Cost effectiveness analysis of Drotrecogin Alfa (Activated) as a treatment for severe sepsis in hospitalised patients

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ABSTRACT

COST EFFECTIVENESS ANALYSIS OF DROTRECOGIN ALFA (ACTIVATED) AS A TREATMENT FOR SEVERE SEPSIS IN HOSPITALISED PATIENTS

INTRODUCTION : Drotrecogin alfa (activated) significantly reduced severe sepsis (SevSep) mortality at 28 days[1]. According to the French budget environment, it is mandatory to evaluate its cost effectiveness ratio on a pragmatic basis. **METHODS** : All SevSep patients in the Cub-Rea database (1997-99 period) defined according to PROWESS[1] and with a hospital length of stay (LOS) ≥ 24 hours (n = 10459) were included. The baseline patients' characteristics are similar to those of the PROWESS criteria study : age (61 years *vs* 60 years), < 60 years (42 % *vs* 44 %), and number of organ failure (2.1 *vs* 2.4). Key patient data recorded: age, gender, type of admission (medical or surgical), admission mode (direct or transfer), number (1,2,3), duration and type of support (respiratory, renal, circulatory) and SAPS II. Stratification according to these criteria and loading of the observed frequencies into a decision-tree for conditional probabilities. Relative Risk of death with drotrecogin alfa (activated) estimated according to the observed classification into 11 neoGHM[2] groups (28 days survival represented by the parametric function of Weibull). SevSep impact on long-term mortality estimated by the Mc Cabe score with 3 hypotheses for life expectancy (LE): Unique LE of 5 years, Mc Cabe > 0 (2 years of survival), Mc Cabe = 0 (4 years LE reduction or half LE reduction versus whole population). Costs estimated by subgroups and by a linear equation (nursing workload, LOS, SAPS II, living or dead status). Calculation of a differential cost effectiveness ratio (Drotrecogin alfa (activated) price: 7 836.95 € for 4 days treatment and a mean patient's weight of 70 kg) and analysis of Monte Carlo's type. **RESULTS :** The expected cost in the model of a SevSep patient treated by standard care is 26 983.3 € *vs* 26 373.6 € observed from Cub-Rea. The expected cost predicted in the model of a SevSep patient treated by drotrecogin alfa (activated) is 34 605.90 €. The survivors LE according to the above hypotheses are 5.0, 10.6, and 6.9 years. Corresponding effectiveness differences in favor of drotrecogin alfa (activated) are 0.33, 0.63, and 0.41 years. The cost per additional year of life saved amounts of 18 446.3 € including all degrees of severity and co-morbidity. The sensitivity analysis model shows that with an expected threshold of 53 357.1 €. 3% of the bootstrap samples are cost-effective. **CONCLUSION :** The predicted cost effectiveness ratio of drotrecogin alfa (activated) in adult SevSep patients is much lower than the international range considered as acceptable (53 357,10 €). Drotrecogin alfa (activated) is cost-effective when including patients with all degrees of co morbidity. **REFERENCES :** *(1) Bernard G. N Engl J Med. 200; 344: 699-70. (2) Misset B. Réan Urg.1998; 7: 367-74.*

INTRODUCTION

Drotrecogin alfa (activated) recently demonstrate in a phase III trial a significant reduced mortality in severe sepsis patients' at 28 days[1]. According to the French budget environment, it is mandatory to evaluate its cost effectiveness ratio on a pragmatic basis and to understand the health economic implication.

