COST-EFFECTIVENESS OF DROTRECOGIN ALFA (ACTIVATED) IN THE TREATMENT OF SEVERE SEPSIS WITH MULTIPLE ORGAN FAILURE

Short title: cost-effectiveness of drotrecogin alfa

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Abstract

Objectives: To estimate the expected cost and clinical benefits associated with the use of drotrecogin alfa (activated) [Xigris; Eli Lilly and Company; Indianapolis, IN] in the French hospital setting.

Methods: The PROWESS study results (1,271 patients with multiple organ failure) were adjusted to 9,948 hospital stays from a database of Parisian area intensive care units (ICUs) – the CubRea database. The analysis features a decision tree with a probabilistic sensitivity analysis.

Results: The cost per life-year gained (LYG) of drotrecogin treatment for severe sepsis with multiple organ failure (European indication) was estimated to be $11,812. At the hospital level, the drug is expected to induce an additional cost of $7,545 per treated patient. The incremental cost-effectiveness ratio ranges from $7,873 per LYG for patients receiving three organ supports during ICU stay to $17,704 per LYG for patients receiving less than two organ supports.

Conclusions: Drotrecogin alfa (activated) is cost-effective in the treatment of severe sepsis with multiple organ failure when added to best standard care. The cost-effectiveness of the drug increases with baseline disease severity, but it remains cost-effective for all patients when used in compliance with the European approved indication.

Key Words

Severe Sepsis ● Intensive care ● drotrecogin alfa (activated) ● cost-effectiveness ● healthcare costs

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Abbreviations

APACHE II = acute physiology and chronic health evaluation; ARR = absolute risk reduction; $CI_{95\,\%}$ = 95% confidence interval; CubRea = intensive care database user group; DAA = drotrecogin alfa (activated) [Xigris; Eli Lilly and Company; Indianapolis, IN]; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LE = life expectancy; LYG = life-year gained; MOF = multiple organ failure; QALY = quality-adjusted life year; RR = relative risk.

Introduction

Severe sepsis (5) is common on French intensive care units (ICUs), affecting 10-15% of admitted patients (1;7;8). The high incidence of sepsis and its reported mortality rate of 20-65% (1;3;7;8;33) are associated with substantial healthcare costs (9;25;26;30;36). The results of the PROWESS (recombinant human activated PROtein C Worldwide Evaluation in Severe Sepsis) trial showed that drotrecogin alfa (activated) [Xigris; Eli Lilly and Company; Indianapolis, IN] (DAA) significantly reduced mortality associated with this condition (4). DAA leads to an absolute risk reduction (ARR) of 6.13% ($CI_{95\%}$: [1.86%; 10.39%]), and to a relative risk (RR) of death using this drug compared with placebo of 0.80 ($CI_{95\%}$: [0.69; 0.94]). Regulatory authorities in the USA and Europe have approved DAA for use in different indications. In the USA, DAA is approved for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (as determined by APACHE II score (21), whereas in Europe it is approved for the treatment of adult patients with severe sepsis and multiple organ failure (MOF) when added to best standard care. Although several DAA cost-effectiveness evaluations based on the USA labeling have been carried out (2;26), few data are available regarding European labeling (31).

Materials and methods

Study design

A total of 9,848 hospital stays between 1997 and 2000 were selected from the French CubRea (Intensive Care Database User Group) database (37). These stays were associated with: 1) one infected site or one positive blood culture; 2) at least two organ failures; and 3) length of stay of more than 24 h. Hospital data were then added to the ICU stay data. The PROWESS results were used to estimate the effectiveness of DAA if used in CubRea patients.

