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ORIGINAL RESEARCH

Assessment of Access Barriers to Rifaximin Among Patients with Hepatic Encephalopathy Using Adjudicated Claims Data

Arun Jesudian · Patrick Gagnon-Sanschagrin · Jessica Maitland · Kana Yokoji · Annie Guérin · Zeev Heimanson · Aaron Samson · Olamide Olujohungbe · Brock Bumpass

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ABSTRACT

***Introduction*:** Continuous treatment with rifaximin 550 mg (hereafter rifaximin) is associated with lower hospitalization rates in patients with hepatic encephalopathy (HE); however, access barriers may exist. This study assessed gaps in rifaximin access and the impact of treatment gaps, particularly those resulting from claim rejections, on hospitalizations and healthcare costs among patients with HE in the United States.

***Methods*:** The IQVIA PharMetrics® Plus database linked with Longitudinal Access and Adjudicated Data (2015–2022) were used to identify adults with HE who had ≥ 1 paid rifaximin prescription fill. Rifaximin treatment gaps were assessed during the 12-month period from the first observed attempt at receiving rifaximin (index date). Adjusted number of overt HE (OHE) hospitalizations and healthcare costs were compared over the 6 months following the index date between Cohort 1, who had no gap due to claim rejection and had < 7 days of treatment gap due to other reasons, and Cohort 2, who had ≥ 1 rejection gap or had ≥ 7 days of non-rejection gap.

***Results*:** During the year following the index date, 94.7% of the 1711 patients experienced a

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A. Jesudian
Weill Cornell Medicine, 1283 York Avenue, New York, NY 10065, USA
e-mail: abj9004@med.cornell.edu

P. Gagnon-Sanschagrin · J. Maitland (✉) · K. Yokoji · A. Guérin
Analysis Group, Inc., 1190 Avenue des Canadiens-de-Montréal, Tour Deloitte, Suite 1500, Montréal, QC H3B 0G7, Canada
e-mail: Jessica.maitland@analysisgroup.com

P. Gagnon-Sanschagrin
e-mail: Patrick.Gagnon-sanchagrin@analysisgroup.com

K. Yokoji
e-mail: Kana.Yokoji@analysisgroup.com

A. Guérin
e-mail: Annie.Guerin@analysisgroup.com

Z. Heimanson
Salix Pharmaceuticals, 400 Somerset Corporate Blvd, Bridgewater, NJ 08807, USA
e-mail: Zeev.Heimanson@salix.com

A. Samson · O. Olujohungbe · B. Bumpass
Bausch Health, 400 Somerset Corporate Blvd, Bridgewater, NJ 08807, USA
e-mail: Aaron.Samson@bauschhealth.com

O. Olujohungbe
e-mail: Olamide.Olujohungbe@bauschhealth.com

B. Bumpass
e-mail: Brock.bumpass@gmail.com

treatment gap, including 34.8% with initiation gaps from first attempt at receiving rifaximin to first paid claim (77.7% of initiation gaps due to rejected claims) and 72.0% with gaps in access during active treatment (14.8% of active treatment gaps due to rejected claims). Compared with Cohort 1 (n = 432; mean age 56.3 years), Cohort 2 (n = 679; mean age 54.8 years) had 1.55 times the incidence rate of OHE hospitalizations [adjusted incidence rate ratio: 1.55 (95% confidence interval: 1.10–2.20)] and incurred US$1579 more in healthcare-associated costs per-patient-per-month (all $p < 0.05$).

Conclusion: Prescription claim rejections frequently led to delays in rifaximin initiation and gaps in access during active treatment. Access barriers to rifaximin were associated with increased hospitalizations and healthcare costs in patients with HE.

Keywords: Access barriers; Antibiotics; Claims database; Hepatic encephalopathy; Healthcare costs; Hospitalization; Liver cirrhosis; Prior authorization; Rifaximin; Treatment gaps

Key Summary Points

Why carry out this study?

Continuous treatment with rifaximin 550 mg is crucial for preventing recurrence and hospitalizations in patients with hepatic encephalopathy (HE).

The extent of access barriers to rifaximin for HE and the impact of prescription claim rejections have not been extensively studied in the United States.

What was learned from the study?

Rifaximin treatment gaps, including those resulting from prescription claim rejections, were common among patients with HE.

Treatment gaps were associated with increased hospitalizations and healthcare costs.

Addressing payer-based access barriers to rifaximin for HE may help increase adherence and improve healthcare outcomes.

INTRODUCTION

Hepatic encephalopathy (HE) is a serious neurologic complication of liver cirrhosis characterized by a broad spectrum of neuropsychiatric abnormalities ranging from personality and behavioral changes, disorientation and confusion, to loss of consciousness [1–3]. Clinically overt HE (OHE) may present as recurring episodes that often necessitate hospitalizations [2, 3]. OHE hospital admissions and readmissions can be costly [4] and impose a considerable burden on patients [5]. Depending on the etiology of the underlying cirrhosis, lifestyle changes (e.g., alcohol abstinence in patients with alcohol-related cirrhosis) and corrections of precipitating factors are important management strategies that precede specific anti-HE treatment [3, 6].

Rifaximin 550 mg (hereafter rifaximin), a twice-daily oral antibiotic, is the only medication approved by the United States (US) Food and Drug Administration for reducing the risk of OHE recurrence in adults [7]. Rifaximin has demonstrated efficacy in preventing OHE recurrence and reducing the risk of OHE hospitalizations in clinical trials [7, 8]. Real-world studies have also found that having timely access to rifaximin following an initial OHE hospitalization, as well as being adherent to treatment, lowers readmission risk and healthcare costs [4, 9, 10]. Despite these proven benefits, a US study showed that approximately 40% of hospitalized patients with a rifaximin prescription for HE did not have the medication in hand when discharged from the hospital, because of access barriers such as having a prior authorization required that was not completed in time [9]. In addition, relatively low adherence to rifaximin has been reported in routine clinical practice despite it being safe and well tolerated [11–13]; for instance, one US study found that the proportion of commercially insured patients with HE who remained adherent [defined as proportion of days covered (PDC) ≥ 80%] at 6 and 12 months after initial rifaximin prescription was 42% and 25%, respectively [11].

