REPORT NUMBER 9

Drotrecogin alfa (activated) in severe sepsis

An Informal Technology Assessment

By

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Background

Drotrecogin alfa (activated) (Xigris, Lilly) is a recombinant form of human Activated Protein C (APC). APC exerts an antithrombotic effect by inhibiting Factors Va and VIIIa. *In vitro* data indicate that APC has indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and may exert an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the thrombin-induced inflammatory responses within the microvascular endothelium. APC has been approved by the FDA for the treatment of patients with sepsis associated with acute organ dysfunction (severe sepsis). The P&T committee has been asked to evaluate this product for the MUHC and in turn requested an informal opinion of the Technology Assessment Unit (TAU) regarding this medication.

The evidence

Phase 1 studies using APC had been performed in 182 healthy adults[1]. Phase 2 studies to determine safety and dose determination have been performed in 131 adults[1]. There has been only 1 phase 3 trial of APC in which total mortality was the primary outcome. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial[2] involved 1,690 patients, 24.7% of patients taking APC and 30.8% in the placebo group died (p=0.005). Because most of the patients who benefited from the drug had severe sepsis, FDA approval was limited to adult patients with severe sepsis associated with acute organ dysfunction who have a high risk of death, as determined by an APACHE II score of 25 or greater. Relative risk of death for these selected patients was reduced by 29% (*P*=.002). The APACHE II score is composed of three risk-related components — acute physiological changes, older age, and the assignment of chronic health points.

The use of APC was associated with greater risk of serious bleeding (3.5 percent vs. 2.0 percent, P=0.06). Although the incidence of intracranial hemorrhage during the infusion period was 0.2 % (2 of 850) in the APC group in the PROWESS trial, a higher incidence (1.5 %[8 of 520]) was observed among patients receiving APC in uncontrolled studies. This emphasizes that serious side effects may be more common outside the highly controlled and artificial settings of a randomized trial.

The NEJM controversy

Since the evidence for the effectiveness of APC comes from only 1 randomized trial, it is not surprising that it has undergone considerable scrutiny. Although APC received FDA approval, the actual vote of the scientific committee was 10-10 demonstrating at least some initial ambivalence or controversy about scientific evidence, despite a 6.1% absolute mortality reduction. It is worth remembering that FDA approval is dependent only on safety and efficacy and does nor formally consider cost-effectiveness.

The controversy continued with the publication of two articles in the Sept. 26 2002 issue of the *New England Journal of Medicine*[3; 4]. According to these physicians from Massachusetts General Hospital in Boston, and consultants to the FDA, the PROWESS data are encouraging but insufficient to make APC the standard of care for severe sepsis. These authors[3] note that study protocol changes occurred during the trial, shifting the study population composition toward patients with less severe underlying disease and more acute infectious illnesses. Other protocol changes included use of a different placebo, elimination of protein C deficiency status as a primary variable and drug production from a new master cell bank (see Appendix 1). These authors are concerned that these changes may have modified outcomes and complicated interpretation of the trial data. They point to differences in the cumulative mortality curves suggest an improvement in protective efficacy of APC after these changes were made (see Figure 1, Table 1). They recommend a new trial to confirm the post hoc analyses, preferably one that prospectively incorporates a prognostic scoring system such as APACHE II.

In the same NEJM issue, FDA officials[4] counter these accusations by noting that any protocol changes should have disadvantaged APC, subgroup analyses with the Apache II score were pre-specified, time changes are within the play of chance and that many independent agencies have endorsed the scientific validity of the PROWESS data.

The strength of the evidence

The PROWESS trial demonstrated a 6.1% absolute reduction in mortality. Despite this large effect size, certain precautions surround its interpretation. First the variability in this estimate is considerable (95% CI 1.9%-10.4%). Care must be taken not to over-estimate the strength of the data or to confuse statistical significance, as measured by the p value (the probability of obtaining this data or more extreme data under the null hypothesis of no effect) with clinical significance. To address these issues, it may be useful to plot the data as a probability density function (see Figure 2).