MATERIAL AND METHODS

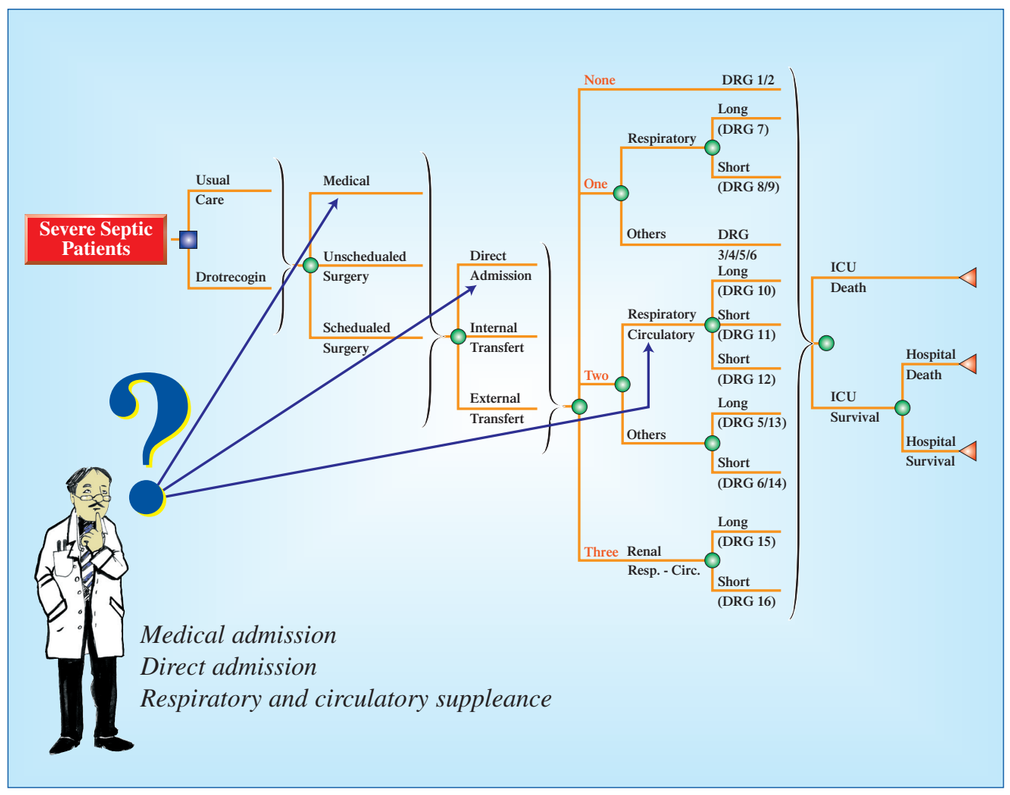
Patients :

All severe sepsis patients in the Cub-Rea[1] database (1997-99 period) defined according to PROWESS[1] trial and with a hospital length of stay (LOS) ≥ 24 hours (n = 10459) were included. The baseline patients' characteristics are similar to those of the PROWESS criteria study : mean age (61 years *vs* 60 years), < 60 years (42 % *vs* 44 %), mean SAPS II 46 *vs* mean APACHE II 25, organ failure : type : respiratory (89% *vs* 75%), circulatory (65% *vs*71%) and renal (35% *vs* 42%) ; number : one (31% *vs* 24%), two (35% *vs* 32%), three (26% *vs* 26%), four (6% *vs* 14%), mean number (2.1 *vs* 2.4).

Decision tree:

Stratification according to key patient data recorded : age, gender, type of admission (medical or surgical), admission mode (direct or transfer), number (1,2,3), duration and type of support (respiratory, renal, circulatory) and SAPS II and loading of the observed frequencies into the decision-tree for conditional probabilities.

Group	Organ support	SAPS II	Omega	Description
I	None	= 23		No support : Expected mortality < 5%
II	None	> 23		No support : Expected mortality > 5%
III	Circulatory	= 31		Circulatory failure : Expected mortality < 10%
IV	Circulatory	> 31		Circulatory failure : Expected mortality > 10%
V	Renal		Ω2+Ω3 > 90	Renal failure, no MV, high work load
VI	Renal		Ω2+Ω3 = 90	Renal failure, no MV, low work load
VII	Respiratory		Ω3 = 140	MV > 10d
VIII	Respiratory	= 33	Ω3 = 140	MV < 10d : Expected mortality < 14%
IX	Respiratory	> 33	Ω3 = 140	MV < 10d : Expected mortality > 14%
X	Respiratory and circulatory		Ω3 = 140	MV > 10d
XI	Respiratory and circulatory	= 51	Ω3 = 140	MV < 10d : Expected mortality < 48%
XII	Respiratory and circulatory	> 51	Ω3 = 140	MV < 10d : Expected mortality > 48%
XIII	Respiratory and renal		Ω3 > 140	MV > 10d + HD or HF
XIV	Respiratory and renal		Ω3 = 140	MV < 10d + HD or HF
XV	Respiratory, renal, circulatory		Ω3 > 140	MV > 10d + HD or HF
XV	Respiratory, renal, circulatory		Ω3 = 140	MV < 10d + HD or HF



Relative Risk of death with drotrecogin alfa (activated) estimated according to the observed classification into 11 néo DRG[3] groups and reach 0.8 at 28 days (28 days survival represented by the parametric function of Weibull).

Impact on long-term mortality :

Severe sepsis impact on long-term mortality estimated by the Mc Cabe score with 3 hypothesis for life expectancy (LE) : Unique LE of 5 years, Mc Cabe > 0 (2 years of survival), Mc Cabe = 0 (4 years LE reduction or half LE reduction *versus* whole population).

