

Cost-effectiveness analysis of rifaximin- α administration for the reduction of episodes of overt hepatic encephalopathy in recurrence compared with standard treatment in France

Anastasiia Kabeshova, Soumaia Ben Hariz, Elyonore Tsakeu, Robert Benamouzig and Robert Launois

Abstract

Background: Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that occurs most often in a context of acute or chronic liver disease. Despite the seriousness of the pathology, only a few treatments have been developed for improving its management. Rifaximin- α is the first treatment that has been clinically developed for overt HE (OHE) episodes. Recent results of clinical studies demonstrated its significant improvement in the health-related quality of life. The objective of the current study was to estimate the long-term cost-effectiveness of rifaximin- α used in combination with lactulose compared with lactulose monotherapy in cirrhotic patients, who have experienced at least two prior OHE events.

Methods: A Markov model was used to estimate rifaximin- α cost-effectiveness, evaluating it from the perspective of all contributors as recommended by French health technology assessment guidelines. Costs were based on current French treatment practices. The transition between health states was based on the reanalysis of the rifaximin- α pivotal clinical trials RFHE3001 and RFHE3002. The main outcome of the model was cost per quality adjusted life year (QALY).

Results: The results indicate that rifaximin- α is a cost-effective treatment option with an incremental cost per QALY gained of €19,187 and €18,517 over two different time horizons (2 and 5 years). The robustness of the model was studied using probabilistic sensitivity analysis.

Conclusion: For the societal willingness to pay threshold of €27,000 per QALY gained, rifaximin- α in combination with lactulose is a cost-effective and affordable treatment for patients who have experienced at least two prior overt HE episodes.

Keywords: cost-benefit analysis, hepatic encephalopathy, lactulose, Markov chains, rifaximin

Introduction

Hepatic encephalopathy (HE) constitutes a complex neuropsychiatric syndrome that most often caused by acute or chronic liver dysfunction [Bass *et al.* 2010; Irimia and Trifan, 2012; Rockey *et al.* 2014; Sharma *et al.* 2013]. HE is an aggravation of an advanced liver disease such as cirrhosis that imposes a burden on patients, their families, and the healthcare system [Bass *et al.* 2010]. Several

studies have demonstrated that HE is associated with lower health-related quality of life (HRQoL) across both physical and mental domains [Sanyal *et al.* 2011]. Two forms of HE are recognized: patients with minimal or covert hepatic encephalopathy (CHE) and those with clinically relevant or overt hepatic encephalopathy (OHE). After an overt episode, patients usually return to be unimpaired or to a covert state of HE, and this is

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considered to constitute a state of remission. The prevalence of OHE at the time of diagnosis of cirrhosis is 10–14% in general, 16–21% in those with decompensated cirrhosis, and 10–50% of patients with transjugular intrahepatic portosystemic shunt [European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, 2014].

Treatment of HE is still a significant area of investigation. The current standard of care for patients with HE is a treatment with nonabsorbable disaccharides lactitol or lactulose [Bass *et al.* 2010]. Recently, several randomized controlled trials have reported rifaximin- α to be more efficacious than lactulose in the treatment of HE [Maharshi *et al.* 2015; Paik *et al.* 2005; Sidhu *et al.* 2015]. When it comes to the quality of life, several studies demonstrated significant improvements in the HRQoL of patients in remission in the rifaximin- α group compared with those in the placebo group [Sanyal *et al.* 2011]. A phase III study [Bass *et al.* 2010] demonstrated that rifaximin- α plus concomitant lactulose therapy (over a 6-month period as compared with placebo plus concomitant therapy) had significantly reduced the risk of an episode of OHE and the risk of hospitalisation due to OHE.

In light of this trade-off, we performed a decision analysis to estimate the cost-effectiveness of these competing therapies in OHE. The objective of the current study was to estimate the long-term cost-effectiveness of rifaximin- α (550 mg twice per day) used in combination with standard treatment (lactulose) compared with lactulose alone, in cirrhotic patients, who have experienced at least two prior OHE events, by adopting the point of view of French health insurance.