The probability of the occurrence of an event is proportional to the area under the curve. For mortality, there is a 99.8% probability of a mortality reduction with APC (area to left of zero = 0.2%). Frequently, it is more informative to know not the probability that one treatment is better than another but to know the probability of a clinically meaningful difference, for example a minimum 1% reduction in mortality. In this case, we remain 99% sure that the improvement in mortality is at least 1%.

Regarding safety, there was an increased risk of serious bleeds with APC and it is appropriate to examine the combined outcome of death or serious bleeding complication, analogous to the thrombolytic trials which examined death or stroke. The PROWESS data is sensitive to the inclusion of these serious bleeding complications as seen by the shifting of the probability density curve. The probability that the combined outcome (death or major bleeding) is reduced by at least a 1% is only 94%. The possibility of obtaining a minimal reduction of 2% in this combined outcome is 87%.

Health outcomes research have begun to consider other outcomes besides mortality; in particular this often involves quality of life measurements. Although there were no clear quality of life measurements in PROWESS, the authors did measure the

number of participants who returned home. Surprisingly there was no significant difference in the number of patients returning home between the treatment groups[1] (262 of 850 patients (30.8%) treated with APC compared to 242/840 (28.8%) of the placebo group, absolute difference 2% (95% CI –2%, 6%, p=0.39) (see Table 2).

Since the authors have accepted to analyze the data according to the APACHE II subgroups, one may argue that other subgroup analyses are equally justified. Since possible mechanisms of action of APC include its antithrombotic and profibrinolytic characteristics, it would appear to reasonable to examine the data stratified according to heparin use[1] (see Table 3). There is a clear advantage for APC in patients not receiving heparin (absolute mortality reduction 15% (95%CI 6, 25, p=0.001). There is no advantage for those receiving heparin (absolute mortality reduction 3% (95%CI -2, 8, p=0.2). Other independent researchers have also observed improved outcomes in sepsis with heparin[5].

The consistency of the evidence

There is another concern regarding data consistency in PROWESS. Figure 3 shows the strong interaction between APACHE II score and outcomes. In the two lowest quartiles, there was no mortality reduction and this has lead the FDA to approve the medication only for patients with an APACHE II score of 25 or more. The measurement of this score becomes crucial in trying to reproduce the PROWESS results. Therefore it is strongly suggested that in clinical practice, the timing of APACHE II scoring to guide the use of APC should not deviate from the timing used in the PROWESS trial. There is also concern about patient selection at the other extreme of risk; possibly patients may be "too sick" to benefit (cf. protocol limiting organ dysfunction to <24 hours and exclusion of moribund patients).

Although one of the proposed mechanisms of action involves the antithrombotic activity of APC, it is disconcerting, or at least perplexing, that no clear association between outcomes and intrinsic APC level could be demonstrated[1] (see Table 4).

Comparison with other interventions

The P&T submission contains an interesting discussion comparing the benefits of APC to those of thrombolytic drugs. This comparison is useful and it helps benchmark the certainty of the benefits and costs of APC treatment. Consideration may be given to the following;

1. The pathophysiology of AMI has been well defined in both animal & human studies. This is not the case for sepsis where suitable animal models are not available

2. The mechanism of action of thrombolytic agents is well defined. This is not the case for APC, where benefit is speculated to be due to antithrombotic, profibrinolytic or anti-inflammatory effects. The uncertainty regarding the mechanism of action is exemplified by the previously observed lack of association between intrinsic APC levels and drug response.

3. Thrombolysis has been proven efficacious in multiple randomized studies totaling over 100,000 patients. APC has been studied in 1 RCT of 1,690 patients. Consequently the precision of estimated benefit is considerably tighter for thrombolysis. For example, the probability that the combined outcome of death or serious bleeding is reduced by the approximate 3% benefit seen with thrombolysis is only 75%

4. The population to be treated with thrombolysis is well and consistently defined (patients with chest pain less then 6-12 hours in duration and associated with precise ECG changes of ST elevation). APC appears effective only in a subset of those with sepsis and this definition using APACHE II scores has not been previously validated.

