort	Unspecified
Wheeler et al. (21)	2008	United States	274	274 (100%)	57 (18)	Retrospective cohort	Yes
Kanji et al. (11)	2007	Canada	261	261 (100%)	56 (17)	Retrospective cohort	Unspecified
Longo et al. (13)	2007	Canada	100	36 (36%)	59.8 (16.7)	Prospective cohort	Yes
Martin et al. (14)	2007	United States	12492	882 (7%)	60.3 (17.5)	Retrospective cohort	Yes

Laterre et al. (12)	2007	Belgium	4459	228 (72%)	DrotAA: 59.5 (17) NonDrotAA: 60.3 (16.5)	Retrospective cohort	Yes
Ridley et al. (17)	2007	England	351	351 (100%)	61.8 (16.3)	Retrospective cohort	Yes
Vincent el al. (20)	2007	Belgium	436	436 (100%)	NR	Retrospective cohort	Yes
Payen et al. (16)	2007	France	4459	3228 (72%)	Surgical: 62.6 (15.9) Nonsurgical: 58.0 (17.4)	Retrospective cohort	Yes
Spriet et al. (18)	2006	Belgium	23	23 (100%)	59 (range 30-83)	Retrospective cohort	None

SD: standard deviation; NR: not reported

*Mean age and standard deviation of study population

Table 2 Descriptive characteristics of included studies

Study (citation)	Study objective(s)	Sources of data collection	Patient eligibility	Comparison groups	Outcome measures	Findings
Steingrub et al. (19)	To provide profile of DrotAA patients in clinical practice and to compare profile to PROWESS RCT.	61 hospitals	NR	Clinic patients on DrotAA and DrotAA patients in PROWESS RCT	28 day mortality	• Rate in the clinic 36.7% • High-risk PROWESS rate 30.9%
Ferrer et al. (9)	To analyze the impact of four treatment strategies for severe sepsis on hospital mortality.	77 intensive care units (ICUs)	• Excluded patients if severe sepsis onset was not determined	Survivors and non-survivors	Hospital mortality	• Propensity adjusted OR was 0.59 for DrotAA patients with multiorgan failure
Hodder et al. (10)	To explore the relation between patients' evolving clinical status (stable, worse, improving) and DrotAA, and their outcome.	Canadian ENHANCE cohort	NR	NA	28 day mortality	• OR range was 0.25 to 1.3(for different covariates in logistic regression)
Van Doorn et al. (4)	To test if DrotAA offers a protective effect for sepsis-related kidney injury.	One hospital	• Severe sepsis-induced cardio-respiratory failure • No pre-existing renal failure	DrotAA and nonDrotAA patients	28 day mortality and !FENa concentrations as marker of tubular dysfunction	• 56% MR for DrotAA patients • 69% MR for nonDrotAA patients • No difference in FENa concentrations between groups
Wheeler et al. (21)	To evaluate the difference between clinic patients on DrotAA and patients in the	ICUs of five teaching institutions	NR	Clinic patients on DrotAA and DrotAA patients from	Hospital mortality	• Clinic hospital MR 42.3%

	PROWESS RCT. To determine the timing of DrotAA in clinical practice.			PROWESS RCT		
Kanji et al. (11)	To describe prescribing practices and clinical outcomes with DrotAA therapy.	37 hospitals	• Severe sepsis (PROWESS criteria)	Survivors and non-survivors both on DrotAA	Mortality	• Overall MR was 45% • Early DrotAA treatment (within 12h of diagnosis) was associated with a decreased mortality (OR=0.51, 95%CI 0.28-0.92)
Longo et al. (13)	To evaluate the effect of DrotAA on long-term HRQoL and resource utilization compared with standard care.	Nine ICUs	• PROWESS study criteria • 2 sepsis-induced organ failures	DrotAA and nonDrotAA patients	HRQoL based on the SF-36 survey‡ and resource use, both outcomes at 28 days, 3,5,7months	• Patients treated with DrotAA overall appeared to do as well or better in HRQoL measurements than those with standard of care (nonDrotAA) and had lower resource use for hospital services.
Martin et al. (14)	To compare baseline characteristics and outcomes with DrotAA and non-DrotAA patients in the PROGRESS database.	PROGRESS database (an international multicentre registry)	• Diagnosis of severe sepsis (≥2 SIRS, infection, ≥1 organ dysfunction) • ≥18 years old	DrotAA and nonDrotAA patients	Hospital mortality	• Propensity adjusted OR was 0.72**,** 95%CI 0.603-0.860 • Relative risk reduction was17% for DrotAA patients
Laterre et al. (12)	To evaluate 28-day survival in placebo group and the treatment effect of DrotAA.	INDEPTH database (of 5 RCT and non-RCT studies)	• Severe sepsis (infection; >3 SIRS symptoms; >1 organ dysfunction)	DrotAA patients and patients on placebo	28 day mortality	• DrotAA patients 28-day MR was 24.1% • Placebo patients 28-day MR was 31.8% • Propensity and variable adjusted OR was 0.79, 95%CI 0.67-0.93