Prior systematic reviews have found that utilization management strategies such as formulary

restrictions, prior authorization requirements, and cost sharing imposed by payers can be barriers to treatment access and are associated with increased time to treatment initiation and lower adherence across various disease conditions, including cardiovascular, dermatological, and gastrointestinal disorders [14–16]. For example, US health plans may require providers to obtain prior authorization for a specific medication by demonstrating the medical necessity of the patient before the medication can be covered and dispensed; however, the process involves additional administrative work and wait time (for approval or denial), which may lead to delayed access, continuity gaps, or abandonment [15, 17]. These payer-based access barriers may partially explain the previously observed delay in rifaximin access and low adherence among patients with HE. One prior study showed that adherence to rifaximin was poorer among patients with HE who had higher out-of-pocket costs [11]. However, the extent of access barriers, as well as the impact of payer claim rejections and delayed approval on healthcare outcomes, has not been extensively studied in HE. To address this literature gap, the current study sought to describe prescription patterns of rifaximin, focusing on gaps in rifaximin access, among commercially insured patients with HE in the US. The impact of rifaximin treatment gaps, specifically for gaps due to prescription claim rejections, on hospitalizations and healthcare costs was also assessed.

METHODS

Data Source

Claims data from the IQVIA PharMetrics® Plus database linked with Longitudinal Access and Adjudication Data (LAAD) covering the period of October 2015 (when the new coding structure using International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] was introduced [18]) to March 2022 (the most recent data available at the time of study onset) were used. The PharMetrics® Plus database consists of employer- and health plan-sourced data containing fully adjudicated medical and pharmacy claims for over 215 million unique enrollees and is representative of the commercially insured US national population for patients under 65 years of age. The database includes records of inpatient services, inpatient admissions, outpatient services, prescription drugs, and other medical care.

LAAD is a patient-centric dataset that integrates IQVIA's prescription, medical claims, and remittance data. The database includes patient longitudinal data, including Formulary Impact Analyzer (FIA) full lifecycle claims data. The final status of fully adjudicated claims in the FIA corresponds to paid (i.e., prescriptions approved and paid for by a health plan and picked up by the patient from the pharmacy), rejected (i.e., prescriptions rejected by the health plan), or reversed (i.e., prescriptions approved by the health plan but not picked up by the patient from the pharmacy). Reasons for rejections are also included.

Data are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA); therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4).

Study Objectives and Designs

A retrospective analysis was conducted among adult patients with HE receiving rifaximin with two study objectives: Objective 1 was to assess patient access to rifaximin and characterize treatment gaps and reasons for claim rejections; and Objective 2 was to compare the risk of OHE hospitalizations and healthcare costs among patients with gaps in rifaximin access versus patients without gaps in rifaximin access.

The study designs are presented in Fig. 1. For both objectives, the index date was defined as the first observed attempt at receiving rifaximin for HE, regardless of the final claim status (i.e., paid, rejected, or reversed). A 3-month pre-index washout period was imposed to ensure that patients were not actively taking rifaximin prior to the index date, as rifaximin is typically supplied for 30 days. This 3-month period was also

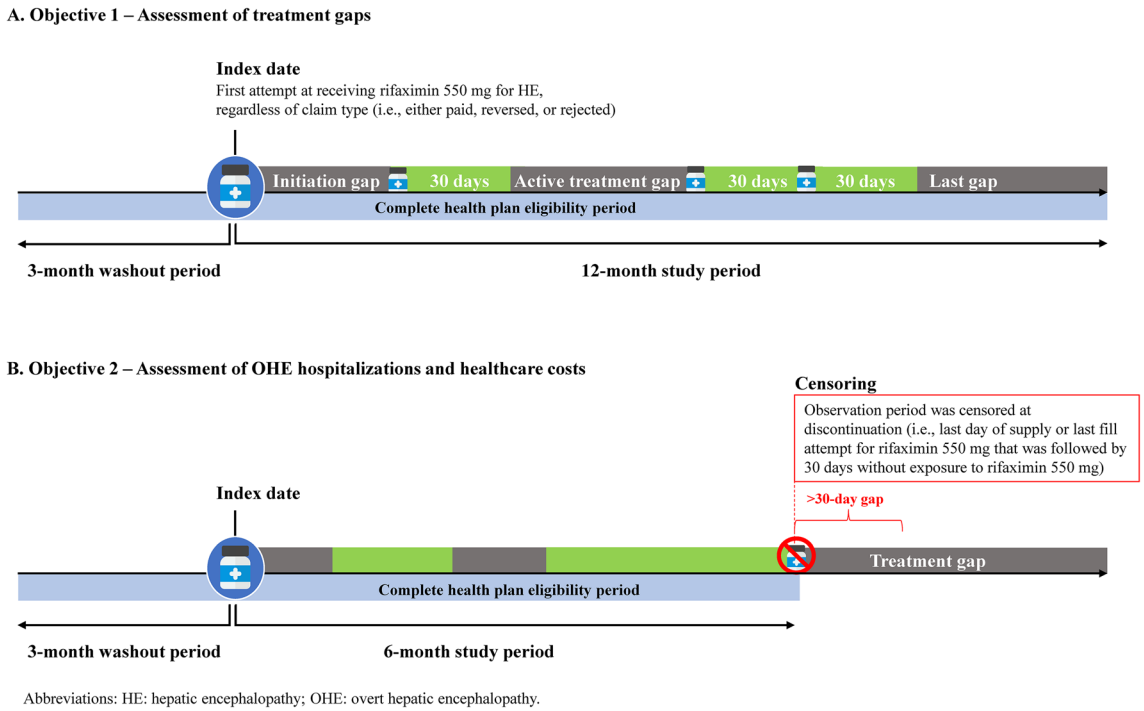


Fig. 1 Study designs

used to assess patient baseline characteristics. The study period was defined as the 12-month (Objective 1) and 6-month (Objective 2) period following the index date.

