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ORIGINAL ARTICLE

Prospective Multicenter Observational Study of Overt Hepatic Encephalopathy

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Abstract

Background Overt hepatic encephalopathy (OHE) is a frequent complication of decompensated cirrhosis.

Aims A multicenter prospective observational study was performed to assess the most commonly recorded presenting manifestations of OHE and its associated health-care burden.

Methods Qualifying patients must have experienced ≥1 OHE episode within 30 days of enrollment (qualifying OHE) and were followed for recurrence (on-study OHE).

Results Two hundred and sixty-five patients were enrolled at 30 sites and followed for up to 9 months (mean 72 days). Seventy-two patients experienced 122 on-study episodes; with 72, 23, and 13 having ≥1, ≥2, or ≥3 on-study episodes with median days to occurrence of the 1st, 2nd, and 3rd episode of 34, 19, and 11, respectively. The most frequently recorded OHE manifestations included confusion (78 %), change in mental status (57 %), disorientation (48 %), lethargy (46 %), and asterixis (45 %). West Haven grade was used inconsistently and recorded for only 28 % of episodes. Most qualifying and on-study episodes occurred on rifaximin (60 and 82 %, respectively) and were associated with hospitalization (68 and 85 %, respectively). Twenty-three patients experienced ≥2 on-study episodes within 2 months of enrollment on average (median 45 days) and accounted for 60 % of on-study episodes.

Conclusions In this prospective study, OHE's most commonly recorded presenting manifestations included confusion, altered mental status, disorientation, lethargy, and asterixis. As reflected by frequent recurrence and hospitalizations, OHE, particularly the approximately 10 % of "high-resource-utilizing" patients with frequent recurrence, continues to pose a major unmet medical need and health-care burden despite the use of rifaximin.

Keywords Altered mental status · Cirrhosis · Chronic liver disease · Clinical trial · Health-care burden · Liver failure · Pharmacoeconomics

Abbreviations

AASLD	American Association for the Study of Liver Diseases
EASL	European Association for the Study of the Liver
HE	Hepatic encephalopathy
ISHEN	International Society of Hepatic Encephalopathy and Nitrogen Metabolism
OHE	Overt HE
WH	West Haven

Introduction

Hepatic encephalopathy (HE) comprises a spectrum of neuropsychiatric abnormalities associated with liver dysfunction ranging from mild to severe [1, 2]. Although the

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West Haven (WH) criteria have long been used for grading HE severity [2, 3], they were not developed in accordance with the FDA guidelines and do not meet the criteria of a well-defined and reliable instrument for measuring outcomes in clinical trials and include characteristics which are imprecise and/or not operationally defined. Moreover, it is unclear whether or how the WH criteria are actually used in clinical practice to document HE episodes. These factors collectively represent major impediments to defining clinical trial populations and efficacy endpoints.

In its position paper, the International Society of Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) categorized HE into covert and overt. Covert HE, previously called "minimal HE," does not include asterixis and its diagnosis requires specialized standardized testing. Overt HE (OHE), defined by ISHEN as WH Grade 2 or greater, involves a change in mental status and the presence of asterixis [3]. While the ISHEN position paper and 2014 joint European-US Practice Guidelines [4] represent major contributions, there is little to no prospectively collected information about what clinical signs and symptoms of HE are actually meaningful to clinicians, as reflected in patient records. Indeed, the Practice Guidelines pertaining to HE emphasize the "limited amount of high-quality evidence to extract from the existing literature" [4].

Several reports suggest that the OHE-related health-care burden is substantial [5, 6], but there is little information regarding the frequency of OHE recurrence or of OHE-related hospitalizations subsequent to the 2010 US approval of rifaximin [7].

This prospective observational study was undertaken to address the following questions:

1. What are the most commonly recorded manifestations of OHE?
2. Are the WH criteria utilized by clinicians and does categorization of HE conform to the ISHEN recommendations?
3. How widely is rifaximin used in this population?
4. Does there continue to be a substantial health-care burden as reflected by OHE recurrence and OHE-associated hospitalizations?