The aim of the study was to determine the cost required to gain one additional life-year among patients with severe sepsis and MOF by adding DAA to the standard care. Costs related to decreased productivity were not included to avoid double counting (they can be assessed in the effectiveness indicator) (18). No information was available on subsequent re-hospitalization of survivors. Only those costs relating to hospitalization during the patients' stay were computed and discounting was therefore unnecessary. The analytic horizon of the study was the patient's lifespan. In the baseline model, the effect was not discounted as this practice is controversial (14). The CubRea database was not expected to be representative of the national patient population since 75% of the departments in the database were medical ICUs. A model was therefore constructed allowing a correction for over-representation of medical patients in the database and extrapolation of the results of the PROWESS trial to the French population. The decision analysis model was created with a decision tree, all the parameters being defined by a probability density function. A probabilistic sensitivity analysis (16) was then completed using Data Professional (TreeAge Software, Inc.). Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc.).

Complete cost of hospitalization

The cost (Euros were converted to US Dollars at a conversion rate of 0.98316 – 2002 rate) considered was the complete cost of hospitalization, including the direct (investigations, consumables and care staff) and indirect (hotel services, laundry, pharmacy and administration) costs of stay on an ICU and the cost of stay in hospital following intensive care. A study based on 211 hospital stays (37) used micro-costing to estimate the cost of ICU hospitalization. A multiple linear regression equation was then developed using the length of stay in intensive care, the Simplified Acute Physiology Score (SAPS II) (24), the Omega score (38) and the status of the patient when leaving the ICU (deceased or alive) in order to predict the patient's ICU costs. The cost of non-ICU stays was estimated using the daily cost for mandatory services. The length of stay is an indicator often used to measure hospital costs, although it should not be considered an accurate estimate of costs when used alone (39). The SAPS II score has been validated as a severity index for patients with severe sepsis (23) and the Omega score has been used predominantly to estimate French ICU costs (12;38).

Costs associated with drotrecogin alfa (activated)

The cost of 1 mg DAA in France is currently $46.70 excluding tax. DAA is available in 5 mg and 20 mg vials. DAA is administrated as a continuous intravenous infusion at 24 µg/kg/h for 96 hours. The average weight of patients from the CubRea database was 71.6 kg and the mean treatment cost was therefore estimated to be $7,705.50 excluding tax. The primary serious adverse event reported in the PROWESS trial was bleeding; the proportion of serious bleeding at 28 days in patients who received DAA was low and was only slightly higher than in the placebo group (3.5% vs. 2.0%, p=0.06) (4). Costs associated with the management of side effects were not considered in the baseline analysis.

Drotrecogin alfa (activated) effectiveness

The primary efficacy endpoint in the PROWESS study (4) was 28-day mortality after initiation of treatment. However, this criterion must be broadened in the context of a pharmacoeconomic evaluation (10). The CubRea database provided follow-up data on patients, including deaths in ICU and patient status upon discharge from hospital.

The PROWESS study findings showed that the drug produced consistent results regardless of patient subgroup. When only patients with MOF were considered, the RR improved from 0.80 to 0.78 ($CI_{95\%}$: [0.66; 0.93]) (15). In the current evaluation, a time-dependent estimate was used instead of the RR reported in the PROWESS study. Survival of patients with severe sepsis and MOF receiving placebo and those receiving DAA in the PROWESS study was estimated using a Weibull survival function (42). The RR used in the model is the ratio of these two survival functions and is consequently a function of the mean length of survival of the patients (Figure 1). It is assumed that risk is reduced in the ICU and also in the hospital wards that follow.

Life expectancy

The unit of effectiveness traditionally used in pharmacoeconomic evaluations is the quality adjusted life year (QALY) (11). As no French cohort study has been conducted to date in ICU patients surviving severe sepsis, there are no data available regarding the life expectancy (LE) or quality of life of this population. However, the Quartin et al study (34) suggests that sepsis reduces the LE of survivors. Accordingly, the survivors' LE was computed as follows: first, the McCabe classification was used to take account of short-term fatal comorbidities (27). Patients without serious concomitant diseases were then allocated the age- and sex-specific LE of the general population using French life tables from 1997 to 2000. Finally, the

LE of survivors was assumed to be half of that estimated for the general population, as described by Quartin et al. (34). As the relative mortality risk for patients with severe sepsis decreases with time and is not significantly different after 5 years, this study may underestimate the patient's LE.