Effectiveness : a clinical case for exemple

> men
> 50 years
> Mc Cabe score = 0

Life expectancy INSEE 97 : 27.8 years

Life expectancy Model : 13.9 years

Usual care	Drotrecogin alfa
Mortality ICU : 0.411	Mortality ICU : 0.335
> Mortality post-ICU : 0.032	> Mortality post-ICU : 0.029
> Survival : 0.557	> Survival : 0.636
Efficacy : 7.74 years	Efficacy : 8.85 years

ΔE = 1.11 years
ΔM = 0.080 avoidable death

Costs calculation :

Costs estimated by subgroups and by a linear equation (nursing workload, LOS, SAPS II, living or dead status). Calculation of a incremental cost effectiveness ratio (Drotrecogin alfa (activated) price: 7 836,95 € for 4 days treatment and a mean patient's weight of 70 kg) and analysis of Monte Carlo's type).

Efficiency

- Usual care
- Drotrecogin
- ΔC

• 1 •
Criteria of jugment : avoidable mortality
➥ ΔC / ΔM

• 2 •
Criteria of jugment : number of years "to live"
➥ ΔC / ΔE

RESULTS

The expected cost in the model of a severe sepsis patient treated by standard care is 26 983,3 € *vs* 26 373.6 € observed from Cub-Rea. The expected cost predicted in the model of a severe sepsis patient treated by drotrecogin alfa (activated) is 34 605.90 €. The survivors LE according to the above hypothesis are 5.0, 10.6, and 6.9 years.

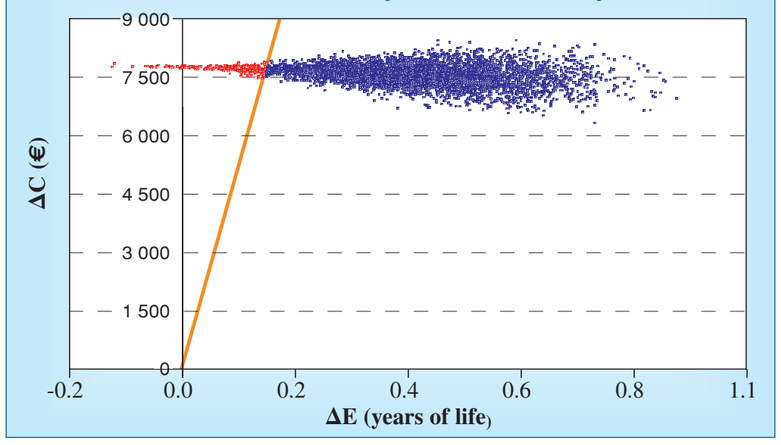
Corresponding effectiveness differences in favor of drotrecogin alfa (activated) are 0.33, 0.63, and 0.41 years. The cost per additional year of life saved amounts of 18 446.3 € including all degrees of severity and co-morbidity.

The sensitivity analysis model shows that with an expected threshold of 53 357.1 €. 96.3 % of the bootstrap samples are cost-effective.

Incremental Cost Effectiveness Ratio

Strategy	C (Euros)	ΔC	E (years)	ΔE	ΔC/ΔE
Usual Care	26 983.3		4.6042		
Drotrecogin	34 605.9	7 622.6	5.0200	0.4158	18 446.3

Probabilist Analysis of Sensibility



DISCUSSION

The differences observed in this retrospective study compared to Angus and coll.[4] findings can be explained. First of all, standards of care change between France and US, second Angus and coll. have added additional costs for life-time healthcare costs beyond day 28. These costs represented 50% of all cost in their work. Assuming the same augmentation the cost per additional year live saved would be 37 690 € including all degrees of severity and co-morbidity approaching Angus and coll. findings.

REFERENCES : *(1) Bernard G. N Engl J Med. 2001; 344: 699-70. - (2) Guidet B . Intensive Care Med 2001; 27; Supp 2 S233. (3) Misset B. Réan Urg.1998; 7: 367-74. - (4) Angus DC Crit Care Med 2001; 30: 493*

CONCLUSION

The predicted cost effectiveness ratio of drotrecogin alfa (activated) in adult severe sepsis patients is much lower than the international range considered as acceptable (53 357,10 €). Drotrecogin alfa (activated) has a cost effectiveness profile similar to, or better, than many well-accepted and common healthcare strategies. Drotrecogin alfa (activated) is cost-effective when including patients with all degrees of co-morbidity. Achieving this profile in practice will be dependent on careful patient selection. For example, restriction to patients at higher risk of death will improve cost-effectiveness because the treatment effect is larger. However, drug administration to patients with poor long-term prognosis will worsen the cost-effectiveness.