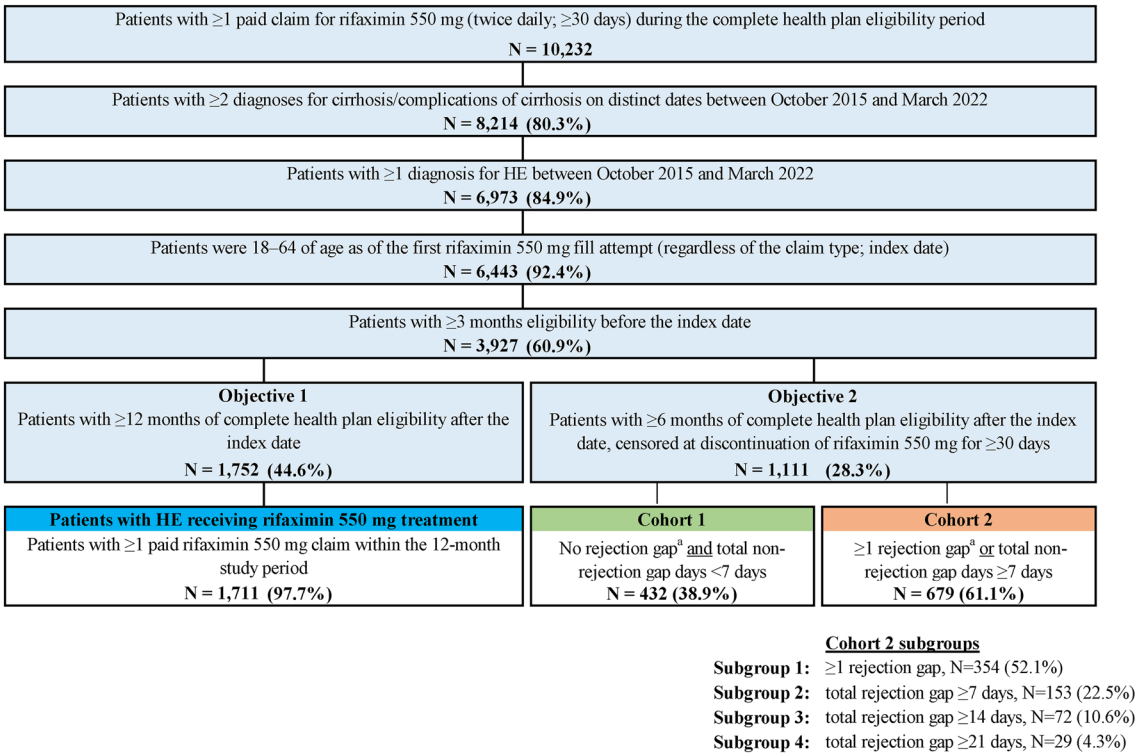
Sample Selection

The sample selection flowchart is presented in Fig. 2. Patients were included if they met the following criteria: (1) had ≥ 1 paid claim for rifaximin for HE (twice daily, 30-day supply; based on national drug codes: 65649–0303-02 and 65649-303-03) during the complete health plan eligibility period; (2) had ≥ 2 diagnoses for cirrhosis or complications of cirrhosis on distinct dates during the data span (see Supplementary Table S1 for diagnosis codes); (3) had ≥ 1 diagnosis for HE (based on the ICD-10-CM General Equivalence Mapping [GEM; K72.01, K72.11, K72.90, K72.91, K70.41, and K71.11]) during the data span; and (4) were aged 18–64 years as of the index date. For Objective 1, patients were required to have continuous health plan enrollment during the 3-month washout and the 12-month study periods. For Objective 2, patients were required to have continuous health plan enrollment during the 3-month washout and the 6-month study periods, while the observation period was censored at discontinuation, defined as > 30 consecutive days without rifaximin access or fill attempts (Fig. 1).

Measures and Outcomes

Objective 1

Treatment gaps (i.e., periods without rifaximin access) were assessed during the 12-month study period and identified based on the service dates of adjudicated claims (paid, rejected, or reversed) and the number of days of supply of each prescription fill. Adjustments were made to move forward overlapping days of supply to the first day that the patient would not have medications from the previous prescription fill, under the assumption that patients



Abbreviation: HE: hepatic encephalopathy.
[a]Rejection gaps were defined as treatment gaps that resulted from a prescription claim rejection for rifaximin 550 mg.

Fig. 2 Sample selection flowchart

would finish the current prescription fill before starting the next refill.

Treatment gaps were classified into: (1) initiation gaps, defined as the period without rifaximin access that spanned from the date of the first fill attempt at receiving rifaximin (i.e., the index date) until the date of the first paid claim for rifaximin; (2) active treatment gaps, defined as the period without rifaximin access that spanned from the last day of supply until the date of the next paid claim for rifaximin; and (3) last gaps or gaps at the end of the study period, defined as the period without rifaximin access that spanned from the last day of supply of the prior period with rifaximin until the end of the 12-month study period. Definitions of the types of treatment gaps are visualized in Fig. 1A. Treatment gaps were further classified as rejection gaps if they followed a prescription claim rejection for rifaximin. The reasons for prescription claim rejections were reported and may include drug not on formulary, prior authorization required (e.g., incomplete submission, medical necessity not demonstrated), plan limitations exceeded, product/service not covered, or refill too soon.