Studies evaluating quality of life after ICU stay have reported a range of coefficients from 0.6 to >0.8 (2;19;20;26). The lowest coefficient was used here, as in the Canadian DAA cost-effectiveness study (26).

Stratification criteria

The decision tree stratified patients according to their admission category (medical, scheduled or unscheduled surgery), origin of admission onto the ICU (community, ward, other institution) and health care profile. The first of these criteria is recognized as a factor linked to mortality (24), the second is an indirect indicator of early infection and the third follows a medico-economic classification of patients proposed by a group of French medical societies (French Society for Anaesthesia and Intensive Care, French Language Intensive Care Society and the National Academy for Public Health) (29). This classification groups patients according to the treatment administered for respiratory, circulatory and renal failure (defined by the authors as organ supports), the duration of support (estimated from the Omega score) and the risk of death (estimated from the SAPS II score). The clinical and economic relevance of this classification has been validated in other studies (13;17). Death can occur in the ICU, or in the hospital after leaving the ICU. The proportion of medical patients used in the study was the only variable that was not obtained from the CubRea database: published findings indicate that this proportion (0.78) was overestimated in the database (1;7;23). A medical admission proportion of 0.70 was used in the decision tree instead.

Sensitivity analysis

A sensitivity analysis was used to estimate the stability of the conclusions of the model assuming variability of key parameters. A simple one-way sensitivity analysis was first completed to assess the effects of the model's assumptions. A probabilistic sensitivity analysis using second order Monte Carlo simulation was then performed (16). A Monte Carlo simulation implies the sampling of any stochastic parameter of the model from its particular probability density function and the estimation of the model outcomes using the sampled parameters instead of their deterministic value. A total of 5,000 random draws of the 385 model parameters were generated.

Results

Patient characteristics

The PROWESS and CubRea patient characteristics are shown in Table 1. The French patients differ from those in the PROWESS trial with respect to organ failure distribution, but are relatively similar in terms of renal, circulatory and respiratory support (15). It is more difficult to compare the different severity scores used in PROWESS and CubRea. Both the APACHE II and SAPS II scores, however, allow the calculation of a mortality risk, which was higher for patients in the PROWESS trial (0.57 vs. 0.48). Assuming both scores have a similar predictive performance (28), patients in the PROWESS trial can be considered to be more severely ill than those in the CubRea database. This assumption requires careful consideration as the predictive power of these scores has been questioned.

Standard care

All patient characteristics (except for LE, which was determined from the assumptions described above) were estimated from the CubRea database after adjusting for non-surgical admissions (Table 2). The cost of care increased considerably with the number of organ supports. The majority of CubRea database patients required respiratory and circulatory support (56.9% of stays). The mean hospital length of survival (in ICU and post-ICU) ranged from 26−31 days, depending on patient category. Hence, the length of stay was close to the 28-day threshold used in the PROWESS trial. The estimated cost per patient in this study, $31,289, is similar to the cost estimated in the Canadian (26) ($32,950 for all patients and $35,104 for those with an APACHE II score of ≥25) and American (2) ($32,066 for all patients) studies. However, these costs are higher than those estimated in other foreign studies (3;25;30;36) and close to those reported for French patients (9).

Cost-effectiveness analysis

The incremental cost and effectiveness, estimated according to patient admission category and number of organ supports, are shown in Table 3. The resulting incremental cost-effectiveness ratios (ICERs) were calculated in dollars per life-year gained (LYG) and per QALY. An average of $11,812 was spent in order to gain one additional life-year using DAA. This figure showed little change depending on the admission category; medical patients required $11,507 per LYG versus $12,573 per LYG for surgical patients. Medical patients actually had a higher mortality risk combined with a younger age in the CubRea database (Table 2). The cost per LYG was lowest among patients requiring the most support: the ICER for patients requiring renal, respiratory and circulatory support was $7,873 per LYG, compared to $12,942 per LYG for two of the three organ supports and $17,704 per LYG if the patient received fewer than two of the three organ supports. These patients were less cost-effective than the others because of their lower mortality risk (26.6% compared to 45.7% and 74.1% for patients with two and three organ supports, respectively). Since the effect of DAA is assessed using a RR of death, the most cost-effective patients are those with a higher mortality risk. Other cost-effectiveness factors, such as LE of the survivors, play a secondary role.