5. The cost of the original thrombolytic agent (streptokinase) was approximately 1/30 the cost of APC.

Costs

"Projected annual acquisition cost to MUHC would be 120 pt X $ 10 720 + 10 % wastage due to preparation/handling/administration 128,640= $ 1,415,240."
MUHC P&T report

The data from the PROWESS study, has been used by several authors[6; 7] to analyze the cost-effectiveness of APC treatment. In their base case scenario, Angus et al[6] determined that APC increased the costs of care by $9,800 and survival by 0.061 lives saved per treated patient. Thus, APC cost $160,000 per life saved (with 15.3% probability that ratio is >$250,000 per life saved). These authors proceeded to model lifetime costs and benefits and estimated increased costs of care by $16,000 and quality-adjusted survival by 0.33 quality-adjusted life-years per treated patient (reference case). Thus, APC cost $48,800 per quality-adjusted life-year (with 82% probability that ratio is <$100,000 per quality-adjusted life-year, see Figure 4). Figure 4 informs about the certainty of these cost-effective calculations for the reference case. There is virtually no probability that the cost-effective ratios are below $20,000, a 5.7% probability that APC costs more and is less effective (area in upper left quadrant) and an approximate 50% probability of exceeding the $50,000/QALY benchmark.

The authors claim the estimates were generally robust to sensitivity analyses, although point estimates of cost-effectiveness ratios deteriorated to >$100,000 per quality-adjusted life-year if survivors lived <4.6 yrs on average (see Figure 5). These authors calculate that APC is more cost-effective if APACHE II >25 ($28,400 per QALY) but cost-ineffective (i.e. treatment cost more and produced fewer health benefits) when applied to patients with a score <25 .

In order to calculate the cost effectiveness of APC, Angus was required to make several modeling assumptions. As earlier studies showed that individuals with sepsis not only have increased short-term mortality but also long-term mortality, Angus assumed that the average survivor, age 58 in PROWESS, would live only 51% the average life expectancy; i.e. 12.3 years following discharge. Since there are no quality adjusted survival data for sepsis survivors, further assumptions were required. They assumed the

average survivor would experience 8.5 quality adjusted life years. While these assumptions may be reasonable, there are **no** published data concerning QALYs in sepsis survivors. Since in a US national study[8] of sepsis, the number of surviving sepsis patients discharged home had decreased to 56% (only 40% in the PROWESS population), the validity of these QALY estimates could be questioned. Moreover, Angus showed that a reduction of life expectancy to 4.6 years or 6.6 years (with an additional 25% decline in their average utility) would lead to point estimates cost-effectiveness ratios >$100,000. This is important as others[7] have calculated that average non-quality adjusted survival following sepsis is only 8 years. With this duration of survival cost effective ratios exceed $60,000 -$70,000 per QALY (see Figure 5). Finally the PROWESS trial had a smaller percentage of patients older than 75 compared to the general sepsis population thereby possibly inflating the number of life years accumulated by APC and possibly further under-estimating the cost-effectiveness ratios.

Another analysis[7] has also suggested the APC is cost-effective for patients with an APACHE score >25 ($24,484 per life-year gained) but not so for scores < 24 ($575,054 per life-year gained). There are some concerns about the model used by these authors. The quality of the life years gained was not assessed, only 4 health states were permitted (dead, alive, ICU or hospital ward with no consideration of those in long term facilities) and costs may have underestimated as the indirect costs of lost salaries were included (most economic analyses ignore indirect costs).

Conclusions

A 6.1% reduction in mortality! How can one be anything but enthusiastic? Although it may initially seem strange to question this intervention, which was demonstrated in a randomized, double blind, placebo controlled trial, the addition of APC to the drug formulary at McGill does pose several interesting questions.

The main concerns about APC therapy have been discussed above. In synopsis, these include the poorly understood mechanism of action, the absence of good animal models, the fact that only 1 randomized study has been performed, the protocol modifications within that study, patient selection within the study, the lack of precision as to the actual size of any benefit or risk, inconsistencies and appropriateness of subgroup analyses within the study, the lack of longer term follow-up, the limited information about quality of life, the difficulties identifying appropriate patients in routine practice, the generalizability of the results and finally the uncertainties of cost-effectiveness.