Adherence to rifaximin over the first 6 months and the first year from the index date was measured using medication possession ratio (MPR), defined as the total days of supply of rifaximin truncated at the end of the period divided by the number of days during the period (i.e., 180 or 365 days), after adjustment for overlapping days of supply.

Objective 2

The impact of treatment gaps on the risk and the number of OHE hospitalizations and total healthcare costs (i.e., medical and pharmacy costs) was assessed over the 6-month study period following the index date, among patients

with continuous health plan enrollment and without discontinuation of rifaximin access or fill attempts (regardless of claim status) during that period. The 6-month study period was selected to ensure a similar level of disease severity across the sample under the assumption that patient disease severity is most similar within this period from the initial attempt at receiving rifaximin [19]. The number of days of treatment gap overlapping with lactulose use, estimated based on the total number of days of supply of lactulose overlapping with the rifaximin treatment gaps, were also assessed. OHE hospitalizations were defined as an inpatient stay with a diagnosis code for HE or ICD-10-CM code G93.40 (encephalopathy, unspecified), G93.41 (metabolic encephalopathy), or G93.49 (other encephalopathy). Number of OHE hospitalizations and cost outcomes were reported per-patient-per-month (PPPM). Cost outcomes were measured from a payer's perspective (i.e., expenses covered by the insurance plan) and inflated to 2022 USD based on the data span using the Consumer Price Index.

Cohorts and Subgroups

For Objective 2, patients were classified into two cohorts: Cohort 1 included patients who did not have a rejection gap and had a total of < 7 days of non-rejection gaps in the 6-month study period; and Cohort 2 included patients who had ≥ 1 rejection gap or had a total of ≥ 7 days of non-rejection gaps in the same period. Patients in Cohort 2 were further classified into four non-mutually exclusive subgroups based on characteristics of rejection gaps: subgroup 1 included patients with ≥ 1 rejection gap; and subgroups 2, 3, and 4 included patients who had a total of ≥ 7, ≥ 14, and ≥ 21 days of rejection gaps, respectively (Fig. 2).

Statistical Analyses

Baseline patient characteristics and treatment gap characteristics were summarized descriptively using means, standard deviations (SD), medians, and interquartile ranges (IQR) for continuous variables, and counts and percentages for categorical variables. Standardized differences were calculated to assess the balance of baseline characteristics between the cohorts; a value of < 0.1 is considered as negligible imbalance [20].

OHE hospitalization and cost outcomes were compared between Cohort 1 and Cohort 2 as well as between Cohort 1 and each of the Cohort 2 subgroups. Generalized linear regression models (GLM) with binomial distribution and a logit link function with robust standard errors were used to estimate odds ratios (OR) of experiencing an OHE hospitalization. GLM with a negative binomial distribution and log link function with robust standard errors was used to estimate incidence rate ratios (IRR) of OHE hospitalizations. GLM with a gamma distribution and log link function with robust standard errors was used to compare total healthcare costs. All models were adjusted for demographics (i.e., age, sex, region, and insurance type), baseline cirrhosis-related procedures (i.e., dialysis, endoscopy/banding, transjugular intrahepatic portosystemic shunt, and paracentesis) [10], and baseline HE-related comorbidities (i.e., portal hypertension, ascites, spontaneous bacterial peritonitis, varices, hepatorenal syndrome, nonalcoholic steatohepatitis).

All analyses were conducted using Statistical Analysis System (SAS) Enterprise Guide, Version 7.1 (SAS, Cary, NC, USA).

RESULTS

Objective 1: Treatment Gaps

A total of 1711 eligible patients were included in the assessment of treatment gaps. During the first 12 months from initial attempt at receiving rifaximin for HE, the median (IQR) MPR of rifaximin was 59.5% (24.9–89.6%), and, during the first 6 months, it was 71.1% (35.6–95.0%). Patients attempted to access rifaximin for a median (IQR) of 8.0 (4.0–13.0) times, of which 6.0 (3.0–10.0) claims were paid, 1.0 (0–2.0) claims were rejected, and 0 (0–1.0) claim was reversed. Treatment gaps were observed in 94.7% of patients, with a median (IQR) of 3.0 (1.0–4.0) gaps per patient and a total duration of

147.0 (38.0–274.0) days, ranging between 1 and 363 days. More specifically, 34.8% of patients had an initiation gap [median (IQR) duration: 7.0 (2.0–29.0) days], 72.0% had an active treatment gap [median (IQR) duration: 7.0 (2.0–24.0) days per gap], and 52.5% had a gap at the end of the study period [median (IQR) duration: 198.0 (59.0–303.0) days].

Of all treatment gaps, 20.4% were due to a prescription claim rejection (Supplementary Table S2), which was observed for 77.7% of initiation gaps [common reasons for rejection included prior authorization required (61.8%), drug not on formulary (6.9%), and product/service not covered (6.3%)]; 14.8% of active treatment gaps [common reasons for rejection included plan limitation exceeded (33.7%), refill too soon (20.3%), and prior authorization required (13.8%)]; and 6.8% of last gaps [common reasons for rejection included plan limitations exceeded (31.1%), refill too soon (18.0%), and prior authorization required (11.5%)].

Objective 2: Impact of Treatment Gaps on OHE Hospitalizations and Costs

Cohort Characteristics

A total of 1111 eligible patients were included in the assessment of OHE hospitalization and cost outcomes. There were 432 patients (38.9%) in Cohort 1 and 679 patients (61.1%) in Cohort 2. Among Cohort 2, the number of patients in subgroups 1 to 4 was 354, 153, 72, and 29, respectively.

