COST-EFFECTIVENESS ANALYSIS OF RIFAXIMIN-λ ADMINISTRATION FOR THE REDUCTION OF THE OVERT HEPATIC ENCEPHALOPATHY EPISODES IN RECURRENCE IN FRANCE

Anastasiia Kabeshova[1], Ph.D.; Soumaia Ben Hariz[1], MS; Elyonore Tsakeu[1], MS; Robert Benamouzig[2], MD; Robert Launois[1], Ph.D.

1: Network for Evaluation in Health Economics, REES France, Paris, France
2: Gastroenterology Department, Avicenne Hospital, Bobigny, France

Abstract

OBJECTIVES: Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that occurs most often in a context of acute or chronic liver disease. Rifaximin-α is the first treatment that has been clinically developed for overt HE (OHE) episodes. The objective of the current study was to estimate the long-term cost-effectiveness of rifaximin-α used in combination with lactulose compared to lactulose in cirrhotic patients, who have experienced at least two prior OHE events.

METHODS: A Markov model was used to determine whether rifaximin-α is a cost-effective therapy for the prevention of OHE taking a collective perspective as recommended by French HTA guidelines. The transition between health states was based on the analysis of the rifaximin-α pivotal clinical trials.

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 the one-way and the probabilistic sensitivity analysis. The results of the Monte Carlo simulations showed that the mean ICER is equal to €13 507 (CI: [€8 887 – €21 733]). The analysis indicates a 99.8% probability that the ICER would be less than €27 000/QALY.

CONCLUSIONS: 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.

Methods

Study carried out at the **University Hospital of Toulouse**:

- observational, retrospective, single-centre; including 62 patients; followed between July 2010 and September 2013.

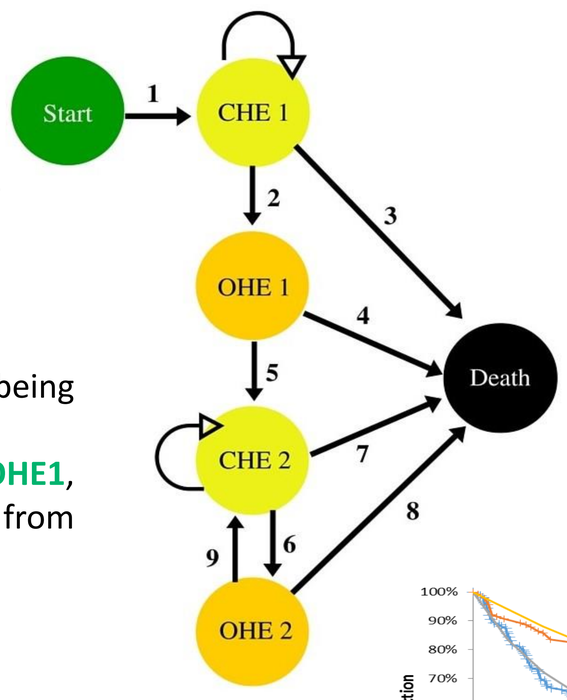
Pivotal clinical study **RFHE3001**:

- adults ≥ 18 years old in remission from previous episodes of OHE, associated with hepatic cirrhosis (equivalent to Conn score ⩾2); average age was 62.4 years.

Model structure :

- Covert states in the model (**CHE1**, **CHE2**) are defined as being equivalent to a Conn score of 0 or 1.
- Breakthrough episodes of overt hepatic encephalopathy (**OHE1**, **OHE2**) 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.

Two different time : 2 and 5 years.
A cycle length of 1 month (defined as 30.4 days).
Costs were based on current French treatment practices.



Kaplan–Meier survival curves of time to breakthrough OHE events were published by Bass. Parametric survival modelling allowed to extrapolate a survival curve beyond the 6-month timeframe of the study using 5 alternative parametric survival distributions.

