Journal of Critical Care 32 (2016) 114–119

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Sepsis/Infection

Adoption and de-adoption of drotrecogin alfa for severe sepsis in the United States☆

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ARTICLE INFO

Keywords:
Intensive care
Critical care
Sepsis
Pharmacoepidemiology
Diffusion of innovation

ABSTRACT

Purpose: Drotrecogin alfa was a landmark drug for treatment of severe sepsis, yet little is known about how it was adopted and de-adopted during its 10-year period of availability.
Methods: We used hospitalization data on fee-for-service Medicare beneficiaries from 2002 to 2011 to characterize trends in the use of drotrecogin alfa in the United States.
Results: Drotrecogin alfa use peaked at 5.87 per 1000 severe sepsis hospitalizations in 2003 and then steadily declined to 0.94 administrations per 1000 severe sepsis hospitalizations in 2010. Large teaching hospitals were more likely to use drotrecogin alfa than small, nonteaching hospitals. The addition of "add-on payments" to hospitals for using drotrecogin alfa in 2002 was associated with significantly increased use ($P < .0001$), and the withdrawal of those payments in 2004 was associated significantly decreased use ($P < .0001$). Neither the publication of international sepsis guidelines with favorable drotrecogin alfa recommendations (in 2004 and 2008) nor the publication of a clinical trial focused on drotrecogin alfa (in 2005) were associated with consistent changes use ($P > .05$).
Conclusions: Drotrecogin alfa use declined over time, with marked changes in use associated with drug-specific financial incentives but not the publication of clinical practice guidelines or clinical trials.

1. Introduction

Implementation evidence-based practice is a persistent challenge in critical care [1]. This is true not only for adoption of therapies for which good evidence exists, such as lung-protective ventilation [2], daily interruption of sedation [3], and venous thromboprophylaxis [4], all of which may be underused, but also for de-adoption of therapies for which good evidence is absent, such as pulmonary artery catheters [5], liberal red blood cell transfusion thresholds [6], and intensive glycemic control [7], all of which may be overused. However, despite these challenges, little is known about how clinicians adopt and de-adopt treatments in the intensive care unit (ICU) [8].

Recombinant activated protein C (drotrecogin alfa) for severe sepsis provides a novel natural experiment for better understanding the adoption/de-adoption process in critical care [9]. Drotrecogin alfa was introduced in 2001 after the Prospective recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial demonstrated a significant mortality reduction in patients with severe sepsis [10]. Over the next decade, the Surviving Sepsis Campaign released 2 international clinical practice guidelines recommending the drug in selected patients, once in 2004 [11] and again in 2008 [12]. In between these 2 guidelines, the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial was published showing no significant benefit in adults with a low risk of death [13]. Finally, in 2011, the PROWESS-SHOCK trial was published showing no impact on survival of adults at high risk of death, prompting the manufacturer to withdraw the drug from the market [14].

How drotrecogin alfa use changed over these 10 years, both in general and in response to the Surviving Sepsis Campaign guidelines and the ADDRESS trial, is unknown. Also unknown is the relative impact of a US government payment policy designed to incentivize use of drotrecogin alfa. This policy, known as the "new technology add-on payment," provides extra payments to hospitals when patients receive expensive drugs and technologies which otherwise might not be affordable under traditional payment models [15]. Based on the relatively high costs, Medicare added drotrecogin alfa to this program in 2002, providing hospitals with a bonus payment covering the costs of administration in Medicare beneficiaries. These payments were stopped in 2004 due to the relative underuse of drotrecogin alfa compared with other therapies in program [16].

Insight into how the use of drotrecogin alfa evolved over its 10 year life span, specifically in regard to changes in guideline publication, trial

Abbreviations: ARIMA, autoregressive integrated moving average; HCRIS, Healthcare Cost Reporting and Information System; ICU, intensive care unit; *ICD-9-CM, International Classification of Diseases, Ninth Edition, Clinical Modification*; MedPAR, Medicare Provider Analysis and Review; US, United States.

☆ There are no financial conflicts of interest to declare.

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http://dx.doi.org/10.1016/j.jcrc.2015.12.007
0883-9441/

Table 1
Events tested for their potential impact on the use of drotrecogin alfa between the release date of November 21, 2001, and the withdraw date of October 25, 2011

Event	Date	Comments
Technology add-on payment begins [15]	October 2002	Medicare adds drotrecogin alfa to an existing program providing extra payments to hospitals to cover the cost of selected new technologies. This payment is in addition to the traditional payment for the hospitalization.
Surviving Sepsis Campaign guidelines—initial publication [11]	March 2004	One recommendation: Drotrecogin alfa "is recommended in patients at high risk of death … and with no absolute contraindications related to bleeding risk or relative contraindication that outweighs the potential benefit" (grade B).
Technology add-on payment ends [15]	October 2004	Medicare removes drotrecogin alfa from the list of treatments and tests eligible for extra payment under the add-on payment programs.
ADDRESS trial [13]	September 2005	Patients with severe sepsis judged to be at low risk for death were randomly assigned to receive drotrecogin alfa or placebo. There were no statistically significant differences in the primary endpoint of 28-d mortality between groups (17.0% vs 18.5%, $P = .34$).
Surviving Sepsis Campaign guidelines—second publication [12]	January 2008	Two recommendations: "Consider [drotrecogin alfa] in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death … if there are now contraindications (2B, 2C for postoperative sepsis)"; "Adult patients with severe sepsis and low risk of death should not receive [drotrecogin alfa] (1A)"

publication, and payment policy, may provide insight into how clinicians adopt and de-adopt treatments in the ICU. To better understand this issue, we used administrative data from the US Medicare program to study trends in drotrecogin alfa use from its introduction in 2002 to its withdrawal in 2011.