Sensitivity analysis

The deterministic model shows that DAA is cost-effective in the treatment of severe sepsis with MOF. Table 4 summarizes the one-way sensitivity analysis of ICER to key variables. Using the upper (0.93) and lower (0.66) bounds of the 95% confidence interval computed for the RR of death for patients with MOF in the PROWESS trial [15], the ICER ranges from $6,450 to $33,894 per LYG. The ICER in the model is sensitive to the value of RR.

Using the PROWESS ARR rather than RR, a ratio of $14,413 per LYG is obtained. As the mortality rate reported in the CubRea database was higher than that observed in the PROWESS trial (Table 1), using the RR inevitably leads to a higher ARR. There are currently no guidelines regarding which estimator, ARR or RR, to use in pharmacoeconomic evaluations (35). Nevertheless, the choice made has little effect on the overall ratio. There is little change in the ICER when the mean body weight increases from 65 to 75 kg; from $11,065 to $12,559 per LYG.

Another consideration is the cost of treating adverse events related to treatment; it was assumed to be negligible in the current study. If this cost increases on average from $0 per patient to $492 (€500) per patient, the ratio increases from $11,812 to $12,581 per LYG.

When an annual discounting rate of 5% for future effects is used, the ICER remains below the most common decision thresholds ($19,961 per LYG, $33,268 per QALY). (22;40)

A probabilistic sensitivity analysis was conducted to account for the uncertainty related to all of the parameters (6). A cost-effectiveness acceptability curve (41) is shown in Figure 2. This curve reports the probability that the ICER of treatment is below any decisional threshold. Assuming a willingness to pay of $50,000 per QALY, this probability is 85% (71% for patients with less than two organ supports, 82% for those with two organ supports and 91% for those with three organ supports). Following Neyman's interpretation of hypothesis testing (32), the model assumes that the probability of DAA being ineffective is 5%, the type I error probability chosen in the PROWESS trial (4). Consequently, the probability of cost-effectiveness can't exceed 95 %, even for an infinite willingness to pay.

Discussion

This study, which was conducted in conformity with international recommendations (43), shows that the ICER for DAA lies within the range considered to be acceptable for interventions (22;40). Although this ratio is relatively sensitive to some of the assumptions in the model, such as the expected effect of the drug on mortality (measured by its RR) and in particular to the discount rate chosen (Table 4), the incremental ratio does not exceed the conventional threshold of $50,000 per QALY until the RR rises to more than 0.92. Since RR was used to model the effect of treatment instead of ARR, the drug was found to be more cost-effective in patients with a high risk of mortality. This effect is reduced in the current study as the RR was adjusted for the length of survival of patients and is lower than that reported in the PROWESS study (0.82 vs. 0.78) (15). Moreover, using an ARR requires populations with similar mortality rates, a condition only partially met in French ICUs (Table 1).

The coefficients of the equation used to estimate the cost of conventional care were estimated from a population of ICU patients and it is possible that estimation among severely septic patients alone would have led to a different equation. However, the mean treatment cost of a patient in the model remains similar to that estimated in other studies (2;26;30). The other estimates in this model were also consistent with other studies. Using a discount rate of 5%, the overall cost-effectiveness ratio reported in this study was $33,268 per QALY for patients with severe sepsis and MOF (Table 4), a result equivalent to the ICERs estimated for patients with APACHE II scores of ≥25 in other studies ($32,872 per QALY in the Canadian study and $27,400 per QALY in the American study). These studies were based on approved USA indications. Although the American and European indications for DAA are different, cost-effectiveness estimates remain similar. This suggests that the European indication based on

organ failure and the USA indication in terms of risk of death (measured by the APACHE II score) may lead to a similar cost-effectiveness.