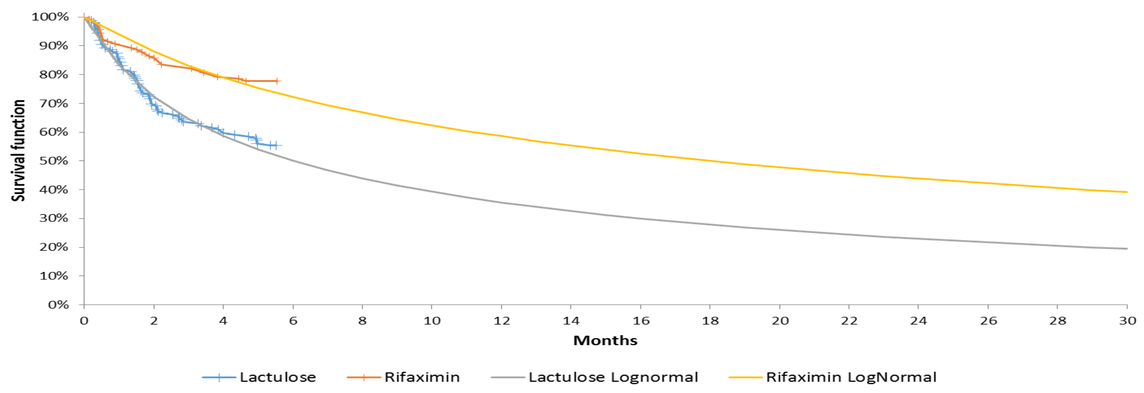
The estimated distribution parameters are used to measure the time-dependency transition probabilities, according to the following formula:

$$tp(t_u) = 1 - \exp\{H(t-u) - H(t)\}$$

where u is the Markov cycle; t_u indicates that t is calculated as integer multiples of the cycle length of the model; $H(t)$ is a cumulative hazard function for lognormal distribution.

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
Log-Normal	**-748,68**	**1499,36**	**1503,09**
Log-Logistic	-752,93	1507,87	1511,60

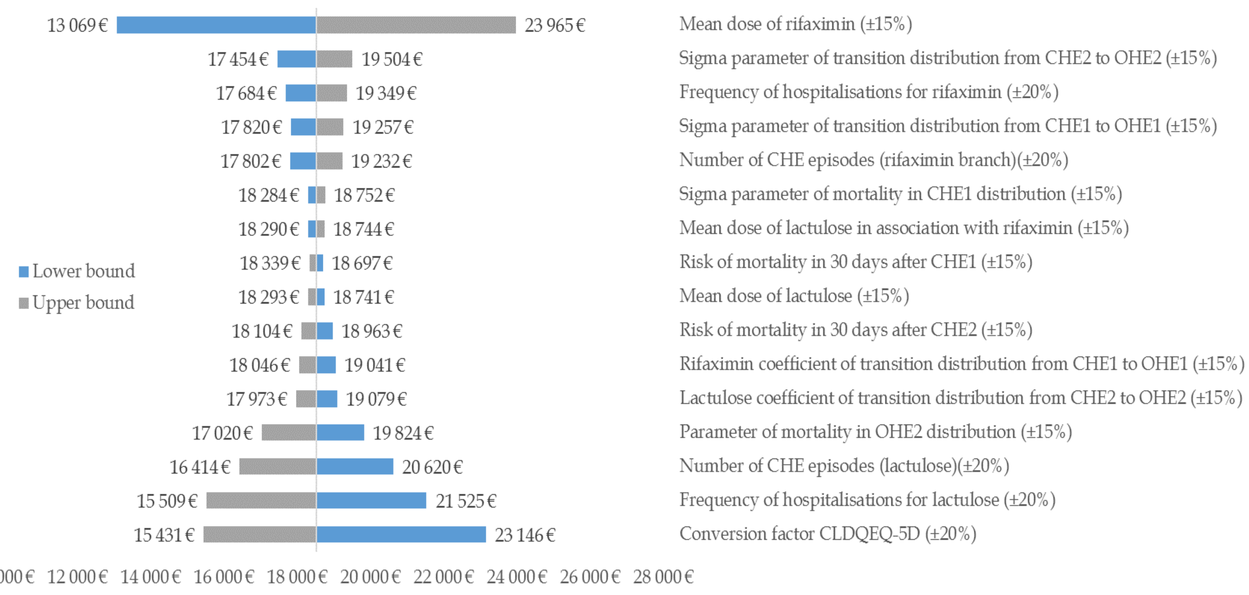
Model fit statistics for five alternative candidate parametric survival distributions of time to first breakthrough overt episode (RFHE3001)

