Impact of Updated Mortality Estimates on the Cost-Effectiveness of Rifaximin for the Treatment of Patients with Overt Hepatic Encephalopathy

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BACKGROUND

- Hepatic encephalopathy (HE) is one of the most significant complications of cirrhosis with a substantial economic burden (HE-related hospitalization charges of $7.2 billion (2009) in the United States [US])[1,2]
- Xifaxan® (Rifaximin) is the only US Food and Drug Administration (FDA)-approved (2010) treatment for the reduction of risk of overt hepatic encephalopathy (OHE) recurrence[3]
- A cost-effectiveness model by *Jesudian AB et al. (2020)* demonstrated that rifaximin ± lactulose (vs. lactulose monotherapy) is cost-effective with an incremental cost-effectiveness ratio (ICER) of $29,161 (2018 US dollars [USD]) per quality-adjusted life years (QALY) gained[4]

OBJECTIVE

- The objectives of the current study are to:
  - **Objective 1:** Identify updated rifaximin-associated OHE mortality estimates for US patients
  - **Objective 2:** Conduct scenario analyses to assess the robustness of the *Jesudian AB et al. (2020)* study ICER estimates (base case), by comparing the base case ICER to the ICER estimates using updated rifaximin-associated OHE mortality identified in objective 1

METHODS

- To identify updated (as of 08/22/2022) rifaximin-associated OHE mortality estimates for US patients (**objective 1**) a targeted literature review (TLR) was conducted
  - The TLR search was conducted using PubMed (MEDLINE), Ovid MEDLINE, and Ovid Embase databases and the Population Intervention Comparator Outcome (PICO) framework (**Table 1**) based on a pre-specified inclusion/exclusion criteria (**Table 2**)
    - Critical appraisal of identified studies was conducted using Cochrane RoB v2.0 (randomized controlled trials), ROBINS-I tool (non-randomized controlled trials), STROBE Checklist (cohort studies and cross-sectional studies)[5-7]

Table 1: PICO framework for the targeted literature review search

Population	Patients with overt hepatic encephalopathy
Intervention	Rifaximin or lactulose
Comparator	Placebo
Outcome	Rate of mortality

PICO: Population, Intervention, Comparator, and Outcome

Table 2: Inclusion and exclusion criteria for targeted literature review search

Inclusion criteria	Exclusion criteria
• Parallel-group RCTs • Studies reporting mortality outcomes	• Studies without the relevant outcome, review articles, non-English language articles, letters to the editor, and animal trials

RCT: Randomized Clinical Trial

- Following the TLR, scenario analyses (**objective 2**) was conducted to assess the impact of updated US mortality estimates (identified from the TLR) on the robustness of the base case model ICER estimates
  - In the scenario analyses, the impact on the cost per QALY gained was assessed under two scenarios:
    - Assuming no mortality benefits associated with rifaximin
    - Assuming rifaximin-associated updated US mortality estimates from literature identified from the TLR
- All the ICERs in the scenario analyses are presented in 2018 USD for comparability with the *Jesudian AB et al. (2020)* ICER estimates

