COST EFFECTIVENESS OF RIFAXIMIN-α IN THE REDUCTION OF RECURRENCE OF OVERT HEPATIC ENCEPHALOPATHY

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Introduction

Hepatic encephalopathy (HE) is a serious neuropsychiatric condition associated with high morbidity and mortality. It is characterised by an underlying impairment in neurocognitive function which is termed minimal or covert HE. This can progress to a more severe state, in which patients experience episodes of neurological dysfunction, lasting from several hours up to several days or even weeks and some patients may end up in a coma. This is known as an overt state. Rifaximin-α is effective in reducing the recurrence of HE events and associated hospitalisations.[1]

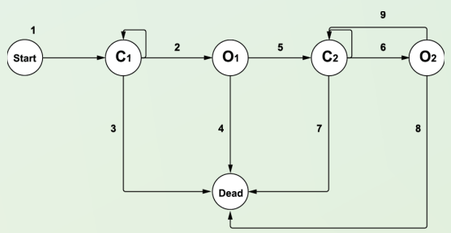
Aims

The aim was to characterise the cost effectiveness of rifaximin-α in addition to standard care versus standard care alone in UK clinical practice. Standard care is defined as maintenance lactulose therapy.

Methods

- Design of analysis
  - A cost utility analysis was conducted using a Markov state transition model, depicting a simplified representation of the disease process, as validated by a number of clinical experts (Figure 1)
  - The model has Markov health states describing covert (C1) HE, overt (O1) HE and death. Patients experiencing overt HE in the model either die or return to a second covert health state (C2) which assumes a higher risk of mortality but no decrease in impact on quality of life (QoL)
- Target population
  - Adult patients with chronic liver disease who have experienced at least one overt HE episode
  - The patient population reflects the patients characteristics of those observed in the pivotal study[1] and the open label extension study (OLE)[2]
- Setting and study perspective
  - The payer perspective was that of the UK National Health Service. Both outpatient and inpatient treatment settings were considered
- Interventions being evaluated
  - Treatment with rifaximin-α + standard care (rifaximin-α group)
  - Placebo + standard care (standard care group)
- Time horizon
  - An updated model evaluated a 5-year, 10-year and lifetime horizon (42 years = death of last patient)
- Annual discounting was applied at a rate of 3.5% for both costs and benefits
- The health outcome was the QALY, the standard unit of measurement for benefit required by the UK National Institute for Health and Care Excellence (NICE)
  - QALYs were determined by modelling transitions from covert to overt HE states and death, and applying utility weightings to each health state

Figure 1. An illustration of the structure of the Markov model



Key

Patients enter the model in the remission state
Covert State (C1) to first-observed over episode (O1)
Covert State (C1) to death
First-observed overt episode (O1) to death
Recovery from first-observed overt episode (O2) to subsequent covert state (C2)
Subsequent covert state (C2) to subsequent overt episode (O2)
Subsequent covert state (C2) to death
Subsequent overt episode (O2) to death
Recovery from subsequent overt episode (O1) to subsequent covert state (C2)

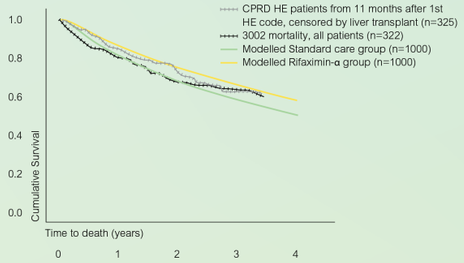
Required model inputs

- Time to first observed HE event was determined from the pivotal trial
- Time to all subsequent events was determined from an OLE study
  - Time to death was determined from the observed mortality rates in the OLE
- Measurement of QoL and quantification of health-related utility
  - QoL was measured during the pivotal study during the covert state only using the
    - Chronic Liver Disease Questionnaire (CLDQ) a disease specific QoL instrument)
    - Short Form 36 (SF-36) a generic QoL instrument
  - Assessments were not made during an overt HE breakthrough episode due to the patients altered mental and neuromotor status
  - Patients were excluded from the study if they experienced a breakthrough episode of HE
  - The average duration of disutility from an overt episode was estimated by a panel of clinical experts to be 11 days[3]
- Estimating resources and costs
  - Costs were based on data from published sources and were in UK pounds sterling at 2012 prices.
    - Drug acquisition costs were £289.95 and £9.09 for rifaximin-α and lactulose per model month (30. 4 days), respectively[4]
  - The total estimated cost of an HE-related admission was £1,040.77 per episode[5] for which:
    - The average length of stay in hospital was estimated by a panel of clinical experts to be 5 days[3]
    - The likelihood of an admission to hospital was 52.88%[1]
  - The cost of an outpatient consultation was £176.275
- Evaluation of uncertainty
  - The impact of uncertainty in the input parameters on the model was explored with one-way and probabilistic sensitivity analysis (PSA)

Results

- In this model- based analysis; treatment with rifaximin-α versus standard care would demonstrate:
  - Reduced progression to HE events
  - Improved patient survival through reduced risk of mortality due to reduction in HE episodes
  - Improved health-related utility during remission / covert states
  - Rifaximin-α appears to offer a cost-effective treatment option for reduction of recurrence of overt HE assuming a cost effectiveness threshold of £30,000 per QALY
- Modelled mortality was a close visual fit to that observed in the open-label extension study and also that observed in matched cohort drawn from the UK Clinical Practice Research Database (CPRD) database (Figure 2) [6]

Figure 2. Comparison of modelled survival with observed survival in the open-label extension study and post-HE survival in a matched observed population drawn from the UK CPRD database.



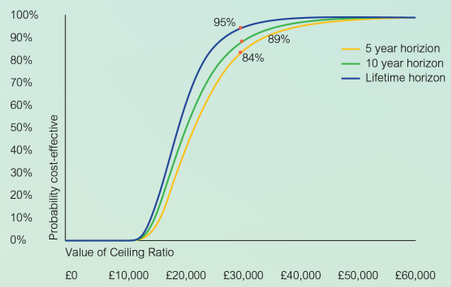
- The incremental cost effectiveness ratio (ICER) were £20,829, £19,207, and £17,681 with a time horizon of 5 years, 10 years and lifetime, respectively (Table 1)

Table 1. Incremental cost effectiveness ratios over 5, 10 and lifetime horizon.

Time horizon (years)	Discounted costs – rifaximin-α group	Discounted costs – standard care group	ICER
5	£15,559	£4,574	£20,829
10	£22,358	£5,887	£19,207
42 (Lifetime)	£28,874	£6,925	£17,681

- Probabilistic sensitivity analysis (PSA)
  - In the 5-year, 10-year and lifetime horizons, rifaximin-α was found to have an 84%, 89% and 95% likelihood of being cost-effective at WTP of £30,000 per QALY, respectively (Figure 3). The probabilistic ICER was £21,000, £19,555 and £18,202

Figure 3. Cost Effectiveness Acceptability Curve (CEAC) for 5, 10 and lifetime horizon



Conclusions

- This model was developed to reflect real world clinical practice, disease progression and related outcomes
- Under these conditions rifaximin is shown to be cost effective by reducing recurrence of overt HE episodes. This remains true under a broad range of clinically plausible scenarios

Limitations

There are limitations to this model since it was based on a combination of trial and epidemiological sources combined with opinions from clinical experts.

As there was no placebo data in the open label extension study, assumptions were validated using real world data derived from CPRD as well as clinical expert opinion. The PSA, however, demonstrated stability of the final estimated ICER.

References

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