In the current model, French patients surviving severe sepsis with MOF can expect to live for an average of 7.9 years (Table 2). Canadian patients surviving severe sepsis (regardless of the number of organ failures) can expect to live for an average of 8.1 years (26). The Canadian calculation was based on a 3-year long cohort study and on national LE tables for the subsequent years, and could be considered to be more reliable than ours. An American study, using the same calculation method as the current one, reports an average LE of 12.3 years for patients surviving severe sepsis (2).

Policy Implications

Our model, based on the European indication for the drug, produces estimates that may be more appropriate in the European context. According to our results, DAA can be considered cost-effective in the European indication. Although severely ill patients have more attractive ICERs, it would be unethical to treat only some subgroups of patients, at least on the basis of the number of organ supports received, since even the least attractive cost-effective ratio remains below the acceptable threshold. However, treating the patients with this new drug will increase ICUs expenses. In France, this problem was taken into account by reporting DAA's cost separately, the drug being fully and directly reimbursed by the sickness funds.

Conclusion

It can be concluded that DAA is cost-effective for the treatment of adult patients when used in the European indication. An estimate of the cost-effectiveness of this new treatment is provided, which is more suitable for European countries, and more specifically for France.

Despite the differences in the patient population considered and the assessment methods used, these results are concordant with those described previously in other studies. More data on the long-term survival and quality of life of patients, as well as on the effect of treatment on current practices, would be valuable in order to have a better idea of the impact of the drug.

References

1. Alberti C, Brun-Buisson C, Goodman SV, et al. European Sepsis Group. Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. Crit Care Med 2003; 168(1):77-84
2. Angus DC, Linde-Zwirble WT, Clermont G, et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. Crit Care Med 2003; 31(1):1-11
3. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29(7):1303-1310
4. Bernard GR, Vincent JL, Laterre PF, et al. Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001; 344(10):699-709
5. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101(6):1644-1655
6. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17(5):479-500
7. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995; 274(12):968-974
8. Brun-Buisson C, Meshaka P, Pinton P, et al. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med. 2004; 30(4):580-588. Epub 2004 Mar 02
9. Brun-Buisson C, Roudot-Thoraval F, Girou E, et al. The costs of septic syndromes in the intensive care unit and influence of hospital-acquired sepsis. Intensive Care Med. 2003; 29(9):1464-1471. Epub 2003 Jul 10
10. Buxton MJ, Drummond MF, Van Hout BA, et al. Modeling in economic evaluation: an unavoidable fact of life. Health Econ 1997; 6(3): 217-227
11. Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluation of pharmaceuticals: Canada. 2nd ed. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 1997.
12. Chaix C, Durand-Zaleski I, Alberti C, et al. A model to compute the medical cost of patients in intensive care. Pharmacoeconomics 1999; 15(6):573-582

13. Coulomb F, Moret L, Boudon M, et al. La classification médico-économique SRLF-SFAR-Image est applicable à un service de réanimation polyvalente d'un centre hospitalier général. Réan Urg 2000; 9(4):241-247
14. Coyle D, Tolley K. Discounting of health benefits in the pharmacoeconomic analysis of drug therapies: an issue for debate? Pharmacoeconomics 1992; 2(2):153-162
15. Dhainaut JF, Laterre PF, Janes JM, et al. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. Intensive Care Med 2003; 29(6): 894-903
16. Doubilet P, Begg CB, Weinstein MC, et al. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making 1985; 5(2):157-177
17. Gastinne H, Raffy C, Richard V, et al. Les groupes homogènes de malades proposés pour la réanimation. Etude de la pertinence de cette classification basée sur un calcul de coûts Réan Urg 2000; 9:249-256
18. Gold MR, Siegel J, Russell L, et al. Cost-effectiveness in health and medicine. New York: Oxford university press, 1996
19. Granja C, Teixeira-Pinto A, Costa-Pereira A. Quality of life after intensive care - evaluation with EQ-5D questionnaire. Intensive Care Med 2002; 28(7):898-907
20. Hurel D, Loirat P, Saulnier F, et al. Quality of life 6 months after intensive care: results of a prospective multicenter study using a generic health status scale and a satisfaction scale. Intensive Care Med 1997; 23(3):331-337
21. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13(10):818-829
22. Laupacis A, Feeny D, Detsky AS, et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J 1992; 146(4):473-481
23. Le Gall JR, Lemeshow S, Leleu G, et al. Customized probability models for early severe sepsis in adult intensive care. patients. Intensive Care Unit Scoring Group. JAMA 1995; 273(8):644-650
24. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270(24):2957-2963
25. Letarte J, Longo CJ, Pelletier J, et al. Patient characteristics and costs of severe sepsis and septic shock in Quebec. J Crit Care 2002; 17(1):39-49