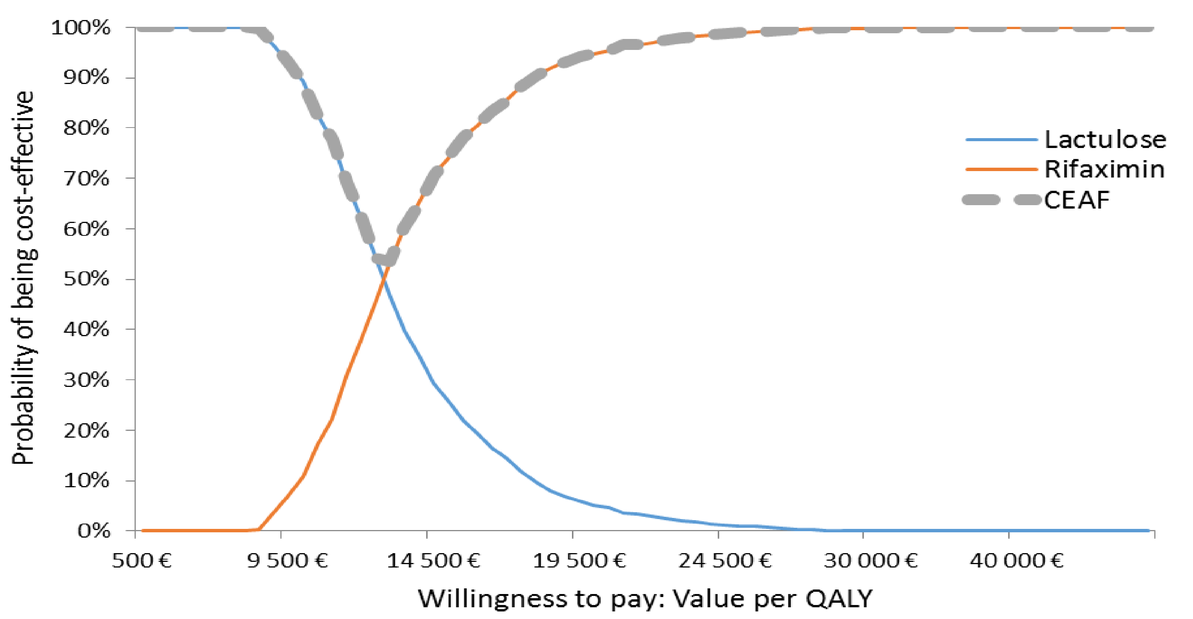


Comparison of original Kaplan–Meier plot and corresponding best-fit parametric survival function (log-normal) for time to first overt HE event (by treatment arm in the RFHE3001 study)

Results

Time horizon	Lactulose		Rifaximin-α		Δ QALY	Δ Costs (€)	ICER (€)
	QALY	Cost (€)	QALY	Cost (€)			
2 years	0,967	5 503	1,078	7 639	0,111	2 136	19 187
5 years	1,778	8 555	2,094	14 411	0,316	5 856	18 517





Probabilistic sensitivity analysis showed that mean ICER = €13,507 (95% CI [8,887–21,733]). CEACs represent the quantification of the uncertainty around the expected cost effectiveness that is plotted with the probability that the expected NMB is positive over a range of values on the vertical axis and WTP/cost effectiveness threshold (λ) on the horizontal axis. Switch point = €12,985.

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 OHE. 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. Indeed, at a threshold of €27,000, the probability that rifaximin-α would be considered cost-effective is 99.8%. The uncertainty intervals and CEACs enable decision-makers to appraise the results based on their risk aversion.

References

1. Bass, N.M., Mullen, K.D., Sanyal, A., et al. (2010) Rifaximin Treatment in Hepatic Encephalopathy. New England Journal of Medicine 362(12): 1071–1081.
2. Briggs, A., Sculpher, M. and Claxton, K. (2006) Decision Modelling for Health Economic Evaluation. 1 edition. OUP Oxford.
3. Latimer, N.R. (2013) Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Medical Decision Making 33(6): 743–54.

28, rue d'Assas – 75006 Paris France; Tel: +33 1 44 39 16 90
E-mail: launois.reesfrance@wanadoo.fr Web: www.rees-france.com