Methods

Structuring choice for decision model framework

The study adopted the perspective of the French national health insurance, which supports all care costs, since HE has been classified as a long-term disease. The base case analysis served to determine the incremental cost-effectiveness of rifaximin- α associated with lactulose (83.87% of patients) *versus* traditional treatment without rifaximin- α (100% of patients) by using data from a study carried out at the University Hospital of Toulouse. It is an observational, retrospective, single-centre

study, including 62 patients, who were followed for 1 year between July 2010 and September 2013. The patient population used for the economic evaluation is adults over 18 years old in remission from previous episodes of OHE, associated with hepatic cirrhosis (equivalent to Conn score ≥ 2). The average age of the patient population of the pivotal clinical study RFHE3001 was 62.4 years. For this reason it was used as the starting age of patients in the model and is consistent with the average age of patients hospitalized for HE in 2013 in France that was about 62.7 years [Chautant, 2013]. Since rifaximin- α is used concomitantly with lactulose in patients that have experienced two previous HE events, the rifaximin- α indication is considered as an add-on for those that have failed lactulose initially. In the second-line setting, there are no active comparators to rifaximin- α for the reduction in recurrence of HE events.

Model structure

The model adapted a previous cost-effectiveness model to the French system [Poole *et al.* 2015]. The model structure, which uses a state transition Markov approach, is shown in Figure 1. Covert states in the model (CHE1 and CHE2) are defined as being equivalent to a Conn score of 0 or 1. Breakthrough episodes of OHE (OHE1 and OHE2) within the model were defined based on a pivotal study as an increase from either a baseline Conn score of 0 or 1 to a score of ≥ 2 or derived from a baseline Conn score of 0 to a Conn score of 1 plus a 1-unit increase in the asterixis grade. To maintain consistency regarding input assumptions, long-term disease progression and mortality have been modelled based on two studies: RFHE3001 and RFHE3002. Two different time horizons were considered in the sensitivity analysis at 2 and 5 years. A cycle length of 1 month (defined as 30.4 days) was chosen to be in line with the interval in which data was collected during the RFHE3001 clinical trial [Bass *et al.* 2010; Sanyal *et al.* 2011]. Health effects were measured in quality-adjusted life years (QALYs) to capture both survival and quality of life effects associated with treatment. The primary objective of the cost-effectiveness analysis was to compare different interventions in HE. QALYs allow such comparisons to be carried out.

Modelling of clinical efficacy

The first clinical end point of the pivotal clinical study RFHE3001 was used to simulate the

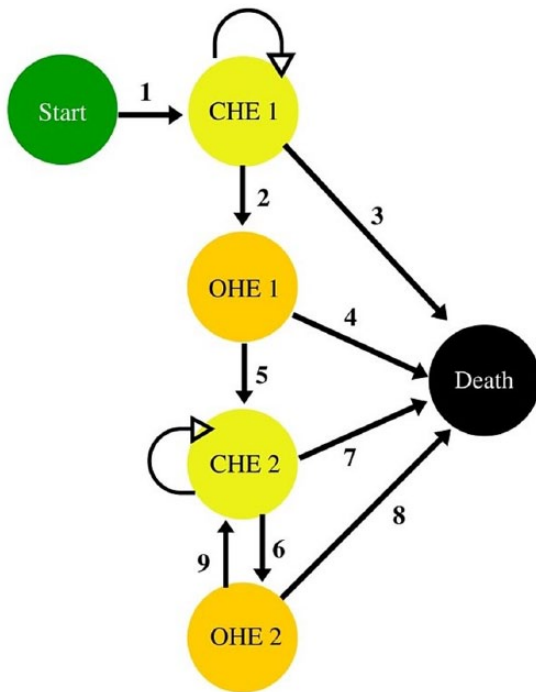


Figure 1. Model structure overview. 1: Patients enter the model in the remission state. 2: Covert state (CHE1) to first-observed overt episode (OHE1). 3: Covert state (CHE1) to death. 4: First-observed overt episode (OHE1) to death. 5: Recovery from first-observed overt episode to subsequent covert state (CHE2). 6: Subsequent covert state to subsequent overt episode (OHE2). 7: Subsequent covert state to death. 8: Subsequent overt episode to death. 9: Recovery from subsequent overt episode to subsequent covert state.