26. Manns BJ, Lee H, Doig CJ, et al. An economic evaluation of activated protein C treatment for severe sepsis. N Engl J Med 2002; 347(13):993-1000
27. McCabe WR, Jackson GG. Gram negative bacteremia I: etiology an ecology. Arch Intern Med 1962: 110:847-855
28. McNelis J, Marini C, Kalimi R, et al. A comparison of predictive outcomes of APACHE II and SAPS II in a surgical intensive care unit. Am J Med Qual 2001; 16(5):161-165
29. Misset B, Naiditch M, Saulnier F, et al. Construction d'une classification médico-économique des patients de réanimation fondée sur les suppléances d'organes Réan Urg 1998; 7:367-374
30. Moerer O, Schmid A, Hofmann M, et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. Intensive Care Med 2002; 28(10):1440-1446
31. Neilson AR, Burchardi H, Chinn C, et al. Cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in Germany. J Crit Care. 2003; 18(4):217-227
32. Neyman J, Pearson ES. On the problem of the most efficient tests of statistical hypotheses. Philosophical Transactions of the Roy. Soc. of London 1933; A231:289-337
33. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. Intensive Care Med 1995; 21(4):302-309
34. Quartin AA, Schein RM, Kett DH, et al. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. JAMA 1997; 277(13):1058-1063
35. Schechtman E. Odds ratio, relative risk, absolute risk reduction, and the number needed to treat--which of these should we use? Value Health 2002; 5(5):430-435
36. Schmid A, Pugin J, Chevrolet JC, et al. Burden of illness imposed by severe sepsis in Switzerland. Swiss Med Wkly. 2004; 134(7-8):97-102
37. Sznajder M, Aegerter P, Launois R, et al. CubRea. A cost-effectiveness analysis of stays in intensive care units. Intensive Care Med 2001; 27(1):146-153
38. Sznajder M, Leleu G, Buonamico G, et al. Estimation of direct cost and resource allocation in intensive care: correlation with Omega system. Intensive Care Med 1998; 24(6):582-589

39. Taheri PA, Butz DA, Greenfield LJ. Length of stay has minimal impact on the cost of hospital admission. J Am Coll Surg 2000; 191(2):123-30

40. Tengs TO, Adams ME, Pliskin JS, et al. Five-hundred life-saving interventions and their cost-effectiveness. Risk Anal 1995; 15(3):369-390

41. Van Hout BA, Al MJ, Gordon GS, et al. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994; 3(5):309-319

42. Weibull WA. A Statistical Theory of the Strength of Materials. Ingenoirs Vetenskaps Akadanien Handlinger 1939; 151:1-45

43. Weinstein MC, O'Brien B, Hornberger J, et al. ISPOR Task Force on Good Research Practices – Modeling Studies Value Health 2003; 6(1): 9-17

Tables

Table 1 Characteristics of patients with severe sepsis and at least two organ failures in the PROWESS trial and CubRea database