Table 3: Studies identified in the targeted literature review

Author (Year)	Country	Study design	Sample size	Mean age (years)	Disease at baseline	Intervention	Control	Study quality	Hospitalized (Y/N)	Mortality rate (%) (follow-up period)	
										Intervention	Control
Study used in the Jesudian AB study											
Mullen et al. (2014[8])	USA	Open-label single arm study	392	56.8	HE	Rifaximin 550 mg twice daily		High risk[#]	N	19.3 (24 months)	NR
Studies included in the scenario analyses											
Landaverde et al. (2020[9])	USA	Prospective cohort	907 (6-month) 358 (12-month)	NR	HE, Cirrhosis	Rifaximin[c]		Low quality[#]	N	5.5 (After 6-month) 8.7 (After 12-month)	
Bajaj et al. (2019[10])	USA	Pooled RCT analysis	381	Rifaximin + lactulose: 56.9; Lactulose:56.6	OHE, Cirrhosis	Rifaximin 550 mg twice daily + lactulose	Lactulose	Some concerns*	N	5.1 (6 months)	6.9 (6 months)
Studies excluded in the scenario analyses: Rifaximin dose is not consistent with US FDA label for HE, conducted outside US, amongst hospitalized HE patients											
Jones et al. (2020[12])	UK	Retrospective Cohort	4,669	59 (SD 13)	HE	Rifaximin[c] and lactulose (monotherapy or in combination)		Low quality[#]	Y	43 (28 days)	
Bohra et al. (2020[13])	Australia	Retrospective Cohort	188	57 (IQR 50-65)	HE	Rifaximin[c]		High quality[#]	N	57 (12-month)	
Poudyal et al. (2019[14])	Nepal	Cross-sectional	132	49.2	Cirrhosis	Rifaximin 550 mg twice daily plus lactulose Lactulose L-Ornithine L-aspartate Lactulose		High quality[a]	Y	13.6 (NR) 13.6 (NR) 22.7 (NR)	
Kulkarni et al. (2018[15])	India	Retrospective cohort	58	NR	HE	Rifaximin 550 mg twice daily		Low quality[#]	Y	15.51 (during hospitalization)	
Hasan et al. (2018[16])	India	RCT	91	64.9	Overt HE	Rifaximin 1,200 mg and lactulose 60-120 ml daily	Lactulose 60-120 ml daily	Low risk*	Y	28.9 (10 days)	21.2 (10 days)
Kang et al. (2017[17])	Korea	Retrospective cohort	421	Rifaximin + lactulose: 58.60, Lactulose: 60.22	HE, Cirrhosis	Rifaximin 1,200mg/day + lactulose Lactulose		High quality[#]	N	36.55; 56.88 29.7; 37 (12 months) 32.4; 40.7 (24 months) 35.9; 62.8 (36 months) 36.6; 55.1 (48 months)	
Ahire et al. (2017[18])	India	Non-randomized comparative	74	50.8	HE, Cirrhosis	Rifaximin 1,200 mg/day + lactulose	Lactulose	High risk[#]	N	6.25 (7-15 days)	14.28 (7-15 days)
Courson et al. (2016[11])	USA	Retrospective cohort	745	NR	HE	Lactulose monotherapy Rifaximin[c] + Lactulose		High quality[#]	Y	22 (In-hospital [6 days])[a] 32 (In hospital [8 days])[a]	
Bannister et al. (2016[19])	UK	Open-label non-randomized trial	321	Based on no. of prior HE episodes 1: 56; 2: 57; 3: 59; ≥ 4: 57	HE	Rifaximin 550 mg twice daily		Low risk[#]	N	23.36 (Mean 1.5 years)	NR
Orr et al. (2015[20])	UK	Retrospective cohort	295	58	HE	Rifaximin 550 mg twice daily		Low quality[#]	Y	5 (30 days) 10 (90 days) 21 (1 year)	
Maharshi et al. (2015[21])	India	Open-label RCT	120	Lactulose 30 ml: 41.8 Rifaximin 400 mg: 39.2	AVB	Lactulose 30 ml	Rifaximin 400 mg	High-risk*	Unclear	13.33 (NR)	15 (NR)
Maharshi et al. (2014[22])	India	Open-label RCT	80	Lactulose 30 ml: 41.6, Rifaximin 400 mg: 38.6	AVB	Lactulose 30 ml	Rifaximin 400 mg/day	High risk*	N	12.5 (5 days)	15 (5 days)
Muhammad et al. (2014[23])	Pakistan	RCT	160	41.0	HE	Rifaximin 550 mg twice daily and lactulose 90 ml daily	Lactulose 90 ml daily	High risk*	Y	21.25 (7 days)	41.25 (7 days)
Gill et al. (2014[24])	Pakistan	RCT	200	40.0	Overt HE	Rifaximin 550 mg twice daily and lactulose 30-60 ml daily	Lactulose 30-60 ml daily	Some concerns*	Y	20 (10 days)	40 (10 days)
Sharma et al. (2013[25])	India	RCT	120	39.4	Overt HE	Rifaximin 1,200 Mg/day and lactulose 90–180 ml daily	Lactulose 90–180 ml daily	Low risk*	Y	23.8 (10 days)	49.1 (10 days)
Sharma et al. (2012[26])	India	RCT	120	Lactulose: 43.4; No lactulose: 42.2	Overt HE, Cirrhosis	Lactulose	No lactulose	Some concerns*	Y (readmission)	9 (12 months)	20 (12 months)

AVB: Acute variceal bleeding; HE: Hepatic encephalopathy; IQR: Interquartile range; NR: Not reported; RCT: Randomized control trials, SD: Standard deviation Y/N: Yes/No
[a] Median length of stay, [b] Not clear whether included patients were hospitalized at the time of study initiation. [c] dosing information not available in the study abstract/full-text

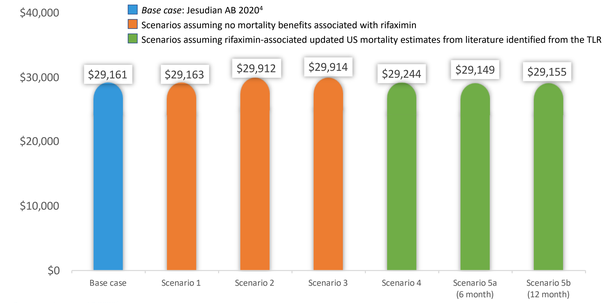
Rifaximin dosing in the study not consistent with the US FDA label for HE
US studies included in the scenario analysis
US study with mortality among hospitalized patients only
UK study used for validation