2. Materials and methods

2.1. Study design and patients

We performed a longitudinal cohort study of Medicare beneficiaries admitted to US hospitals receiving drotrecogin alfa. We used the Medicare Provider Analysis and Review (MedPAR) file, which contains administrative claims data on all hospital admissions for individuals enrolled in fee-for-service Medicare. Fee-for-service Medicare insures more than 70% of adults 65 years and older in the United States and is considered representative of the US elderly population as a whole. MedPAR is also the only national data set of hospital admissions in the United States, making it a unique data resource for this study.

We used the MedPAR files from 2002 (the release year of drotrecogin alfa) to 2011 (the withdraw year of drotrecogin alfa). All hospital admissions in MedPAR were eligible for the analysis. To obtain data on hospital characteristics, we linked MedPAR to the Medicare Healthcare Cost Reporting Information System, which contains facility-level data on all US hospitals participating in the Medicare program.

2.2. Variables

Patient characteristics were obtained from the hospitalization records in MedPAR. We identified drotrecogin alfa use through the *International Classification of Diseases, Ninth Version, Clinical Modification* (*ICD-9-CM*) procedure code 00.11 ("infusion of drotrecogin alpha [activated]) [15]. *Severe sepsis* was defined using *ICD-9-CM* codes in the manner of Angus et al [17]; *comorbidities* were defined using *ICD-9-CM* codes in the manner of Elixhauser [18]; *ICU admission* was identified using ICU-specific revenue codes [19]; *mechanical ventilation* was identified using *ICD-9-CM* procedure codes [20]; and the primary reason for the hospitalization was obtained using diagnosis-related groups [21].

Hospital characteristics were obtained from Healthcare Cost Reporting Information System, including total hospital beds; total ICU beds; ownership status categorized as nonprofit, for profit, and government; teaching status categorized as nonteaching (no residents), small teaching (resident-to-bed ratio > 0 but ≤0.25), and large teaching (resident-to-bed ratio >0.25); community size categorized as small (metropolitan statistical area <250 000 residents), medium (metropolitan statistical area ≥250 000 residents but <1 million residents), and large (metropolitan statistical area ≥1 million residents); and region categorized by US census regions as Northeast, Midwest, South, and West.

2.3. Analysis

The analysis was performed at the level of the hospitalization, such that patients might be included twice if they received drotrecogin alfa in 2 separate hospitalizations. We summarized the characteristics of hospitalizations involving receipt of drotrecogin alfa using the mean and SD for continuous variables or frequency and percent for categorical variables.

We visually examined temporal changes in drotrecogin alfa use by plotting month-specific use over time, from November 21, 2001 (the US approval date), to October 25, 2011 (the withdraw date). We focused on 2 statistics of interest: total episodes of use, which provides insight into usage patterns independent of the total severe sepsis cases (which is known to have increased over the study period [22]), and

Table 2
Characteristics of patients receiving drotrecogin alfa

Characteristics	All patients (n = 29 369)
Age (y)	69.2 ± 12.7
Female	14 077 (47.9)
Race, n (%)	
White	24 351 (82.9)
Black	3559 (12.1)
Other	1459 (5.0)
ICU admission, n (%)	27 537 (93.8)
Mechanical ventilation, n (%)	20 287 (69.1)
Severe sepsis, n (%)	27 973 (95.2)
Organ failure, n (%)[a]	26 960 (91.8)
Cardiac dysfunction	21 868 (74.5)
Kidney dysfunction	17 015 (57.9)
Liver dysfunction	1796 (6.4)
Neurologic dysfunction	1890 (6.4)
Diagnosis-related groups, n (%)	
Septicemia	12 157 (41.4)
Respiratory system diagnosis with ventilation	3697 (12.6)
Infectious diseases with operating room procedure	2632 (9.0)
Mechanical ventilation	3333 (11.3)
Major bowel procedures	1347 (4.6)
Other circulatory system diagnoses	357 (1.2)
All other DRGs	5846 (19.9)
Comorbidities, n (%)	
Chronic pulmonary disease	2216 (7.5)
Congestive heart failure	6603 (22.5)
Diabetes mellitus	2198 (7.5)
Solid tumor without metastasis	689 (2.3)
Metastatic cancer	723 (2.5)
Liver disease	743 (2.5)

DRGs indicates Diagnosis Related Groups.
[a] Patients may have more than one of the following organ dysfunction group: cardiac (hypotension, shock, thrombocytopenia, coagulation defects, defibrination syndrome), kidney (kidney failure) and liver (necrosis of liver, hepatic infarction), and neurologic (delirium, encephalopathy, anoxic brain damage).