Ridley et al. (17)	To review clinical impact of DrotAA outside clinical trials.	ICUs in five hospitals	NR	DrotAA patients in clinics and DrotAA patients in ICNARC study	Hospital mortality	• Hospital mortality rate for DrotAA was 46.7% • When compared with expected mortality based on APACHE score, DrotAA appeared to be associated with lower MR
Vincent el al. (20)	To provide an overview of patients' profile treated with DrotAA compared with PROGRESS patients.	Belgium registry and Belgium section of PROGRESS database (international, multi-centre registry)	NR	DrotAA patients from Belgium registry and nonDrotAA patients from PROGRESS database	Hospital mortality	• Propensity adjusted hospital MR for DrotAA patients was 50.7% • Non-DrotAA MR was 63.5% • Absolute mortality reduction controlled for age and organ dysfunction was 12.8%
Payen et al. (16)	To evaluate the safety and efficacy of DrotAA.	INDEPTH database integrating 5 clinical trials	• Met 3 of 4 *SIRS criteria	NA	28 day mortality and severe bleeding	• DrotAA patients 25.1% MR • NonDrotAA patients 31.8% MR
Spriet et al. (18)	To compare local hospital mortality with the Belgium registry and PROWESS RCT.	University hospital	• Severe sepsis • At least 2 organ dysfunctions	Survivors and non-survivors both on DrotAA	Hospital mortality	• Overall MR€ was 40% • 28-day MR was 26% • Belgium registry MR was 52% • 28-day PROWESS was 26%

MR: Mortality rate; HRQoL: health-related quality of life; NR: Not Reported; SIRS: systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment; OR: Odds Ratio; ICNARC: Intensive Care National Audit and Research Centre

*SIRS criteria: suspected or known infection, at least 1 new sepsis attributable organ dysfunction within 24h of study enrolment

! FENa: fractional excretion of sodium used as a marker of tubular dysfunction in septic acute kidney injury

‡SF-36 survey: 10-point difference in the physical functioning domain

€ Overall MR defined by the authors as primary end point to evaluate the efficacy of DrotAA

APPENDIX 1: METHOD

Articles were included if they had been published between October 1, 2006 and November 23, 2010. Language of publication was not restricted.

Studies were eligible for inclusion if they directly compared DrotAA-treated and non-DrotAA-treated patients. Cohort studies that compared survivors and non-survivors of severe sepsis were also included if they reported measures of association relating to the use of DrotAA.

Keywords used in the search were “Drotrecogin alfa,” “sepsis,” “activated protein C,” and “Xigris.” The on-line sources of Cochrane Library and York University Centre for Reviews and Dissemination were first searched for updated reviews. Studies were identified by searching the following electronic databases: MEDLINE, MEDLINE In-process and other non-indexed citations, EMBASE, Global Health, and NASW Clinical Register.

One reviewer (IP) screened studies, determined the eligibility, and decided on the inclusion of articles in the systematic review. A second reviewer (IN) independently searched bibliographies of included studies and extracted the data. Data extracted included information explicitly stated in the text and relevant information available in on-line supplements.

Information was extracted from each included systematic review on the year of publication, the country where the study took place, and total study population. Similarly, the number of patients taking DrotAA, the mean age of participants, the study design, and authors’ conflict of interest were also recorded. In addition, detailed information was collected on the main objectives of the study, sources of data collection used in the study analysis, the main study outcomes analysed, the participant eligibility criteria, and main study findings. As well, if a comparison group was specified, we described the characteristics of the comparison group and the comparison group selection criteria.

Descriptive statistics were used to summarize the number, frequency, and proportion of included studies within the specified characteristic criteria using Microsoft Office Excel 2003

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