To assist in interpreting cost-effective ratios, the following rough guidelines may be helpful. Typically ratios below $20,000 have been considered an excellent buy[9], while those between $50,000 to $100,000 have a varied interpretation according to the country. For example, below $100,000 has been considered acceptable in the US, while the upper limits in Denmark, the UK and Canada are often benchmarked at $30,000, $50,000 (30,000 pounds), $50,000, respectively. Most health care systems agree that ratios >$100,000 are not economically attractive. Two studies would suggest that in the elderly, even with high APACHE II scores, APC cost effectiveness ratios may become unfavorable due to shortened long term survival. Clearly more long term information will be required before reliable predictions of APC cost-effectiveness can be provided and informed decisions reached.

Moreover, there are limitations of using incremental cost-effectiveness ratios to assess the economic attractiveness of a new technology. Use of these ratios ignores the reality that hospital budgets are generally fixed and unlikely to have the elasticity to absorb new costs (projected at >$1,400,000 at the MUHC for APC). Economics is based on the fundamental concepts of scarcity (cf. hospital budget), choices (since resources are limited, choices are mandatory) and opportunity cost (new choices compel the abandoning of some old choices with a loss of their health benefits). On the basis of these concepts, MUHC resources would be used more efficiently by the introduction of APC if and only if the value of what is gained exceeds the value of what must be forgone. Obviously although the cost-effective ratio of a new technology alone can't adequately inform this decision, a low ratio does increase our chance of making a good choice. Higher ratios increase the risk that the benefits accrued by the new technology may be less than those associated with the technology being replaced.

Table 1 PROWESS mortality results sub-divided according to timing before or after the protocol modifications

STRATA	THERAPY	Alive at Day 28 N (%)	Died by Day 28 N (%)	Total
Protocol: original	Placebo	251 (70)	109 (30)	360
	rhAPC	258 (72)	102 **(28)**	360
		P=0.5665		**720**
Protocol: amended	Placebo	330 (69)	150 (31)	480
	rhAPC	382 (78)	108 **(22)**	490
		P=0.0012		**970**
				1690

Table 2   PROWESS disposition of patients

	rhAPC (640) N (%)		Placebo (581) N (%)		Total (1221) N (%)	
Home – No Supp.	123	(19)	107	(18)	230	(18)
Home – Paid Supp.	44	(7)	39	(7)	83	(7)
Home - Unpaid Supp.	95	(15)	96	(17)	191	(16)
Not Discharged	270	(42)	234	(40)	504	(41)
Other Hospital	32	(5)	29	(5)	61	(5)
Skill Nursing Home	76	(12)	76	(13)	152	(12)

Table 3   PROWESS results stratified by use of heparin

Heparin	rhAPC		Placebo	
	N (850)	Mortality (%)	N (840)	Mortality (%)
No	216	52 (24)	203	80 (39)
Yes	634	158 (25)	637	179 (28)

Table 4   PROWESS results stratified by use APC level

Protein C Activity Class	rhAPC		Placebo		Relative Risk	95% CI for RR
	Total N	N (%)	Total N	N (%)		
Unknown	51	14 (28)	65	16 (26)	1.12	0.60, 2.07
40%	330	91 (28)	285	119 (43)	0.66	0.53, 0.82
41-60%	240	65 (27)	227	56 (25)	1.10	0.81, 1.49
61-80%	139	26 (19)	158	40 (25)	0.74	0.48, 1.14
> 80%	90	14 (16)	105	28 (27)	0.58	0.33, 1.04