transition time to first breakthrough overt HE episode. Kaplan–Meier (KM) survival curves of time to breakthrough OHE events were published by Bass and colleagues [Bass *et al.* 2010]. Parametric survival modelling allowed us to extrapolate an event-free survival curve beyond the 6-month timeframe of the study. Five alternative parametric survival distributions were fitted to the data set based on RFHE3001. Log-likelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC) were calculated to determine the best model fit (Table 1). The distribution with the smallest values of model fit statistics is the best fit to the data. The techniques used to justify chosen survival modelling methods were: statistical tests, visual inspection, external data, and clinical validity [Diaby *et al.* 2014; Latimer, 2013]. Using this criterion the choice of the lognormal distribution seems justified (Table 1 and Figure 2). Visual inspection of the five different fits indicates that the lognormal

is the best fit of the data. The estimated distribution parameters for survival curves are used to measure the time-dependency transition probabilities, according to the following formula: $tp(t_u) = 1 - \exp\{H(t-u) - H(t)\}$, where u is the Markov cycle, t_u indicates that the moment in time t is calculated as integer multiples of the cycle length of the model, and $H(t)$ is a cumulative hazard function that can be calculated for lognormal distribution [Briggs *et al.* 2006]. More information about clinical efficacy, modelling of mortality, valorisation of health states and net monetary benefit can be found in the online supplementary data.

Cost estimates

The costs were calculated based on the medical fees recognized by French health insurance. There is no co-pay because HE is classified as ALD 6, which is an aggravation of cirrhosis. This analysis incorporates the direct healthcare costs of therapies, doctor visits, hospital visits, diagnostic tests and complications of cirrhosis and HE. The costs of therapies were obtained from the public database of drugs. The costs of OHE episodes were estimated using the average cost of living for HE observed in France in 2014 [Ministère des affaires sociales et de la santé, 2014].

Patient utilities

Patient health state utility values were used to adjust survival for the decrease in health-related quality of life from the various treatment interventions. Utility in the covert state was derived using the published results from *post hoc* analysis of the RFHE3001 [Sanyal *et al.* 2011]. That data showed that in the covert remission state the rifaximin- α treated patients experienced an incremental improvement in QoL as measured by the Chronic Liver Disease Questionnaire (CLDQ) over those receiving lactulose only. A relationship was derived between EQ-5D-3L questionnaire and disease-specific questionnaire CLDQ.

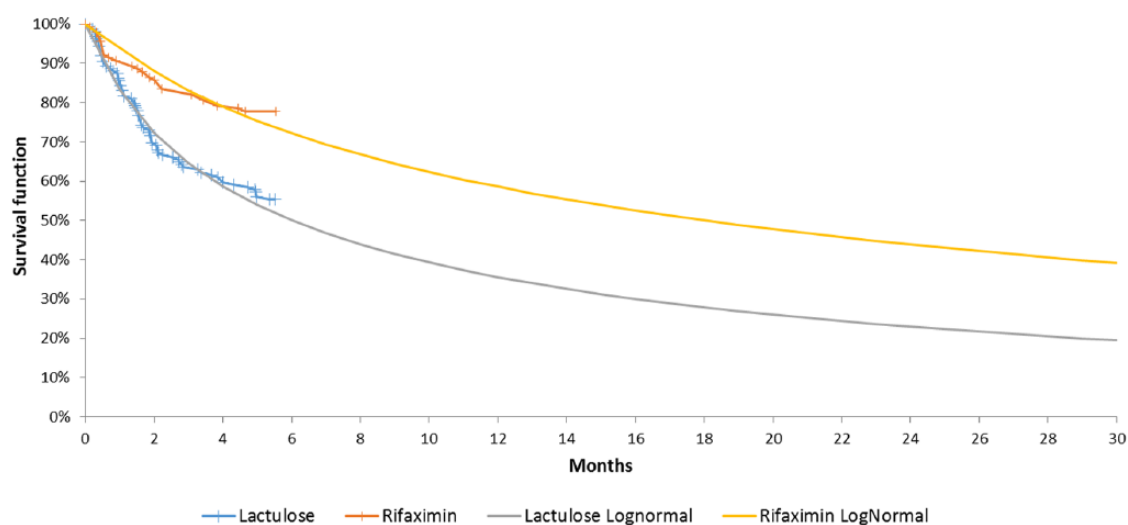
Base-case and sensitivity analyses

Baseline values for the costs, utilities, and expected survival benefit were used for the base-case analysis. The primary outcome measure for this analysis was the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the number of QALYs saved. The