Methods

One hundred seventy-six centers responded to a feasibility survey assessing their experience with OHE, and 120 of those were selected for participation in the prospective, observational study, Protocol HPN-100-022. Thirty-five sites were activated of which 30 enrolled patients. Upon the acquisition of Hyperion Therapeutics, Inc. by Horizon Pharma, Inc. in May of 2015, a decision was made to focus research efforts on the urea cycle disorder program and to discontinue the development of glycerol phenylbutyrate for HE, at which time Protocol HPN-100-022 was terminated. The study was approved by the local IRB/EC at each participating site, and all qualifying patients or their legal representatives were consented to allow for extraction of information from their medical records prior to participation. There were no specific study visits, or interventions; rather, patients were "observed" as part of their routine standard of care.

The study enrolled adult patients with a clinical diagnosis of cirrhosis of any cause based on biopsy, imaging (e.g., ultrasound, computed tomography), or other criteria. Qualifying subjects must have experienced an episode of OHE within 30 days of enrollment (qualifying HE episode) and either the subject or their legal representative needed to be able to provide written informed consent. Exclusion criteria included use of long-acting benzodiazepines or barbiturates, anticipated transplantation within 6 months, or any other reason that the investigator felt would preclude participation.

Once enrolled, patients were followed for OHE recurrence (on-study HE). Clinical manifestations of both qualifying and on-study HE episodes (e.g., disorientation, lethargy, somnolence, coma, asterixis, and WH grade), as recorded in the patients' charts, were captured on case report forms. Additional data recorded included patient demographics, rifaximin use, whether the episode was associated with hospitalization (i.e., OHE was among the admitting diagnoses), and the source of information used to make the determination of OHE episode occurrence.

Descriptive statistical analyses (i.e., number of observations, mean, standard deviation, median, minimum, maximum, and frequency counts for continuous variables; number and percent for categorical variables) were prespecified for OHE diagnostic criteria (clinical signs and symptoms such as disorientation, lethargy, somnolence, coma; WH grade), as well as for rifaximin use and hospitalizations.

Results

Disposition and Baseline Characteristics

Ninety-three percent of screened patients (265 of 284) qualified for the study and were enrolled between September 2014 and May 2015 at 30 sites (Table 1). At the time of study termination on June 26, 2015, 85 % of patients were still in the study: 32 had died and 9 patients had undergone liver transplantation. Patients were followed on-study for a mean (SD) of 72 (45) days.

Table 1 Baseline patient characteristics

	All enrolled patients $N = 265$	Patients with no on-study OHE episodes $N = 193$	Patients with ≥1 on-study OHE episodes $N = 72$	Patients with ≥2 on-study OHE episodes $N = 23$
Age (years)				
Mean	59.9	59.75	60.1	60.0
Median	61	60	62	63
Min, max	22, 85	22, 85	41, 79	43, 72
Sex, *n* (%)				
Female	104 (39)	79 (40)	25 (35)	8(35)
Male	161 (61)	114 (59)	47 (65)	15(65)
Race, *n* (%)				
Asian	3 (1)	3 (1)	0	0
Black or African American	21 (8)	14 (7)	7 (10)	2(9)
White	229 (86)	166 (86)	63 (88)	21(91)
Other	11 (4)	9 (5)	2 (3)	0
Not collected due to local regulations	1 (<1)	1 (<1)	0	0
Country, *n* (%)				
United States	251 (95)	183 (94)	68 (94)	23 (100)
Great Britain	12 (5)	9 (5)	3 (4)	0
Canada	1 (<1)	0	1 (1)	0
Taiwan	1 (<1)	1 (<1)	0	0
Rifaximin use at baseline, *n* (%)				
Yes	159 (60)	109 (56)	50 (69)	21 (91)
No	103 (39)	81 (42)	22 (31)	2 (9)
Not assessed	3 (1)	3 (1)	0	0
Hospitalization associated with qualifying OHE episode *n* (%)				
Yes	180 (68)	125 (65)	55 (76)	17 (74)
No	85 (32)	68 (35)	17 (24)	6 (26)
Time since OHE diagnosis (years)[a]				
Mean	1.32	1.14	1.88	2.89
Median	0.62	0.60	0.66	0.60
Min, max	0.03, 10.06	0.03, 7.75	0.08, 9.56	0.39, 9.56