Ordered analysis p <0.00001. Unordered analysis p < 0.00001.
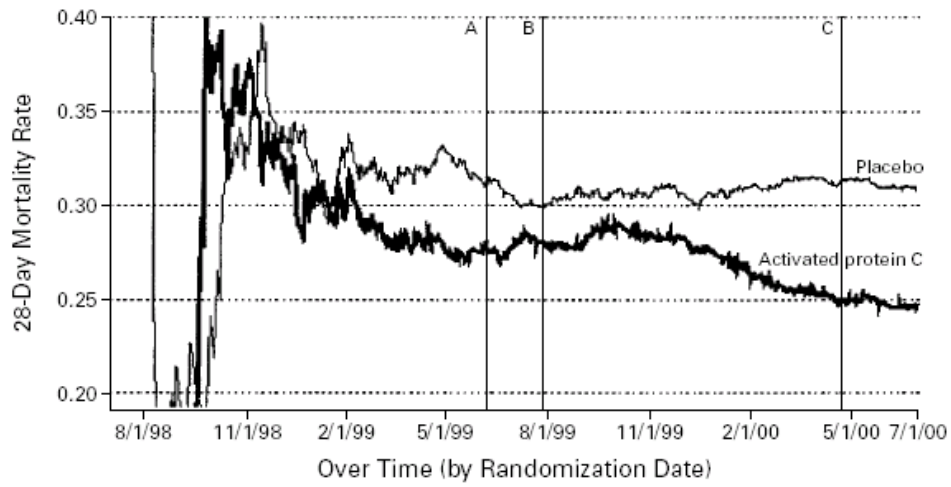
Figure 1

Figure 1. 28-Day Cumulative Mortality over Time for All Patients.
The amended version of the protocol was introduced at the time indicated by line A. The first interim analysis occurred at the time indicated by line B. The