	PROWESS* (n = 637)	CubRea (n = 9 848)
Median age (years)	65.1	65.2
Mean severity, (SD)	25.9 (7.8) [APACHE II]	50.6 (18.2) [SAPS II]
Medical stay ($CI_{95\%}$†)	70.3% (0.66−0.74)	77.9% (0.77−079)
Two organ failures ($CI_{95\%}$)	42.5% (0.38−0.47)	51.7% (0.50−0.53)
Four or more organ failures ($CI_{95\%}$)	23.3% (0.20−0.27)	11.1% (0.10−0.12)
Ventilation ($CI_{95\%}$)	82.9% (0.79−0.86)	92.3% (0.91−0.93)
Vasoactive drugs ($CI_{95\%}$)	83.5% (0.80−0.87)	83.2% (0.82−0.84)
Dialysis/hemoperfusion ($CI_{95\%}$)	24.2% (0.20−0.28)	25.3% (0.24−0.26)
Mortality ($CI_{95\%}$)	33.9%‡ (0.30−0.38)	43.5%§ (0.42−0.45)

* Patients receiving placebo

†Calculated using a binomial probability distribution

‡24-day mortality

§Deaths in intensive care (mean length of survival: 21 days)

Table 2 Characteristics of patients receiving care according to the model

	All	Admission			Organ supports		
		Medical (70%)	UPS* (21%)	PS† (9%)	<2 (18%)	2 (60%)	3 (22%)
Males	64.2%	64.0%	63.2%	68.8%	62.7%	64.1%	66.5%
Comorbidities‡							
All	43.2%	44.7%	36.2%	48.7%	34.7%	43.8%	48.1%
Survivors	35.3%	37.0%	27.9%	40.1%	29.5%	37.0%	37.8%
Deaths							
In intensive care	43.2%	44.6%	40.0%	39.6%	17.8%	40.5%	71.3%
Total hospital	48.4%	49.8%	48.4%	43.4%	26.6%	45.7%	74.1%
Length of stay (days)§	27.4	26.2	29.9	31.2	26.8	28.4	26.4
Cost ($)	31 289	30 476	31 905	36 316	18 653	31 505	40 973
Mean age (years)	62.4	61.7	63.9	64.0	60.2	63.4	61.4
Life expectancy (years)							
All	4.08	3.96	4.34	4.42	6.49	4.03	2.12
Survivors	7.90	7.89	8.00	7.80	8.85	7.42	8.17

*UPS: unplanned surgery

†PS: planned surgery

‡Defined as McCabe score >0

§In intensive care and in subsequent departments

Table 3 Cost-effectiveness of drotrecogin alfa (activated)

	ΔCost ($)	ΔEffectiveness (life-years*)	ICER† per life-year	ICER per QALY‡
All patients combined	7545	0.64	11 812	19 686
Admissions:				
Medical	7508	0.65	11 507	19 178
Unplanned surgery	7704	0.60	12 776	21 293
Planned surgery	7453	0.62	12 084	20 140
Less than two organ supports	7400	0.42	17 704	29 507
Two organ supports	7333	0.57	12 942	21 570
Three organ supports	8187	1.04	7873	13 122

*Average life years gained per patient treated

†Incremental cost-effectiveness ratio

‡Quality adjusted life year

Table 4 Sensitivity analysis of the incremental cost-effectiveness ratio

	Incremental cost-effectiveness ratio ($/LYG*)
Baseline	*11 812*
RR comparable for all patients	
0.66	6450
0.78	10 398
0.93	33 894
Effect of the drug alone in intensive care	
RR as a function of LOS†	13 902
ARR‡ of 7.4%	14 413
Expected treatment cost ($ inc. tax)	
7 390	11 065
8 344	12 559
Expected cost of complications ($)	
98 (100 €)	11 966
246 (250 €)	12 196
492 (500 €)	12 581
Effects of discounting	
1.5%	13 901
3.0%	16 283
5.0%	19 961