[a] Since only the year of diagnosis was collected in the case report forms, the time since diagnosis was estimated for all participants assuming the diagnosis was made mid-year

Diagnostic Features of HE Episodes

Three hundred eighty-seven OHE episodes (265 qualifying and 122 on-study) were recorded. Physicians recorded an average (SD) of 5.0 (2.75) symptoms (range 1–17) for the qualifying HE episodes and 4.8 (2.57) symptoms (range 1–12) for the on-study HE episodes. WH grade was recorded in 28 % of all episodes (33.2 and 6.3 % of qualifying and on-study OHE episodes, respectively). Of the top 6 enrolling sites, which collectively enrolled nearly half of all study participants, the mean percentage of OHE episodes for which WH grading was available was 24 % and ranged from 3 to 75 %; only one of these high-enrolling sites recorded the WH grade in over 40 % of patients. The specific clinical manifestations records for the OHE episodes, some of which were categorized as WH grade 1, are summarized in Table 2.

The five most frequently recorded clinical manifestations included confusion (78 %), change in mental status (57 %), disorientation (48 %), lethargy (46 %), and asterixis (45 %). Other symptoms recorded in >10 % of HE episodes are summarized in Table 3. Physicians also identified 120 symptoms that were recorded verbatim in the e-CRF in the "other" category; these were generally assessments of changes in mental status, fatigue, changes in personality, non-specific GI symptoms as well as speech, memory, and sleep-related symptoms.

Most OHE episodes were identified by medical personnel, either the patient's own physician or another clinician, while 25 and 8 % of the qualifying (25 %) and on-

Table 2 The most frequently recorded clinical manifestations of HE associated with a West Haven (WH) grade

Covert HE		Overt HE					
WH 1 $N = 39$		WH 2 $N = 46$		WH 3 $N = 19$		WH 4 $N = 4$	
	n (%)		n (%)		n (%)		n (%)
Lethargy	18 (46)	Confusion	33 (72)	Confusion	17 (89)	Coma	4 (100)
Confusion	17 (44)	Asterixis	27 (59)	Disorientation to Time	14 (74)	Change in mental state	4 (100)
Difficulty in concentration	17 (44)	Lethargy	25 (54)	Disorientation to time, place, person	14 (74)	Lethargy	3 (75)
Forgetfulness	17 (44)	Change in mental status	22 (48)	Change in mental status	13 (68)	Somnolence	3 (75)
Asterixis	15 (38)	Disorientation to time, place, person	21 (46)	Disorientation to place	10 (53)	Confusion	3 (75)
Changes in mental status	12 (31)	Changes in sleep pattern	17 (37)	Disorientation to person	8 (42)	Disorientation to time	2 (50)