Table 1. Model fit statistics for five alternative candidate parametric survival distributions of time to first breakthrough overt episode (RFHE3001).

Parametric distribution	Log-Likelihood	AIC	BIC
Exponential	-758.56	1519.11	1522.84
Weibull	-755.58	1513.16	1516.89
Gompertz	-749.02	1500.05	1503.78
Lognormal	-748.68	1499.36	1503.09
Log-logistic	-752.93	1507.87	1511.60

AIC, Akaike information criterion; BIC, Bayesian information criterion.
The distribution with the smallest values of model fit statistics is the best fit to the data (in bold).

**Figure 2.** Comparison of original Kaplan–Meier plot and corresponding best-fit parametric survival function (log-normal) for time to first overt HE event (by treatment arm in the RFHE3001 study).

incremental cost was the difference in cost between the rifaximin- α arm and the control arm.

One-way and probabilistic sensitivity analyses were performed. Deterministic or one-way analysis calculates the ranges for ICERs when varying each parameter of interest. A tornado diagram demonstrated the impact that a fixed change in each parameter has on the main outcomes. The probabilistic sensitivity analysis (PSA) was performed using a Monte Carlo simulation. A total of 1000 simulated trials were run, where each input was sampled at random from probability distribution functions assigned to each variable. For PSA, each key parameter was fitted with a particular parametric function of distribution to reflect the substantial uncertainty of the input parameters (Table 2). When the average of each parameter was measured on a large sample of individuals, the normal distribution approximated its statistical

distribution according to the central limit theorem. Gamma distribution was used to simulate the cost variables through its statistical properties (the central limit theorem is not applicable). Beta distribution was used for utility values. A cost-effectiveness acceptability curve (CEAC) was used as a graphical representation of the quantitative measure of uncertainty around the expected cost-effectiveness. The cost-effectiveness acceptability frontier (CEAF) was constructed for the technologies being compared [Briggs *et al.* 2002]. More detailed information about modelling and net monetary benefit can be found in the online supplementary data.

The model was developed in Microsoft Excel 2013. A parametric survival analysis was provided with DigitizeIt 2.0.6, R 3.2.2, and Stata 13 using survival data extracted from the published Kaplan–Meier curves.

Table 2. Distributional assumptions of input parameters used in the model.

Variable	Distribution	SE	Parameters		Source		
			SE	Mean	α	β	
Average daily dose of lactulose (placebo arm)	Normal	2.657					RFHE3001 (Pivotal trial)
Average daily dose of lactulose (rifaximin- α arm)	Normal	3.083					RFHE3001 (Pivotal trial)
Frequency of outpatient visits	Normal	0.148					Chautant [2013]
Percentage hospitalised at HE episode	Normal	0.030					[Chautant [2013]
Episode duration (utility) - lactulose	Normal	0.260					Clinical experts
Episode duration (utility) - rifaximin- α	Normal	0.150					Clinical experts
CLDQ-EQ5D Conversion factor	Normal	0.006					RFHE3001 <i>post hoc</i> analysis
Frequency of outpatient visits	Gamma	0.524					Clinical experts
SG utility for Conn Score 0	Beta	0.020	0.915		182	17	Kind <i>et al.</i> [1999]
SG utility for Conn Score 1	Beta	0.026	0.839		167	32	Kind <i>et al.</i> [1999]
SG utility for Conn Score 2	Beta	0.033	0.683		136	63	Kind <i>et al.</i> [1999]
SG utility for Conn Score 3	Beta	0.035	0.487		97	102	Kind <i>et al.</i> [1999]
SG utility for Conn Score 4	Beta	0.029	0.216		43	156	Kind <i>et al.</i> [1999]
Percentage of patients with Conn score 1 at first episode (ITT)	Beta	3.7%	0.160		15.8	83.2	RFHE3001 (Pivotal trial)
Percentage of patients with Conn score 2 at first episode (ITT)	Beta	5.0%	0.520		51.5	47.5	RFHE3001 (Pivotal trial)
Percentage of patients with Conn score 3 at first episode (ITT)	Beta	4.1%	0.220		21.8	77.2	RFHE3001 (Pivotal trial)
Percentage of patients with Conn score 4 at first episode (ITT)	Beta	1.7%	0.030		3.0	96.0	RFHE3001 (Pivotal trial)
Percentage of patients with Conn score 0 at first episode (ITT)	Beta	2.7%	0.669		199.3	98.7	RFHE3001 (Pivotal trial)
30-day probability (OHE1)	Beta	0.027	0.111		15	120	RFHE3002 observed proportions
30-day probability (OHE2)	Beta	0.019	0.077		15	179	RFHE3002 observed proportions

