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Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis with multiple organ failure

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Objectives: The aim of this study was 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 recombinant human activated PROtein C Worldwide Evaluation in Severe Sepsis (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 (Intensive Care Database User Group) 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.

Keywords: Severe sepsis, Intensive care, Drotrecogin alfa (activated), Cost-effectiveness, Health care costs

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Severe sepsis (5) is common on French intensive-care units (ICUs), affecting 10–15 percent of admitted patients (1;7;8). The high incidence of sepsis and its reported mortality rate of 20–65 percent (1;3;7;8;33) are associated with substantial health care 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 percent ($CI_{95\ percent}$, 1.86 percent–10.39 percent]), and to a relative risk (RR) of death using this drug compared with placebo of 0.80 ($CI_{95\ percent}$, 0.69–0.94]). Regulatory authorities in the United States and Europe have approved DAA for use in different indications. In the United States, 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 (i) one infected site or one positive blood culture; (ii) at least two organ failures; and (iii) length of stay of more than 24 hours. 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, therefore, was 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 because 75 percent of the departments in the database were medical ICUs. A model, therefore, was 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 U.S. dollars at a conversion rate of 0.98316, the 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 in an ICU and the cost of stay in hospital after 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) 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 of 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 per hour for 96 hours. The average weight of patients from the CubRea database was 71.6 kg; therefore, the mean treatment cost was 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 percent versus 2.0 percent, $p = .06$) (4). Costs associated with the management of side effects were not considered in the baseline analysis.

Drotrecogin Alfa (Activated) Effectiveness

The primary efficacy end point 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

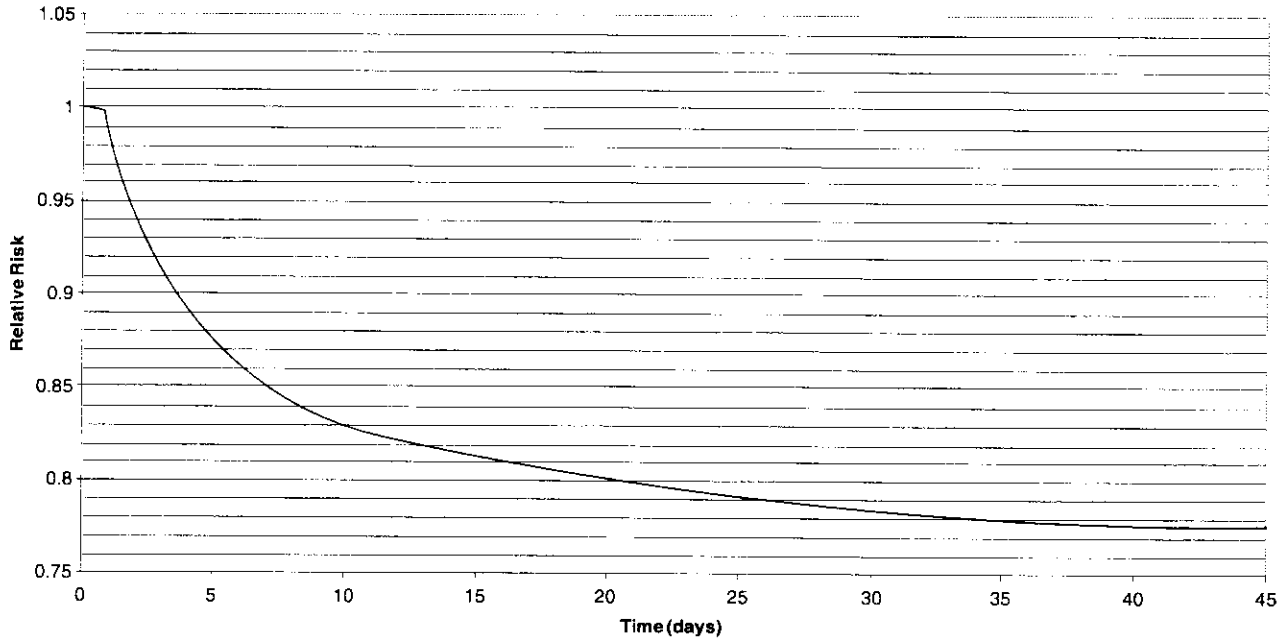

Figure 1. Relative risk of death in patients treated with drotrecogin alfa (activated) compared with those receiving conventional care only over time.

improved from 0.80 to 0.78 ($CI_{95\,percent}$, 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 study by Quartin et al. (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.

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 ($CI_{95\%}$[b])	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%[c] (0.30–0.38)	43.5%[d] (0.42–0.45)

[a] Patients receiving placebo.
[b] Calculated using a binomial probability distribution.
[c] 24-day mortality.
[d] Deaths in intensive care (mean length of survival: 21 days).
PROWESS, recombinant human activated PROtein C Worldwide Evaluation in Severe Sepsis; CubRea, Intensive Care Database User Group; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II, Simplified Acute Physiology Score II; $CI_{95\%}$, 95 percent confidence interval.