Cohort characteristics are presented in Table 1. On the index date, Cohort 1 had a mean age of 56.3 years and 38.4% were female; for Cohort 2, mean age was 54.8 years and 42.4% were female. In both cohorts, patients' insurance types included preferred provider organization (Cohort 1: 82.2%, Cohort 2: 74.2%), health maintenance organization (Cohort 1: 12.5%, Cohort 2: 18.7%), and point of service (Cohort 1: 3.5%, Cohort 2: 5.2%).

During the 3 months pre-index, clinical characteristics were similar between the two cohorts (Table 1). Most patients were seen by gastroenterologists (Cohort 1: 72.2%, Cohort 2: 71.4%); common HE-related comorbidities included portal hypertension (Cohort 1: 79.6%, Cohort 2: 78.9%) and ascites (Cohort 1: 60.0%, Cohort 2: 59.8%); and mean Charlson comorbidity index score was similar between the two cohorts (Cohort 1: 4.4, Cohort 2: 4.5).

During the 6-month study period, the median (IQR) duration of rifaximin treatment gaps in Cohort 1 was 0.0 (0.0–2.0) days, of which 0.0 (0.0–0.0) days overlapped with lactulose use, and the median (IQR) duration of rifaximin treatment gaps in Cohort 2 was 19.0 (10.0–29.0) days, of which 6.0 (0.0–19.0) days overlapped with lactulose use.

OHE Hospitalizations

Overall, 12.3% of patients in Cohort 1 and 17.1% of patients in Cohort 2 had an OHE hospitalization during the 6-month study period. After adjustment, compared with Cohort 1, Cohort 2 was 55% more likely to have an OHE hospitalization during this period (adjusted OR 1.55; $p < 0.05$). Relative to Cohort 1, adjusted OR for an OHE hospitalization in subgroup 1 was 1.57 ($p < 0.05$) and in subgroups 2 to 4 who had increasing number of days of rejection gaps was 1.94 (1.12–3.35; $p < 0.05$), 2.50 (1.21–5.17; $p < 0.05$), and 2.47 (0.77–7.94; $p = 0.13$), respectively (Fig. 3).

The incidence rate of OHE hospitalizations PPPM was 0.18 for Cohort 1 and 0.26 for Cohort 2. After adjustment, compared with Cohort 1, Cohort 2 had 1.55 times the rate of OHE hospitalizations PPPM (adjusted IRR 1.55; $p < 0.05$). Relative to Cohort 1, adjusted IRR of OHE hospitalizations for subgroups 1–4 was 1.53, 2.07, 2.33, and 3.19, respectively (all $p < 0.05$; Fig. 4).

Total Healthcare Costs

The total healthcare costs PPPM were $9864 in Cohort 1 and $11,361 in Cohort 2. After adjustment, compared with Cohort 1, Cohort 2 incurred $1579 higher total healthcare costs PPPM (adjusted cost difference: $1579 for total costs; $2556 for medical costs; – $565 for pharmacy costs; all $p < 0.05$). In the subgroups, adjusted cost difference PPPM relative to Cohort

Table 1 Cohort characteristics

Characteristics[a]	Cohort 1 (no rejection gap, total non-rejection gap days ≤ 7 days)[b] *n* = 432	Cohort 2 (≥ 1 rejection gap or total non-rejection gap days > 7 days)[b] *n* = 679	Standardized difference[c]
Demographics			
Age (years), mean ± SD [median]	56.3 ± 6.8 [58.0]	54.8 ± 7.3 [56.0]	0.22
Sex, *n* (%)			
Male	266 (61.6)	391 (57.6)	0.08
Female	166 (38.4)	288 (42.4)	0.08
Region, *n* (%)			
South	231 (53.5)	391 (57.6)	0.08
Midwest	96 (22.2)	137 (20.2)	0.05
Northeast	73 (16.9)	91 (13.4)	0.10
West	32 (7.4)	60 (8.8)	0.05
Type of insurance, *n* (%)			
Preferred provider organization	355 (82.2)	504 (74.2)	0.19
Health maintenance organization	54 (12.5)	127 (18.7)	0.17
Point of service	15 (3.5)	35 (5.2)	0.08
Consumer directed health care	< 11 (< 11/432)	< 11 (< 11/679)	–
Indemnity/traditional	< 11 (< 11/432)	< 11 (< 11/679)	–
Health savings account	< 11 (< 11/432)	< 11 (< 11/679)	–
Clinical characteristics			
Baseline gastroenterology consult[d], *n* (%)	312 (72.2)	485 (71.4)	0.02
Baseline cirrhosis-related procedures[e,f]			
Paracentesis	127 (29.4)	182 (26.8)	0.06
Endoscopy/banding	50 (11.6)	78 (11.5)	0.00
TIPS	< 11 (< 11/432)	20 (2.9)	–
Dialysis	< 11 (< 11/432)	< 11 (< 11/679)	–
Baseline HE-related comorbidities[e], *n* (%)			
Portal hypertension (includes varices, ascites, and TIPS)	344 (79.6)	536 (78.9)	0.02
Ascites	259 (60.0)	406 (59.8)	0.00
Varices	196 (45.4)	302 (44.5)	0.02
Without bleeding	146 (33.8)	213 (31.4)	0.05