HE, hepatic encephalopathy; ITT, intention to treat; SE, standard error; $\alpha > 0$, $\beta > 0$, shape parameters of Beta distribution.

Results

The initial cost-effectiveness analysis compared the rifaximin- α + lactulose with lactulose monotherapy under different time horizons: at 2 and 5 years. Adjusted lognormal distributions for survival curves report that after 5 years there is only 25.9% and 10.8% of survivors left in rifaximin- α and lactulose group, respectively. The cost-effectiveness results are shown in Table 3. The new therapeutic combination (rifaximin- α + lactulose) is more expensive and more effective than conventional treatment. The ICER at 5 years is equal to €18,517.

Tornado analysis revealed that the model was sensitive to several variables. Figure 3 displays the results of one-way sensitivity analyses for these variables in decreasing order of influence, and variations of each variable. The biggest ICER variation was obtained by changing the rifaximin- α mean dose, conversion mapping factor, and frequency of hospitalizations. The other variable estimates do not have impact significantly the model when varied over a wide range.

For the probabilistic sensitivity analysis, the results of the Monte Carlo simulations are shown

Table 3. Base-case model results of QALY, cost and incremental cost per QALY of maintenance rifaximin- α therapy arm and standard care arm over two different time horizons.

Time horizon	Lactulose		Rifaximin- α		Δ QALY	Δ Costs (€)	ICER (€)
	QALY	Cost (€)	QALY	Cost (€)			
2 years	0.967	5503	1.078	7639	0.111	2136	19,187
5 years	1.778	8555	2.094	14,411	0.316	5856	18,517

QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

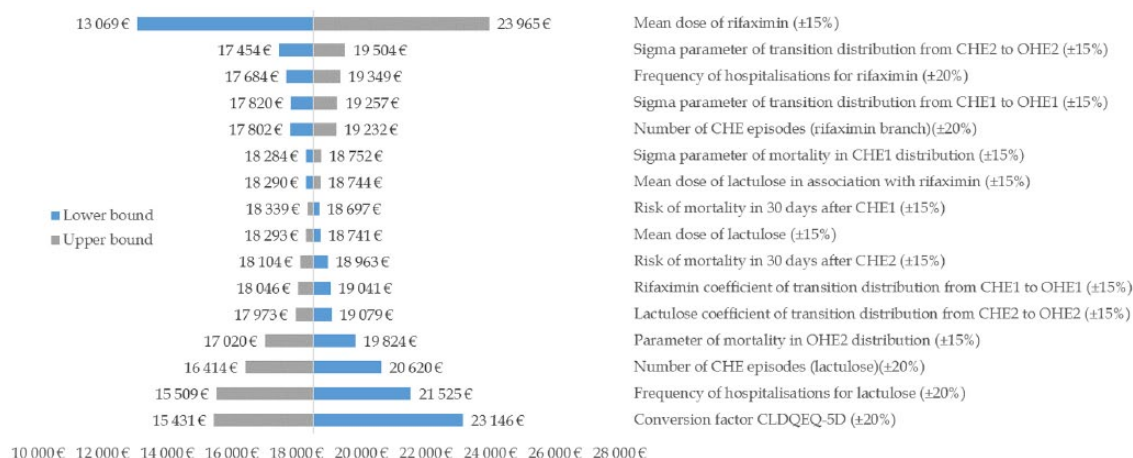


Figure 3. Tornado analysis. The value of each variable increased and reduced by 20% or 15%; in order to create the tornado diagram around the base-case incremental cost-effectiveness ratio (ICER) result [€18,517].