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 versus 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 percent of stays). The mean hospital length of survival (in ICU and post-ICU) ranged from 26 to 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 to gain 1 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 with $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 percent compared

Table 2. Characteristics of Patients Receiving Care According to the Model

		Admission			Organ supports		
	All	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%
Co-morbidities[a]							
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)[b]	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

[a] Defined as a McCabe score >0.
[b] In intensive care and in subsequent departments.
UPS, uplanned surgery; PS, planned surgery.

Table 3. Cost-Effectiveness of Drotrecogin Alfa (Activated)

	ΔCost ($)	ΔEffectiveness (life years[a])	ICER[b] 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	7,873	13,122

[a] Average life years gained per patient treated.
[b] Incremental cost-effectiveness ratio.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

with 45.7 percent and 74.1 percent for patients with two and three organ supports, respectively). Because the effect of DAA is assessed using an 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 percent 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 currently are no guidelines regarding which estimator, ARR or RR, to use in pharmaco-economic 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 percent 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 percent (71 percent for patients with less than two organ

Table 4. Sensitivity Analysis of the Incremental Cost-Effectiveness Ratio

	Incremental cost-effectiveness ratio ($/LYG)
Baseline	11,812
RR comparable for all patients	
0.66	6,450
0.78	10,398
0.93	33,894
Effect of the drug alone in intensive care	
RR as a function of LOS	13,902
ARR of 7.4%	14,413
Expected treatment cost ($ 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

LYG, life year gained; RR, relative risk; LOS, length of stay; ARR, absolute risk reduction.

supports, 82 percent for those with two organ supports, and 91 percent 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 percent, the type I error probability chosen in the PROWESS trial (4). Consequently, the probability of cost-effectiveness cannot exceed 95 percent, 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. Because 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 versus 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 percent, the

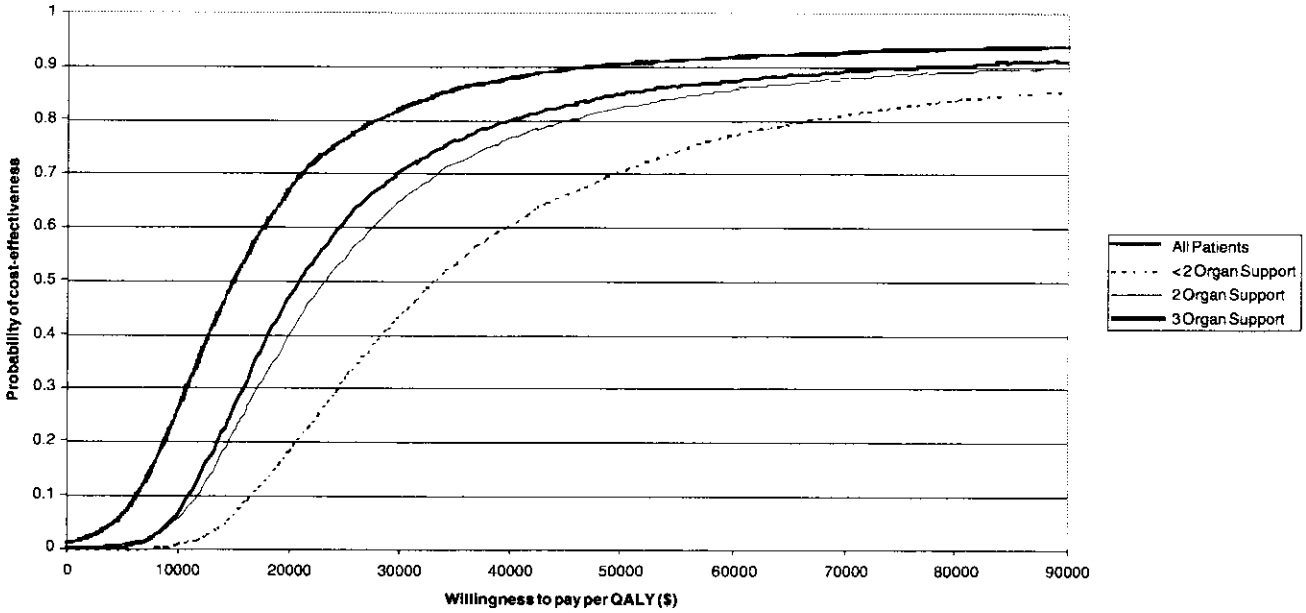

Figure 2. Drotrecogin alfa (activated) acceptability curve for patients with severe sepsis and multiple organ failure. QALY, quality-adjusted life year.

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 U.S. indications. Although the American and European indications for DAA are different, cost-effectiveness estimates remain similar. This finding suggests that the European indication based on organ failure and the American 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, because 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 to have a better idea of the impact of the drug.

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