* Life-year gained

† Length of stay

‡ Absolute risk reduction

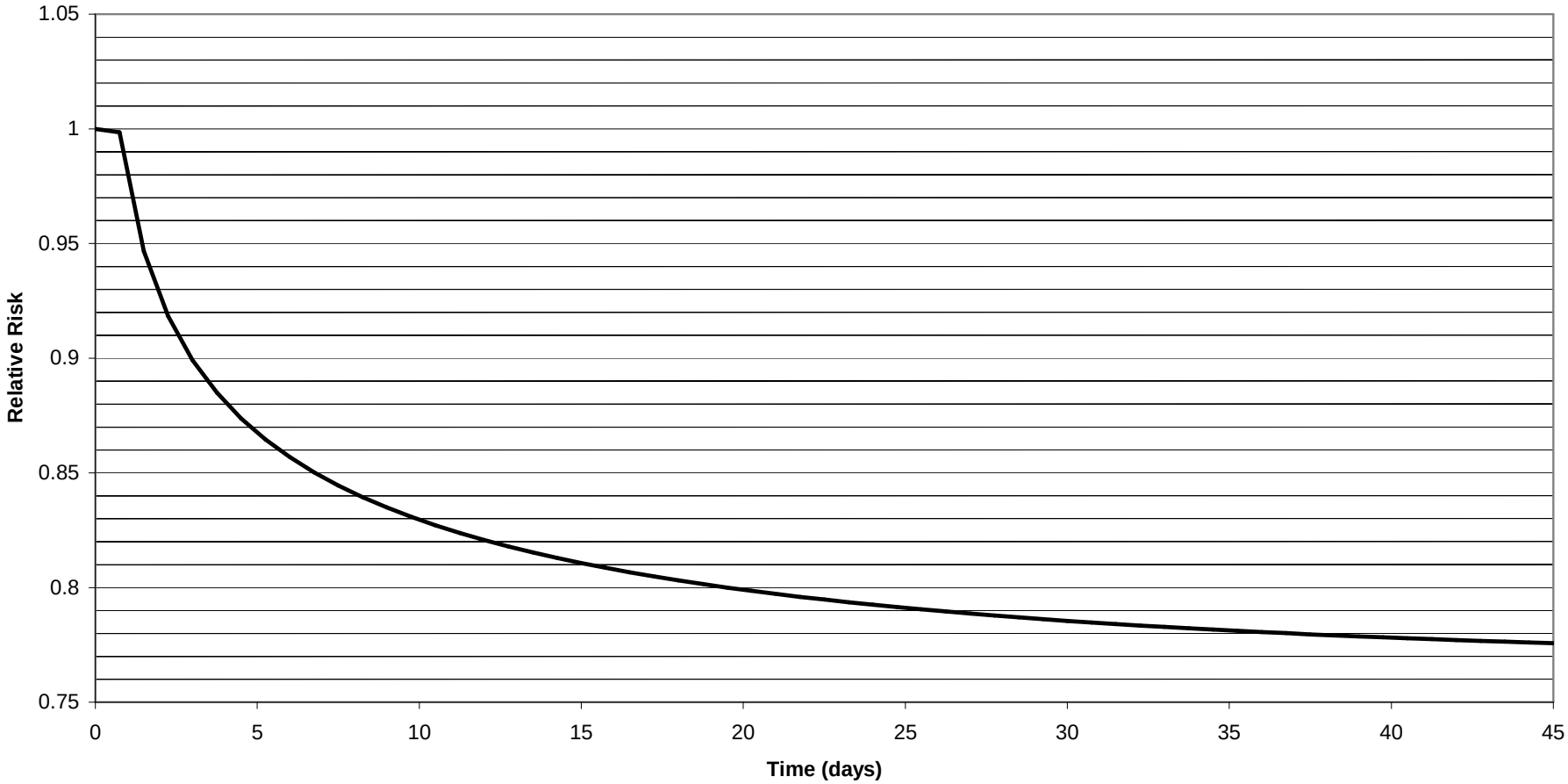
Figures

Captions:

Figure 1 Relative risk of death in patients treated with drotrecogin alfa (activated) compared to those receiving conventional care only over time.

Figure 2 Drotrecogin alfa (activated) acceptability curve for patients with severe sepsis and multiple organ failure.

Relative risk of death in patients treated with drotrecogin alfa (activated) compared to those receiving conventional care only over time



Drotrecogin alfa (activated) acceptability curve for patients with severe sepsis and multiple organ failure