change in the manufacturing of the drug also occurred at approximately this time. The second interim analysis occurred at the time indicated by line C. The graph is from the FDA.[4]

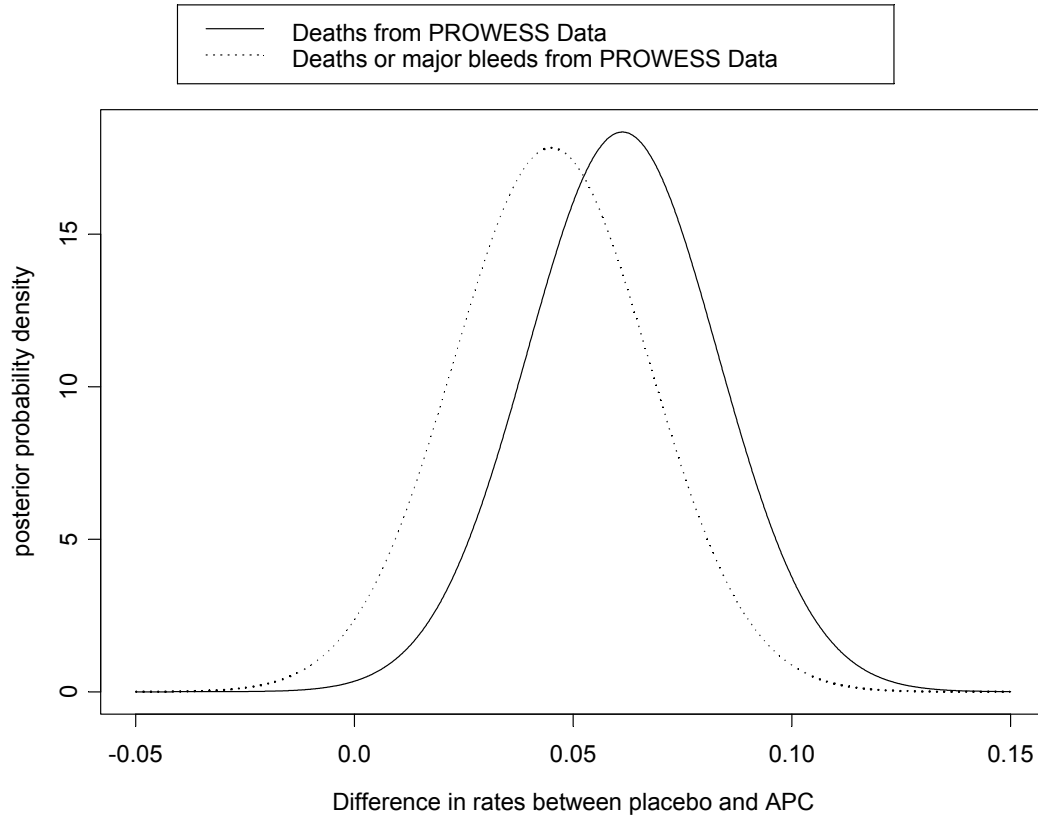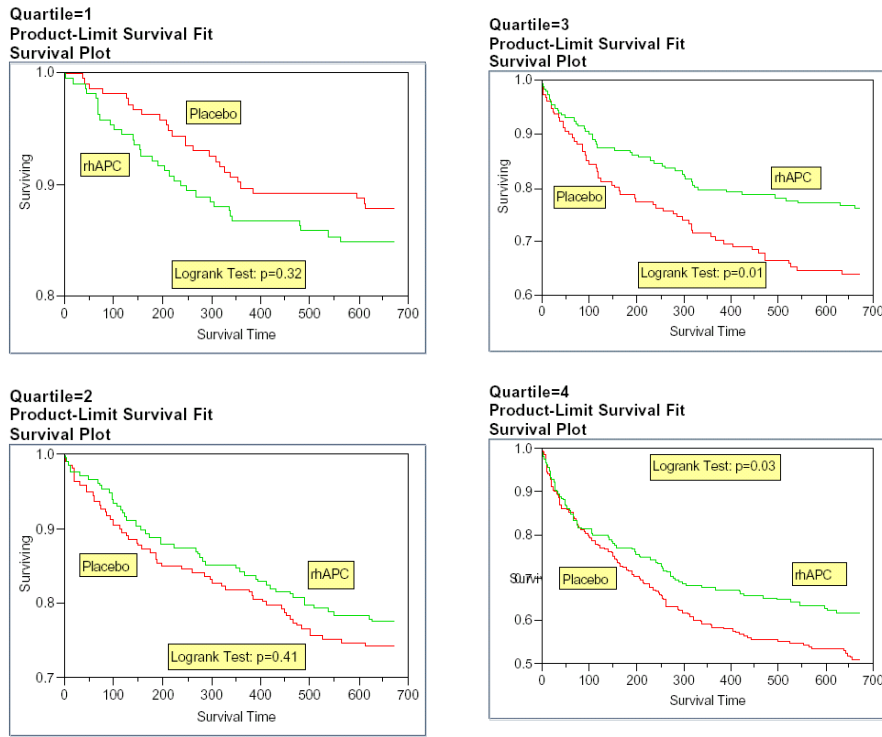Figure 2 Probability density function for the PROWESS study data