in the scatter plot in Figure 4. Each point represents one of the 1,000 trials run where each input was assigned a random value according to its probability density function. The average ICER is equal to €13,507 (95% confidence interval [€8887–21,733]). The mean incremental costs and the mean incremental QALYs are equal to €5147 and 0.40, respectively. The dashed diagonal lines indicate the €27,000 thresholds. Trial points that fall to the right and below these diagonal lines indicate a cost-effectiveness below the given threshold level. This analysis indicates a 99.8% probability that the ICER would be less than €27,000/QALY. Figure 5 represents two CEACs for two treatment arms and a CEAF curve. The value of threshold, where expected net benefit of rifaximin- α becomes greater than expected net benefit of standard treatment, was identified with CEAF and is equal to €12,985 (Figure 5, the lowest point on the dashed line). At this point there is a 51.4% of chance that rifaximin- α would be cost-effective as the first treatment in cirrhotic patients have experienced at least two prior OHE events.

Discussion

The decision analysis was performed to identify the most cost-effective therapeutic approach for the treating of HE under varying clinical and financial conditions. The results of this study showed the ICER of rifaximin- α in association with lactulose compared with lactulose monotherapy is equal to €18,517 from the base-case analysis over a 5-year lifetime. This ICER value means that, by adopting the strategy with rifaximin- α , it costs €18,517 per patient to generate one additional life year gained compared with the lactulose strategy. As observed on the cost-utility scatterplot, 100% of simulations occur in the North East quadrant. This position indicates that rifaximin- α with lactulose is more expensive and more beneficial in comparison with lactulose treatment. The probabilistic results generated comparable findings for ICER that is equal to €13,507 (95% confidence interval [€8887–21,733]). The acceptability curve can be used to interpret the cost-effectiveness of the treatment for any given willingness-to-pay threshold. The CEAC indicates that from the threshold of