Table 3 Diagnostic features of overt HE (OHE) episodes

Symptom	All OHE $N = 387$ n (%)	Qualifying OHE $N = 265$ n (%)	On-study OHE $N = 122$ n (%)
Confusion	300 (77.5)	203 (76.6)	97 (79.5)
Changes in mental status	221 (57.1)	142 (53.6)	79 (64.8)
Disorientation to time, place, or person	187 (48.3)	126 (47.5)	61 (50)
Lethargy	179 (46.3)	125 (47.2)	54 (44.3)
Asterixis	175 (45.2)	127 (47.9)	48 (39.3)
Disorientation to time	158 (40.8)	108 (40.8)	50 (41)
Disorientation to place	126 (32.6)	84 (31.7)	42 (34.4)
Somnolence	110 (28.4)	75 (28.3)	35 (28.7)
Forgetfulness	87 (22.5)	70 (26.4)	17 (13.9)
Changes in sleep pattern	83 (21.5)	63 (23.8)	20 (16.4)
Difficulty in concentration	78 (20.2)	66 (24.9)	12 (9.8)
Disorientation to person	73 (18.9)	47 (17.7)	26 (21.3)
Changes in activities of daily life	51 (13.2)	41 (15.5)	10 (8.2)
Slurred speech	42 (10.9)	34 (12.8)	8 (6.6)
Changes in personality	41 (10.6)	28 (10.6)	13 (10.7)
Irritability	35 (9.0)	23 (8.7)	12 (9.8)
Inappropriate behavior	33 (8.5)	25 (9.4)	8 (6.6)
Coma	7 (1.8)	4 (1.5)	3 (2.5)

study episodes were identified solely based on caregiver input (Table 4).

Rifaximin Use

Sixty percent of patients were on rifaximin at the time of study entry and 67 % of all recorded OHE episodes occurred while patients were on rifaximin. Of the 72 patients who had at least one on-study HE episode, 57 (79 %) were on rifaximin at the time of the episode (Fig. 1, bottom panel). In this group of patients, the median time to the first on-study OHE for patients on rifaximin at baseline was 21 days compared to 37 days in those not on rifaximin; 21 patients on rifaximin had a second event compared to 2 patients not on rifaximin at baseline.

OHE Recurrence and Hospitalizations as a Reflection of Health-Care Burden

Twenty-seven percent of patients experienced at least one on-study OHE episode, with a mean (SD) of 0.46 (1.05) on-study OHE episodes per patient (Fig. 1, top panel).

Table 4 Primary information sources used for identification of overt HE (OHE) episodes

Source	All OHE episodes $N = 387$ n (%)	Qualifying OHE episodes $N = 265$ n (%)	On-study OHE episodes $N = 122$ n (%)
Observed by patient's physician	132 (34)	98 (37)	34 (28)
Observed by medical professional other than the patient's physician	180 (45)	102 (39)	78 (64)
Based on caregiver input	75 (19)	65 (25)	10 (9)