Figure 3

Quartile=1
Product-Limit Survival Fit
Survival Plot

Placebo

rhAPC

Logrank Test: p=0.32

Quartile=3
Product-Limit Survival Fit
Survival Plot

rhAPC

Placebo

Logrank Test: p=0.01

Quartile=2
Product-Limit Survival Fit
Survival Plot

Placebo

rhAPC

Logrank Test: p=0.41

Quartile=4
Product-Limit Survival Fit
Survival Plot

Logrank Test: p=0.03

Placebo

rhAPC

Figure 3. Kaplan-Meier survival curves by APACHE II quartiles

Figure 4   Simulations from the reference case described by Angus, using
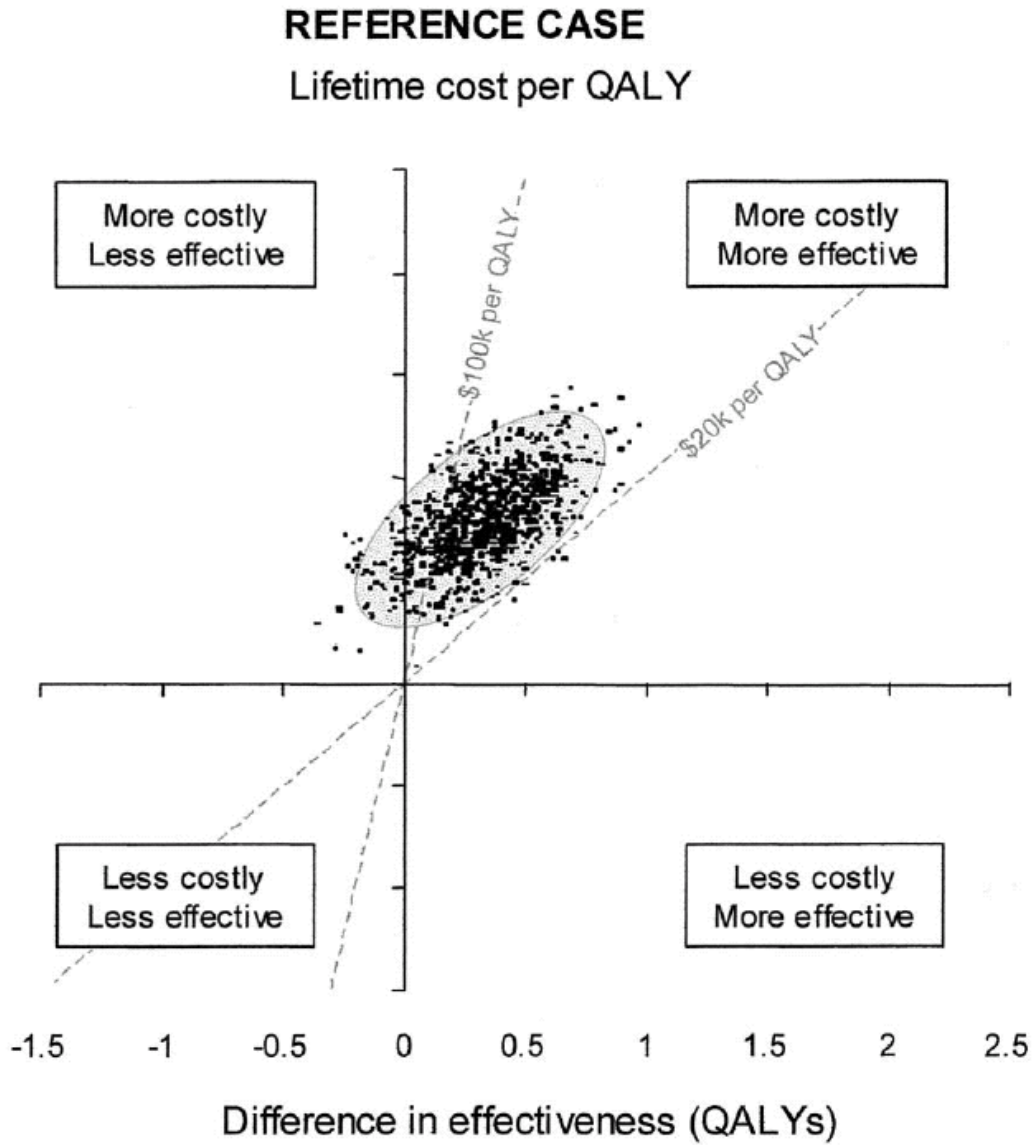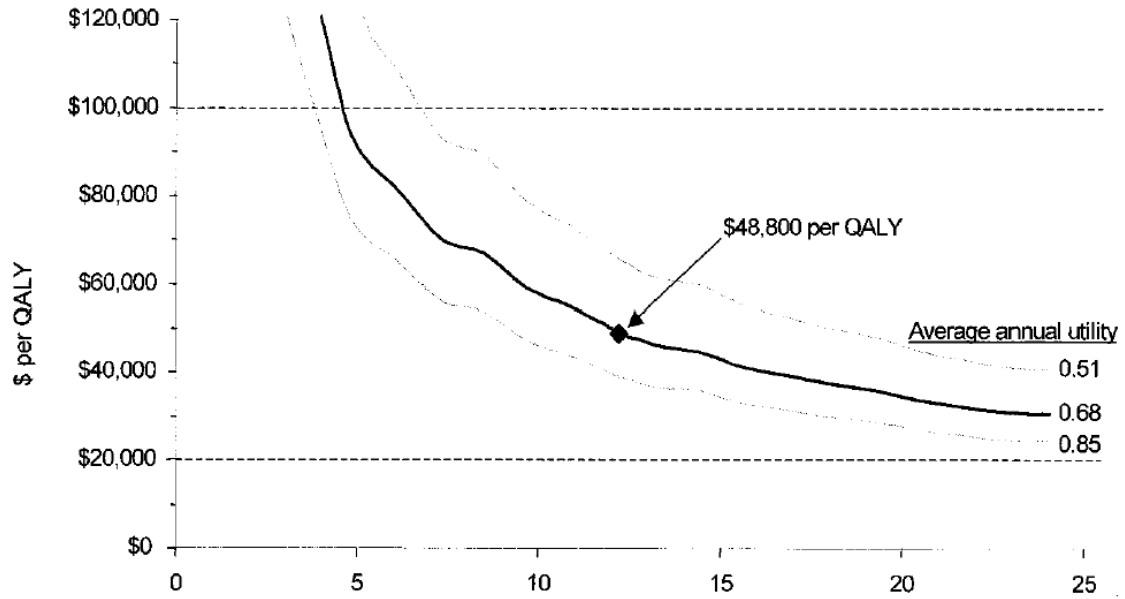PROWESS 28 day survival data with long term 12.3 years average survival. (Reproduced
from Angus[6]