Table 1 continued

Characteristics[a]	Cohort 1 (no rejection gap, total non-rejection gap days ≤ 7 days)[b] *n* = 432	Cohort 2 (≥ 1 rejection gap or total non-rejection gap days > 7 days)[b] *n* = 679	Standardized difference[c]
With bleeding	50 (11.6)	89 (13.1)	0.05
Nonalcoholic steatohepatitis	87 (20.1)	122 (18.0)	0.06
Spontaneous bacterial peritonitis	24 (5.6)	34 (5.0)	0.02
Hepatorenal syndrome	21 (4.9)	31 (4.6)	0.01
Potential factors associated with HE			
CirCom score	**0.9 ± 1.7 [0.0]**	**0.9 ± 1.7 [0.0]**	0.02
1–2, *n* (%)	20 (4.6)	36 (5.3)	0.03
3–4, *n* (%)	64 (14.8)	101 (14.9)	0.00
5–6, *n* (%)	< 11 (< 11/432)	< 11 (< 11/679)	–
CCI[g], mean ± SD [median]	**4.4 ± 2.0 [4.0]**	**4.5 ± 2.0 [4.0]**	0.03
0–2, *n* (%)	67 (15.5)	109 (16.1)	0.01
3–4, *n* (%)	208 (48.1)	302 (44.5)	0.07
≥ 5, *n* (%)	157 (36.3)	268 (39.5)	0.06
Frailty index[h], mean ± SD [median]	**17.3 ± 6 [16.3]**	**17.3 ± 5.5 [16.5]**	0.00
≤ 10%, *n* (%)	21 (4.9)	32 (4.7)	0.01
11%–30%, *n* (%)	397 (91.9)	630 (92.8)	0.03
31%–50%, *n* (%)	14 (3.2)	17 (2.5)	0.04
> 51%, *n* (%)	< 11 (< 11/432)	< 11 (< 11/679)	–
Selected comorbidities[e,i], *n* (%)			
Unspecified liver cirrhosis	342 (79.2)	519 (76.4)	0.07
Alcohol use	219 (50.7)	376 (55.4)	0.09
Alcoholic cirrhosis	209 (48.4)	347 (51.1)	0.05
Dehydration/electrolyte imbalance	180 (41.7)	309 (45.5)	0.08
Thrombocytopenia	167 (38.7)	271 (39.9)	0.03

CCI Charlson comorbidity index, *CirCom* Cirrhosis Comorbidity index, *CPT* Current Procedural Terminology, *DRG* diagnosis-related group, *HE* hepatic encephalopathy, *ICD-10-PCS* International Classification of Diseases, 10th Revision, Procedure Coding System, *SD* standard deviation, *TIPS* transjugular intrahepatic portosystemic shunt

[a]Demographics were reported at index date. Clinical characteristics were assessed for the 3-month baseline periods. Cell sizes of fewer than 11 patients are as presented as < 11, with the corresponding percentage as < 11/total sample size %, per vendor requirement

[b]Rejection gaps were defined as treatment gaps that resulted from a prescription claim rejection for rifaximin 550 mg

Table 1 continued

[c] Standardized difference < 0.1 is considered as negligible imbalance

[d]Gastroenterology consult was identified using procedure group (143: gastroenterology services [non-surgical]) and provider type (275: gastroenterology)

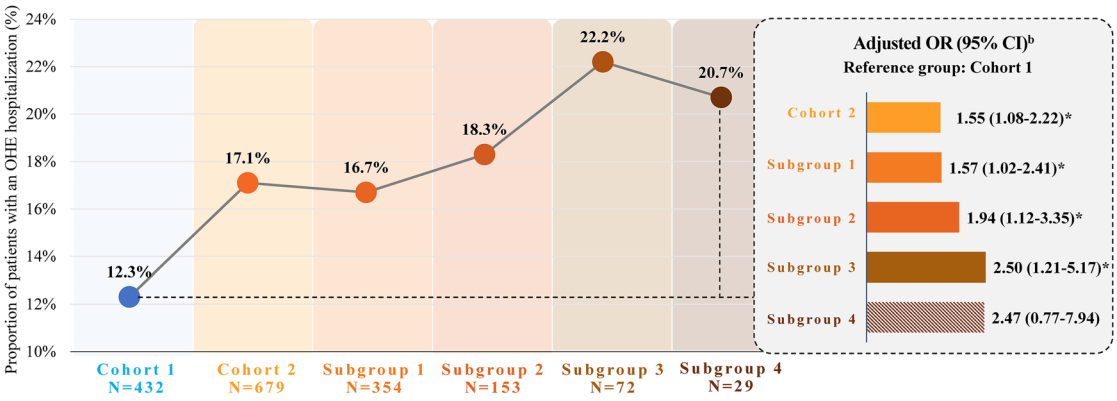
[e]Categories are not mutually exclusive

[f]Identified based on procedure and diagnosis codes—paracentesis: CPT 49082, 49083; endoscopy/banding: CPT 43244; TPS: ICD-10-PCS 06183J4, 06184J4, 06183JY, and DRG 405, 406, 407; dialysis: CPT 90935–90999

[g]Source: [23]

[h]Source: [24]

[i]Source: [25]



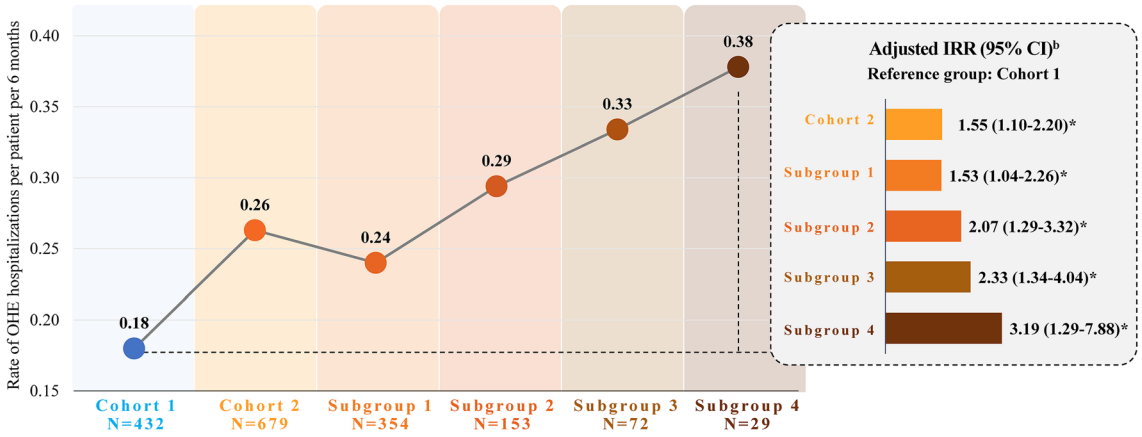
Abbreviations: CI: confidence interval; HE: hepatic encephalopathy; OHE: overt hepatic encephalopathy; OR: odds ratio.
*Indicates significant at the 5% level; gradient fill indicates non-significance.
[a]Cohort 1 included patients who did not have any rejection gap and had total <7 days of non-rejection gap in the first 6-month study period. Cohort 2 included patients who had ≥1 rejection gap or had total ≥7 days of non-rejection gap in the same period. Patients in Cohort 2 were further classified into four non–mutually exclusive subgroups based on characteristics of rejection gaps: subgroup 1 included patients with ≥1 rejection gap; and subgroups 2, 3, and 4 included patients who had total rejection gap of ≥7, ≥14, and ≥21 days, respectively.
[b]Adjusted for demographics, baseline cirrhosis-related procedures, and baseline HE-related comorbidities.