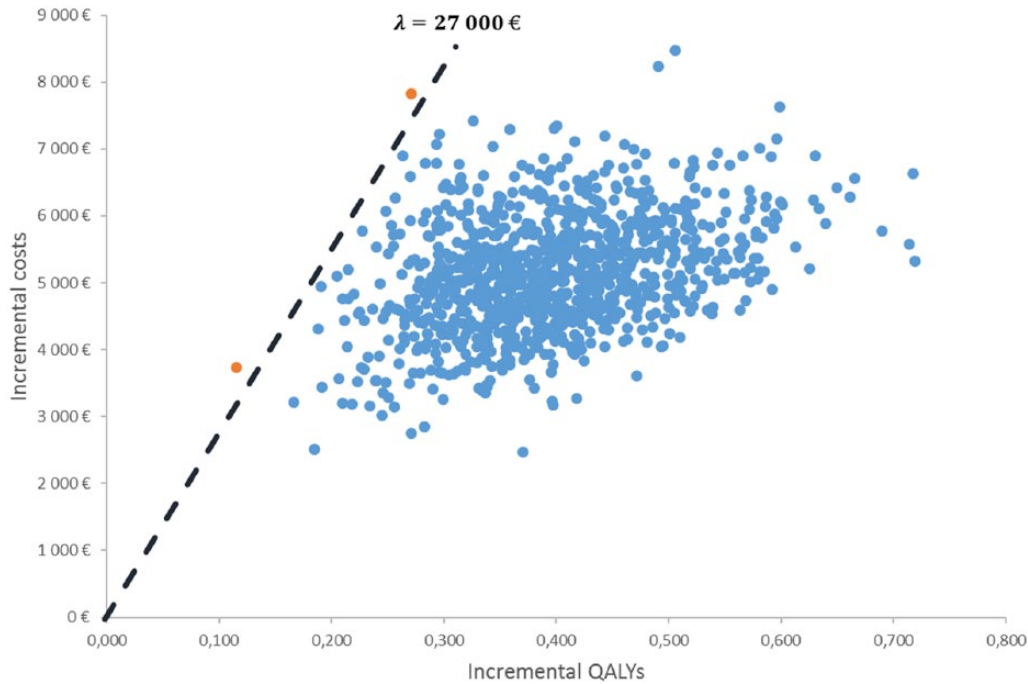


Figure 4. Cost-effectiveness plane of rifaximin- α versus placebo monotherapy. The horizontal axis displays the gain on additional quality-adjusted life years (QALYs) when using rifaximin- α instead of placebo, and the vertical axis displays the additional costs. For example, if a payer had a budget of €27,000 per QALY gained, then through all Monte Carlo simulations (broken line) only 0.2% of the cohort would fall within the budget.

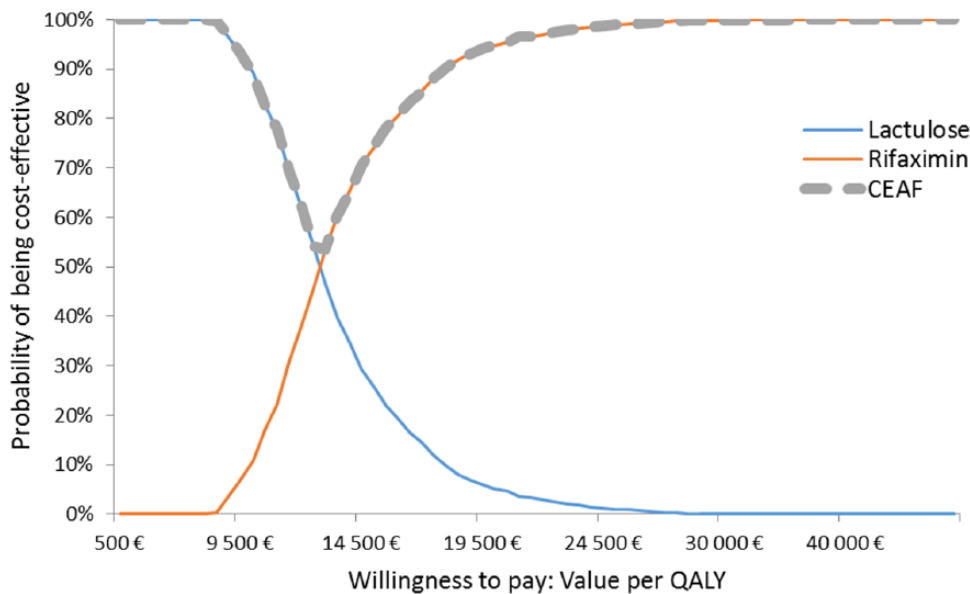


Figure 5. Cost-effectiveness acceptability curve and cost-effectiveness acceptability frontier based on incremental cost-effectiveness ratio (ICER) between rifaximin- α and a placebo comparator. The horizontal axis displays the willingness-to-pay budgetary thresholds to gain one additional quality-adjusted life year (QALY) when using rifaximin- α , and the vertical axis displays the percentage of 1000 patients that fall within the available budget. The switch point where rifaximin- α became a cost-effective treatment corresponds to €12,985 per QALY gained.

€12,985 rifaximin- α becomes a cost-effective treatment with a probability of 51.4%. However, this value is not enough to accept the cost-effectiveness of a new treatment, and that means that the value of €12,985 of willingness-to-pay does not allow all patients to receive the new effective treatment. Indeed, at a threshold of €27,000, there would be a 99.8% probability that rifaximin- α would be considered cost-effective.