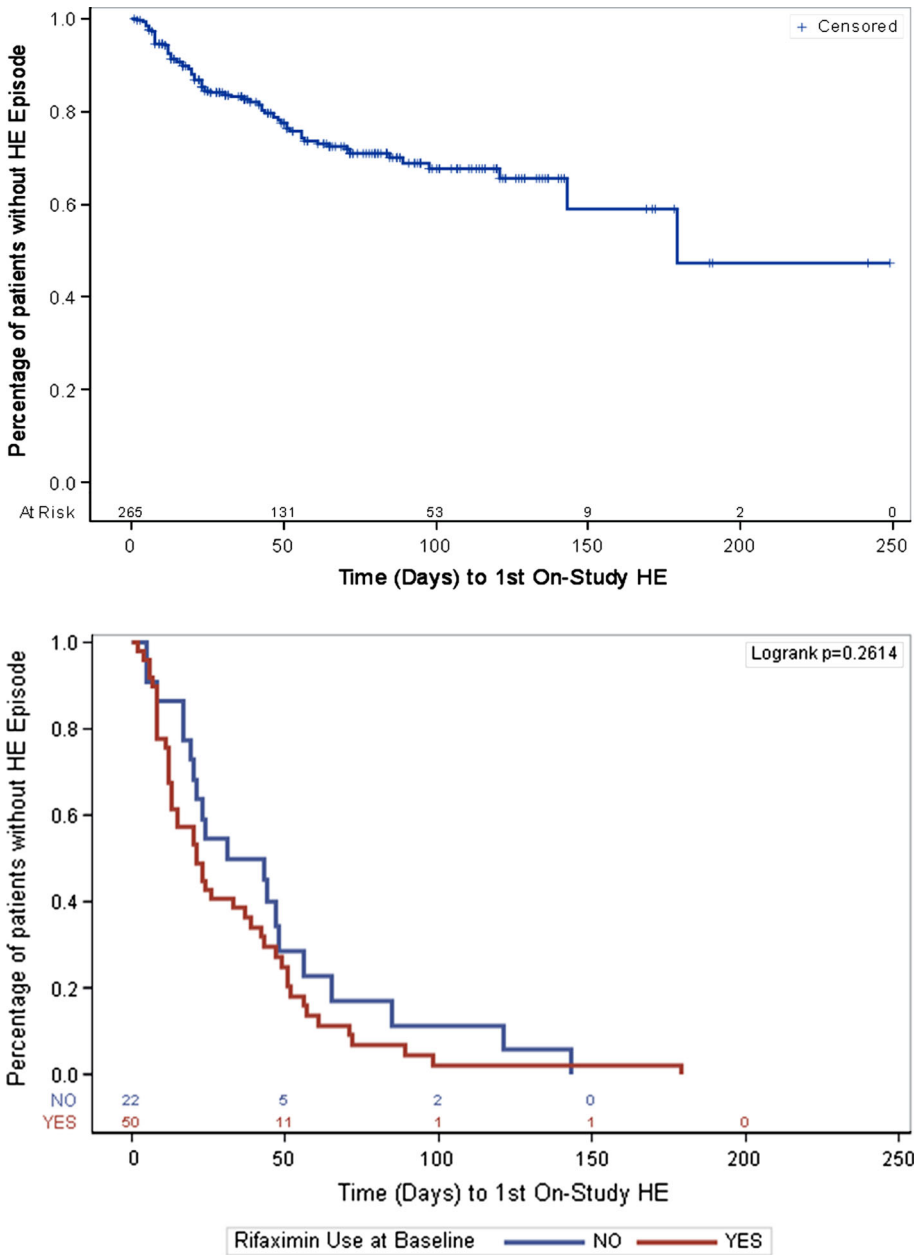

Fig. 1 Time to the first on-study OHE episode for all patients (*top*) and time to the first OHE episode for patients with an on-study episode by rifaximin use at baseline (*bottom*). The *top panel* depicts time to the first on-study OHE episode among all enrolled patients ($N = 265$). The time is calculated from the time of enrollment to the first on-study episode. The *bottom panel* depicts time to the first on-study event for 72 patients who experienced an on-study event, based on baseline rifaximin use

Among the 87 patients who were followed for at least 3 months, approximately one-third (32 %) experienced at least one on-study OHE episode with a mean (SD) of 0.8 (1.5) per patient. As a corollary, among patients with at least one on-study HE episode, over 75 % of the first on-study episodes occurred within 3 months. The median time from enrollment to the first on-study OHE episode ($N = 72$) was 34 days (Fig. 1), and the time between OHE episodes decreased to 19 days ($N = 23$) and 11 days ($N = 13$) for the second and third on-study episodes, respectively. Of 387 HE episodes recorded, 284 (73 %) were associated with hospitalization, including 68 % of the qualifying and 85 % of the on-study episodes.

High-Resource Utilizers

OHE recurrence and related hospitalizations were not evenly distributed among patients. Rather, 23 of 265 patients (9 %) experienced ≥2 on-study OHE episodes and these 23 patients accounted for 73 (60 %) of the 122 on-study OHE episodes, 88 % of which resulted in hospitalization. The baseline characteristics of these 23 patients were similar to the overall population [(mean (SD) age of 60 (8) years, 65 % male, median time since OHE diagnosis of 0.6 years; Table 1], although rifaximin use tended to be more frequent (91 vs. 60 %; Table 1) than in the overall population.

Discussion

This observational study was initiated as a lead-in to an anticipated phase 3 pivotal interventional study of patients with OHE [8] and represents one of largest prospectively collected datasets focused specifically on real-world documentation of HE intended to inform the design of future clinical trials.