Fig. 3 Impact of treatment gaps on risk of OHE hospitalizations[a]

1 was $1994 ($p < 0.05$) for subgroup 1; $2146 ($p = 0.08$) for subgroup 2; $3395 ($p = 0.05$) for subgroup 3; and $3413 ($p = 0.19$) for subgroup 4 (Fig. 5; Supplementary Table S3).

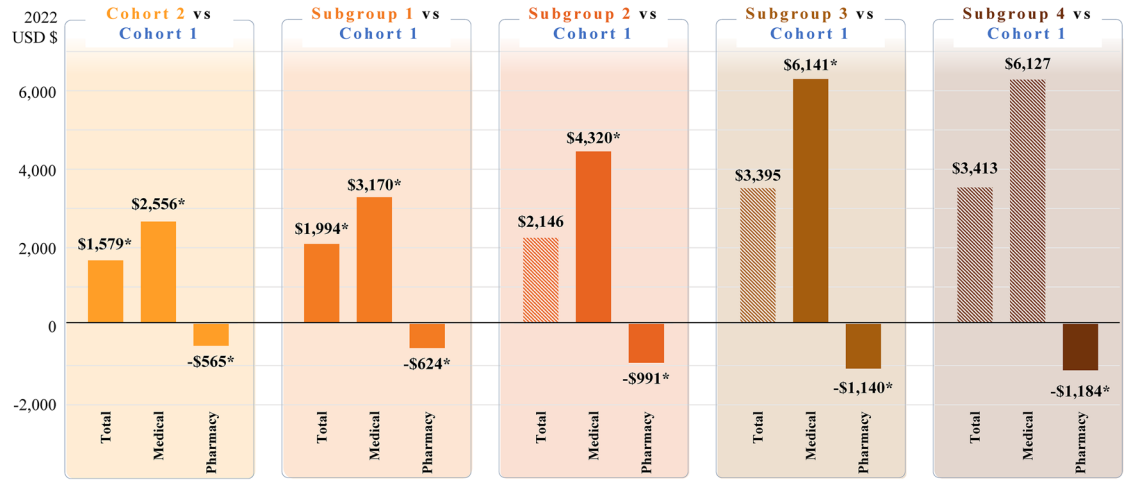
DISCUSSION

In this retrospective analysis among patients with HE receiving rifaximin, nearly 95% of patients were observed to experience treatment gaps within 12 months of their initial attempt at receiving rifaximin, leading to delays in rifaximin initiation for approximately one-third of the patients (34.8%) and gaps in exposure during active treatment for nearly three-quarters (72.0%). Over half (52.5%) of patients were no longer on rifaximin at the end of the 12-month study period. Consequently, adherence to rifaximin was relatively low, which is aligned with the observations in several prior real-world studies [11–13]. Prescription claim rejections were found to be responsible for one in five observed treatment gaps, suggesting that payer-based access barriers to rifaximin exist and are common. Furthermore, treatment gaps were associated with poorer OHE hospitalization and cost outcomes. Within the first 6 months from initial attempt at receiving rifaximin, patients with ≥ 1 rejection gap or with a total of ≥ 7 days of non-rejection gaps were 55% more likely to experience an OHE



Abbreviations: CI: confidence interval; HE: hepatic encephalopathy; IRR: incidence rate ratio; OHE: overt hepatic encephalopathy.
*Indicates significant at the 5% level.
[a]Cohort 1 included patients who did not have any rejection gap and had total <7 days of non-rejection gap in the first 6-month study period. Cohort 2 included patients who had ≥1 rejection gap or had total ≥7 days of non-rejection gap in the same period. Patients in Cohort 2 were further classified into four non–mutually exclusive subgroups based on characteristics of rejection gaps: subgroup 1 included patients with ≥1 rejection gap; and subgroups 2, 3, and 4 included patients who had total rejection gap of ≥7, ≥14, and ≥21 days, respectively.
[b]Adjusted for demographics, baseline cirrhosis-related procedures, and baseline HE-related comorbidities.

Fig. 4 Impact of treatment gaps on rate of OHE hospitalizations[a]



Abbreviations: HE: hepatic encephalopathy; OHE: overt hepatic encephalopathy; USD: United States Dollars.
*Indicates significant at the 5% level; gradient fill indicates non-significance.
[a]Cohort 1 included patients who did not have any rejection gap and had total <7 days of non-rejection gap in the first 6-month study period. Cohort 2 included patients who had ≥1 rejection gap or had total ≥7 days of non-rejection gap in the same period. Patients in Cohort 2 were further classified into four non–mutually exclusive subgroups based on characteristics of rejection gaps: subgroup 1 included patients with ≥1 rejection gap; and subgroups 2, 3, and 4 included patients who had total rejection gap of ≥7, ≥14, and ≥21 days, respectively.
[b]Cost differences per-patient-per-month were estimated using Cohort 1 as the reference group and adjusted for demographics, baseline cirrhosis-related procedures, and baseline HE-related comorbidities.