REFERENCE CASE

Lifetime cost per QALY

Figure 5   Sensitivity of the reference case described by Angus to the average
projected survival. (Reproduced from Angus[6]

Appendix 1   PROWESS Protocol changes

• Simplify the primary analysis such that the primary analysis was confined to patients meeting the diagnosis of severe sepsis.
• Eliminate a primary planned analysis of Protein C deficiency (analyze as secondary instead) and "septic shock" from the primary and secondary analyses.
• Clarify exclusion criteria for patients with esophageal varices.
• Add exclusion criteria for patients having undergone bone marrow, lung, liver, pancreas, or small bowel transplantation.
• Add exclusion criteria for patients who were considered moribund and where death was imminent (within 24 hours).
• Add exclusion criteria for patients whose family had not committed to aggressive management of the patient.
• Add exclusion criteria for patients with acute pancreatitis without known infection.
• Clarify exclusion criteria for patients with a history of malignancy.
• Add exclusion criteria for patients having organ failure for greater than 24 hours at the time of meeting all inclusion criteria.
• Change placebo from normal saline to 0.1% HSA.
• Replace "septic shock status" with "Protein C activity class" as a covariate for the primary analysis.

Reference List

1. http:www.fda.gov/ohrms/dockets/ac/01/briefing/3797b1_02_FDAbriefing.pdf: accessed April 29 2003.

2. Bernard, Gordon R., Vincent, Jean-Louis, Laterre, Pierre-Francois, LaRosa, Steven P., Dhainaut, Jean-Francois, Lopez-Rodriguez, Angel, Steingrub, Jay S., Garber, Gary E., Helterbrand, Jeffrey D., Ely, E. Wesley, Fisher, Charles J., and The Recombinant Human Activated 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 344(10), 699. 2001.

3. Warren, H. Shaw, Suffredini, Anthony F., Eichacker, Peter Q., and Munford, Robert S. Risks and Benefits of Activated Protein C Treatment for Severe Sepsis. N Engl J Med 347(13), 1027. 2002.

4. Siegel, Jay P. Assessing the Use of Activated Protein C in the Treatment of Severe Sepsis. N Engl J Med 347(13), 1030. 2002.

5. Davidson, Bruce L., Geerts, William H., and Lensing, Anthonie W. A. Low-Dose Heparin for Severe Sepsis. N Engl J Med 347(13), 1036. 2002.

6. Angus DC, Linde-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW, Laterre PF, Vincent JL, Bernard G, van Hout B: Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med* 2003;31:1-11

7. Manns, Braden J., Lee, Helen, Doig, Christopher James, Johnson, David, and Donaldson, Cam. An Economic Evaluation of Activated Protein C Treatment for Severe Sepsis. N Engl J Med 347(13), 993. 2002.

8. Martin, Greg S., Mannino, David M., Eaton, Stephanie, and Moss, Marc. The Epidemiology of Sepsis in the United States from 1979 through 2000. N Engl J Med 348(16), 1546. 2003.

9. Laupacis A, Feeny D, Detsky AS, Tugwell PX: How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992;146:473-81