Obtained results were compared with the results of published cost-effectiveness studies in other countries. Since its inception in 1999 NICE has adopted a cost-effectiveness threshold range of £20,000–30,000 per QALY gained [Claxton *et al.* 2013], that corresponds to €27,507–41,260 (using an exchange rate of 0.7271 from December 2015). As well as in French model, in Sweden the treatment with rifaximin- α associated with lactulose *versus* lactulose only demonstrated a reduction of HE events, reduced the risk of OHE episodes, improved health-related utility during remission/covert states, reduced admissions to hospital and, in a 5-year perspective, showed a base-case ICER of €16,438 [Poole *et al.* 2015]. However, previously, in the published decision analysis, Huang and colleagues showed that the use of rifaximin- α alone as a upfront therapy for HE is unlikely to be highly cost-effective under most circumstances [Huang *et al.* 2007]. They found that rifaximin- α monotherapy has an incremental cost of more than \$26,000 per QALY gained when compared with lactulose monotherapy. This result is significantly higher than the ICER value obtained in the present study, especially when compared with the probabilistic result. Nevertheless, the result of Huang and colleagues is hardly comparable with the current study because they evaluated a hypothetical cohort of 50-year-old patients with cirrhosis and HE that had not previously been treated. This is not the same population that was taken into consideration in the present economic evaluation, which is the adults in remission from two previous episodes of HE. Also, in favour of the current study, Huang and colleagues concluded that a hybrid salvage strategy, such as rifaximin- α and lactulose, may be highly cost-effective. Other reviewed publications investigated liver transplant patients started on lactulose or rifaximin- α therapy after presenting with stage 2 HE [Neff *et al.* 2006], or sought to compare frequency and duration of HE-related hospitalizations during rifaximin- α *versus* lactulose treatment [Leevy and Phillips, 2007]. These studies are not economic

evaluations, but the cost analyses studies, that compared the outcomes and the costs associated with HE hospitalizations in patients treated with rifaximin- α and lactulose. Both analyses showed that patients are receiving lactulose incurred higher hospitalization costs for the treatment of HE than those treated with rifaximin- α : US\$13,285 for lactulose and US\$7958 for rifaximin- α in the study of Neff and colleagues; and US\$56,635 for lactulose and US\$14,222 for rifaximin- α in the study of Leevy and Philips.

This analysis has several strengths and unique features. To the best of the authors' knowledge, this is the first decision analysis that measures the cost-effectiveness of competing agents in HE in France and, in particular, considers the health economic implications of rifaximin- α with lactulose. It is relevant because previous publication suggested measuring the cost-effectiveness of these competing management strategies in representative samples of community-based patients with HE prospectively, and also to examine the effects of combination therapy in refractory HE [Huang *et al.* 2007]. Second, rather than conducting only base-case analysis, several analyses were carried out to gauge health economic outcomes across several domains, including cost-effectiveness, cost-utility and decision making. Whereas it is often difficult to decide how best to make a policy decision, the results of sensitivity analysis allow healthcare decision makers to make explicit and direct comparisons between competing strategies. Third, the reported results will help to implement rifaximin- α in French HE treatment practice, allowing an improvement in patients' quality of life. The present study also has several limits. First of all, other potential strategies, such as rifaximin- α monotherapy, or rifaximin- α salvage after initial neomycin, were not explored. Although these treatment approaches would be relevant variants of this model analysis. Second, this study does not include patients with evidence of active gastrointestinal bleeding, hepatic coma severe electrolyte abnormalities, renal insufficiency, psychiatric disorders, active infection, and respiratory distress. Third, three different available utility sources were used to feed the model. Despite using the mapping algorithm, this can reproduce a substantial bias. Fourth, the mortality adjustments applied following first and second OHE episodes that are based on those reported in the OLT RFHE3002 clinical study. Another limitation is that the structural uncertainty was not

completely reduced, some other scenarios can be explored.

Conclusion

In conclusion, this analysis reveals that in France for patients with recurrent HE in the context of liver cirrhosis rifaximin- α reduces episodes of overt HE. Rifaximin- α in association with lactulose improves the quality of life and reduces expenditure for the French healthcare system. In other words rifaximin- α is a cost-effective treatment strategy when compared with lactulose monotherapy. The presented uncertainty intervals and cost-effectiveness acceptability curves enable decision-makers to appraise the results based on their risk aversion.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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