Fig. 5 Impact of treatment gaps on total healthcare costs[a,b]

hospitalization and incurred $1579 higher total healthcare costs PPPM compared with those with no rejection gap and a total of < 7 days of non-rejection gaps. These findings provide insights into the impact of treatment gaps and low adherence on the clinical and cost burden in HE.

Consistent with prior research among commercially insured patients with HE [4, 10], our findings demonstrate that increased frequency

and duration of rifaximin treatment gaps, indicative of lower overall adherence, are associated with elevated risk of hospitalizations and increased healthcare expenditures. For instance, a retrospective cohort study found that non-adherent patients (defined as PDC < 80%) had significantly higher risk of hospitalizations and longer length of stay and incurred $2340–$2891 (2019 USD) higher total healthcare costs per month than adherent patients [10]. It is notable that in the current study, much shorter treatment gaps were considered and found to negatively impact patient outcomes. For example, a PDC of < 80% over 6 months would translate to a total treatment gap of at least 36 days, while in the current study, any total gap longer than 7 days was considered. Another retrospective cohort study found that relative to patients with HE who received rifaximin with no gap following discharge, those who had a gap in receiving rifaximin of less than 30 days following the discharge had 31% increased risk of 30-day rehospitalization and 61% higher annual rate of hospitalization [4]. Analyses of subgroups by total gap duration in the current study showed that the hospitalization and cost burden trended proportionally higher with longer total duration of rejection gaps, suggesting that payer rejections could be directly attributable to poorer patient outcomes in HE. Together with results from the literature, the current findings suggest that ensuring prompt access to rifaximin and maintenance of an adherent treatment regimen by mitigating payer-based access barriers may reduce the risk of hospitalizations and healthcare costs in HE.

Understanding of reasons underlying treatment gaps may help identify modifiable factors to improve overall adherence to rifaximin. Using the LAAD database that contains lifecycle data of prescription claims, the current study was able to characterize treatment gaps and distinguish those that were consequences of prescription claim rejections by payers. Overall, prescription claim rejections accounted for 77.7% of initiation gaps, 14.8% of active treatment gaps, and 6.8% of last gaps experienced by patients. Further investigations into the reasons of rejected claims revealed that prior authorization requirements and plan limitations were common reasons for rejection-related treatment gaps. Aligning with the current observations, payer-based access barriers arising from utilization management strategies have been recognized to result in treatment delays and lower adherence [14–16, 21]. Among patients with HE receiving rifaximin, enrollment in high-deductible health plans and high out-of-pocket costs have also been shown to be associated with decreased adherence [11], suggesting that payer-related factors could have hindered patients with HE from receiving continuous treatment. Other clinical factors may also contribute to explain some of the observed treatment gaps, specifically for the last gaps, including the receipt of liver transplant and the potential for recompensation in some patients, such as those with decompensated alcohol-related cirrhosis following persistent alcohol abstinence [22].

Low adherence resulting from payer-based access barriers has been shown in the literature to negatively affect clinical and economic outcomes in many other therapeutic areas, such as diabetes, cardiovascular diseases, and psychiatric disorders [14]. While future studies investigating effects of utilization management strategies on health outcomes in HE are warranted, findings in the current study suggest that improving patient access to rifaximin by addressing payer-based access barriers associated with treatment gaps may have the potential to reduce the overall burden of HE.

Findings from this study should be considered with limitations. This study focused on commercially insured patients, and hence the results may not be generalizable to patients with HE in the US who had other types of health insurance. In-hospital administered medications were not visible within the claims database; therefore, any rifaximin that could have been received during a hospitalization was not considered. In addition, this study focused on on-label use of rifaximin for HE of 550 mg, and rifaximin at other doses (i.e., 200 mg) was not assessed. In the same vein, information on out-of-pocket purchases of HE medications (including rifaximin) was only partially available in claims data and was not assessed, which may have led to an underestimation of rifaximin usage. In addition, claims-based studies are subject to billing inaccuracies

and omissions in coded diagnosis, procedures, and pharmacy claims, as well as limited availability of clinical information (e.g., reasons for treatment gaps). Finally, owing to the retrospective nature of the analyses, causal relationships could not be drawn.

CONCLUSIONS

Commercially insured patients with HE often experience access barriers to rifaximin resulting from prescription claim rejections, which frequently lead to delays in rifaximin initiation and gaps in access during active treatment. These treatment gaps were associated with increased OHE hospitalizations and healthcare costs. Reducing payer-based barriers to treatment access may help improve patient outcomes and mitigate the economic burden of HE.

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Data Availability. The datasets generated and analyzed during the current study are not publicly available because they were used pursuant to a data use agreement. The data are available through requests made directly to IQVIA.

Declarations

Conflict of Interest. Arun Jesudian served as a consultant to Bausch Health US, LLC and received speaking fees from Salix Pharmaceuticals at the time this work was performed. Patrick Gagnon-Sanschagrin, Jessica Maitland, Kana Yokoji, and Annie Guérin are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Bausch Health US, LLC, which funded the development and conduct of this study and manuscript. Zeev Heimanson is an employee of Salix Pharmaceuticals. Aaron Samson is a Rutgers Institute for Pharmaceutical Industry Fellow at Bausch Health US, LLC. Olamide Olujohungbe is an employee of Bausch Health US, LLC. Brock Bumpass was an employee of Bausch Health US, LLC at the time the study was conducted and is currently an employee of Alnylam.

Ethical Approval. Data are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA); therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4).

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