The criteria used by clinicians for diagnosis of OHE, as noted in patient records, were generally compatible with professional guidelines published by ISHEN. For example, similar to ISHEN guidelines which emphasize altered mental status as the critical distinguishing feature of OHE, along with the presence of asterixis, the most frequent manifestations of overt HE as recorded by investigators included confusion (78 %), change in mental status (57 %) disorientation (48 %) as well as asterixis (45 %).

The WH grade was recorded in only 33 % of all OHE episodes and exhibited striking site to site variability (~3–75 %) among the top enrolling sites. Moreover, when it was applied, the WH grading was often inconsistent with current recommendations and in that some patients with evident clinical manifestations such as lethargy, which presumably reflects level of consciousness, were categorized as WH 1. These findings collectively illustrate that although the WH grading system has been in existence for decades, it is not widely, consistently, or always accurately applied.

These findings underscore the need for operational criteria to facilitate uniformity and agreement with respect to diagnoses in both clinical trials and practice that includes specific descriptors, similar in number to those used in clinical practice as identified in this study, pertaining, for example, to mental status and level of consciousness [9]. Moreover, the finding that a substantial fraction of OHE diagnoses (approximately one-fifth of all OHE episodes, both qualifying and on-study) were based primarily upon information from caregivers, demonstrate the potential utility of an instrument that would enable timely and standardized caregiver input [10].

The OHE-associated health-care burden as reflected by the 265 patients in this study is substantial. Approximately one-third of all patients followed for at least 3-months experienced OHE recurrence, and about three quarters of all OHE episodes were associated with hospitalization. Of interest, a subgroup (9 %) of severely affected patients experienced frequent OHE recurrence and accounted for a disproportionate share of all OHE episodes (73 of 122) and hospitalizations. These 23 severely affected patients, who from the standpoint of healthcare utilization might be considered "high-resource utilizers," accounted for 60 % of all on-study events and approximately one-quarter of all episodes recorded in the study. Apart from a slightly longer time since OHE diagnosis and more frequent use of rifaximin, the baseline demographics of these 23 patients did not differ from the study population as a whole. A recent report suggests that elevated fasting blood ammonia may be useful in identifying these patients at highest risk of OHE recurrence [11]. Further studies are required to determine whether there are useful clinical or biochemical markers of this subpopulation.

Finally, the OHE-associated health-care burden is substantial. Indeed, 67 % of all OHE episodes occurred while patients were receiving rifaximin, and 59 and 91 % of the first and second on-study OHE episodes, respectively, occurred in patients who were on rifaximin at baseline (Table 1). While the high frequency of rifaximin use in this study may reflect a selection bias in that the most severely affected patients are most likely to be prescribed rifaximin, the findings nonetheless underscore the persisting OHE-associated health-care burden despite the availability of rifaximin.

The major limitation of the present study is that because it was terminated early, enrollment was largely restricted to the USA and fewer patients (265 as compared with a target of up to 750) were enrolled. Nonetheless, the study is unique with respect to both its prospective non-

interventional design and, with a total of 387 OHE episodes captured, its scope. Also, because patients anticipated to undergo liver transplantation within 6 months were excluded, it is possible that the results may in fact underestimate the frequency of recurrence and OHE-related disease burden.

In summary, these findings demonstrate that despite best-available medical therapy, there remains an important unmet need for OHE therapy, in particular, for the group of patients who experience frequent OHE recurrence. Future studies will need to address this high-resource-utilizing subpopulation and be designed so as to enable consistent incorporation of caregiver input into a reproducible approach for OHE diagnosis and grading.

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Compliance with ethical standards

Conflict of interest R. Rowell, M. Santoro, A. Enriquez, M. Jurek, M. Mokhtarani, D.F. Coakley, B.F. Scharschmidt are/were employees of, or are consultants to, Horizon Pharma, (formerly Hyperion Therapeutics). C.S. Landis, M. Ghabril, V. Rustgi, A.M. DiBisceglie, B. Maliakkal, D.C. Rockey, J. Bajaj and J. Vierling were paid through their institutions for services as investigators in this study.

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