* Cochrane RoB v2.0 is a well-accepted tool to assess the risk of bias for randomized trials. RoB 2.0 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Within each domain, a series of signaling questions aim to elicit information about features of the trial that are relevant to the risk of bias. The overall judgment about the risk of bias ('Low' or 'High' risk of bias or can express 'Some concerns') for a study is generated by an algorithm that uses the judgment of responses from the signaling questions in each domain.[6]
[#] ROBINS-I assesses the risk of bias in the results of non-randomized studies of interventions and is structured into several domains of biases. ROBINS-I includes signaling questions that inform the risk of bias judgments for each domain and the overall risk of bias judgment as 'Low', 'Moderate', 'Serious' or 'Critical' risk of bias.[5]
[5, 6] STROBE Checklist for cohort studies and cross-sectional studies provides general reporting recommendations for descriptive observational studies and studies that investigate associations between exposures and health outcomes. STROBE checklist addresses cohort, case-control and cross-sectional studies, and allow categorizing studies into high, low or moderate quality.[7]
[c, 9] For cohort and cross-sectional studies, treatments cannot be classified as intervention and comparator, hence are not reported separately.

RESULTS

- From the initial 7,500 studies identified from the TLR, a total of 19 relevant studies were identified (based on the inclusion/exclusion criteria) following title/abstract screening and full-text screening
- Only 4 studies were relevant to the US population (**Table 3**)
  - Of these four, *Mullen et al. (2014)* was used by the *Jesudian AB et al. (2020)* study.[4,8] *Landaverde et al. (2020)* and *Bajaj et al. (2019)* were published after the *Jesudian AB et al. study* (2018-2019) was conducted and used in the scenario analyses (**Figure 1**); and *Courson et al. (2016)* reported mortality among hospitalized patients only[9,10,11]
- At the time of the *Jesudian AB et al. (2020)* cost-effectiveness model development, only *Mullen et al. (2014)* was available as a source for mortality rates among non-hospitalized HE patients in the US
  - Further, the study authors validated the ICER using mortality estimate from *Mullen et al. (2014)* by comparing to ICER results using mortality estimates reported by *Bannister et al. (2016)*-- a high-quality study that reported mortality estimates among non-hospitalized patients in the United Kingdom[19]
    - The mortality estimates obtained from *Bannister et al. (2016)* were similar to that obtained from *Mullen et al. (2014)*
- In the scenario analyses (**Figure 1**), the results under both scenarios were similar to the base case results from *Jesudian AB et al. (2020)*:
  - $29,163-$29,914 per QALY gained when no mortality benefits associated with rifaximin is assumed (scenarios 1-3)
  - $29,244 and $29,149-$29,155 per QALY gained when the mortality estimates from *Bajaj et al. (2019)* and *Landaverde et al. (2020)* is used, respectively (scenarios 4, 5a, 5b)

Figure 1: Scenario analysis



Base case: Jesudian AB 2020[4]
Scenario 1: Two weeks mortality after hospitalization for rifaximin + lactulose arm is assumed to be same as lactulose arm (0.9%)
Scenario 2: In-hospital two-week mortality during OHE hospitalization for rifaximin + lactulose arm is assumed to be the same as lactulose arm (49.1%)
Scenario 3: Assuming scenarios 1 and 2
Scenario 4: Mortality estimates from Bajaj et al. 2019[10]
Scenario 5a (6-month): 6-month mortality estimates from Landaverde et al. 2020[9]; *Scenario 5b (12-month):* 12-month mortality estimates from Landaverde et al. 2020[9]

CONCLUSION

- The mortality estimate for the non-hospitalized population from *Mullen et al. (2014)*, used in the *Jesudian AB et al. (2020)* study, corroborated well with another high-quality publication (*Bannister et al. [2016]*) and was the best available evidence for US population at the time of the study in 2018-19
- Assuming no rifaximin-associated mortality benefits and using mortality estimates from recent studies in the US population demonstrate that mortality benefit associated with rifaximin use is not a key cost-effectiveness value driver
- Changes in the mortality estimates or assumptions do not significantly impact the ICER of rifaximin for the treatment of OHE presented *in Jesudian AB et al. (2020)*
- The authors critically evaluated quality (RoB 2 tool, ROBINS-I checklist, and STROBE framework, as applicable[5-7]) of the relevant studies identified in the TLR. Some of these studies do not study Xifaxan 550 mg BID. There are studies that did not use Xifaxan 550 mg BID according to the US FDA label for the approved indication for HE (i.e. reduction in risk of OHE recurrence) and we cannot speak to the propriety of off label use of any rifaximin for HE that is not Xifaxan 550 mg BID for the reduction in risk of OHE recurrence[3]

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DISCLOSURES

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- The study sponsor was involved in several aspects of the research, including study design, the interpretation of the data, and the production of the poster