EXPLORE Part B: A Prospective, International, Long-term Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Symptoms

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Conclusions

- **For patients with AHP and recurrent attacks, including patients with relatively few attacks, the burden of disease is high, as evidenced by their having chronic symptoms between attacks and impaired QoL**

Introduction

- Acute hepatic porphyria (AHP) is a family of four rare genetic diseases caused by deficiency of enzymes that regulate hepatic heme biosynthesis[1–3]
  - Acute intermittent porphyria is the most common type; the other types are variegate porphyria, hereditary coproporphyria, and delta-aminolevulinic acid (ALA) dehydratase deficiency porphyria[1,4]
  - Depletion of the hepatic-free heme pool leads to induction of ALA synthase 1, the rate-limiting enzyme of heme biosynthesis[3,4]
  - The resulting accumulation of the toxic heme intermediates ALA and porphobilinogen is likely responsible for the disease manifestations[4–6]
- AHP is characterized by acute neurovisceral attacks, which may be recurrent and life-threatening, cause chronic neuropathy, and negatively affect quality of life (QoL)[3,4,7,8]
  - Intravenous hemin is recommended for treatment of acute attacks and can be used prophylactically; acute side effects include headache and phlebitis, and chronic side effects include iron overload and venous thrombosis[9,10]
  - Hormonal suppression with gonadotropin-releasing hormone (GnRH) analogs has shown variable efficacy as prophylaxis for recurrent premenstrual attacks[11,12]
- EXPLORE (NCT02240784) was a two-part prospective natural history study of patients with AHP who experienced recurrent attacks[13]
  - Part A followed patients by telephone and clinic visits for up to 12 months
    - Patients often had attacks that required hemin or other treatment at a healthcare facility[13]
    - Chronic symptoms impaired daily functioning[13]
  - Part B included eligible Part A patients as well as newly enrolled patients and provided long-term evaluation of pain intensity and changes in disease activity for up to 3 years
- The objective of this analysis was to evaluate disease activity, pain, and impact of symptoms on QoL in patients enrolled in EXPLORE Part B

Methods

Patients

- Patients with AHP who were ≥12 years old and eligible for Part B enrollment were required to provide written informed consent and meet one of these criteria:
  - ≥1 attack that required increased pain medication, antiemetic, or carbohydrate intake, or hemin administration or hospitalization for symptoms and signs of AHP (eg, severe abdominal pain, vomiting, tachycardia, constipation, hypertension, hyponatremia), within the previous 12 months
  - Hemin prophylaxis an average of ≥1 time per month within the 12 months before baseline
  - GnRH analog prophylaxis

Assessments

- Part B assessments were conducted by mail and confirmed by telephone every 3–6 months over 3 years
- Changes in porphyria symptoms, potential precipitants of attacks, medical history, and medications taken were captured on a porphyria follow-up questionnaire
- Pain intensity and impact were measured with the Brief Pain Inventory-Short Form (BPI-SF), a 0–10 scale with higher scores indicating worse pain
- QoL was evaluated with the EuroQol visual analog scale (EQ-VAS) and the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30),[14] both of which are 0–100 scales with higher scores indicating better functioning

Statistical Analysis

- Results were analyzed using descriptive statistics
- Data were analyzed for all Part B enrollees; subgroup analyses were performed to assess findings in patients with ≥3 attacks or prophylaxis and patients with <3 attacks without prophylaxis

Results

Patients

- In total, 136 patients from 18 countries (including 43 Part A patients) were enrolled in Part B
- **Table 1** summarizes patients' baseline demographic and disease characteristics
  - Mean age was 41 years
  - Most patients were female (90%) and white (85%) and had acute intermittent porphyria (90%)

Table 1. Baseline Demographic and Disease Characteristics of Patients with AHP Enrolled in EXPLORE Part B

Characteristic	Total Population (N=136)
Age at time of consent, y	
Mean (SD)	41.0 (12.6)
Median (range)	40.0 (17–83)
Female, n (%)	123 (90.4)
Race, n (%)	
White	115 (84.6)
Asian	9 (6.6)
Black/African American	6 (4.4)
Other	5 (3.7)
Not stated	1 (0.7)
Geographic region, n (%)	
Europe	70 (51.5)
North America	56 (41.2)
Other (Africa, Asia, Australia)	10 (7.4)
Years since AHP diagnosis[a]	
Mean (SD)	11.3 (11.7)
Median (range)	6.3 (0.0–45.7)
AHP etiology, n (%)	
Acute intermittent porphyria	123 (90.4)
Variegate porphyria	11 (8.1)
Hereditary coproporphyria	2 (1.5)
Months on study	
Mean (SD)	17.7 (11.0)
Median (range)	14.6 (2.0–41.5)

AHP, acute hepatic porphyria; SD, standard deviation.
[a]Sample size is 134.

Disease History

- Within the 12 months before enrollment, all patients had a median (range) of 3 (0–52) acute attacks; 46% were receiving hemin and/or GnRH prophylaxis (**Table 2**)
- The subgroup of 26 patients with <3 attacks a year without prophylaxis had a median (range) of 1 (0–2) acute attacks within the 12 months before enrollment, with pain being the most common symptom (**Table 2**)
  - During attacks, most patients required hemin (69%) and pain medication (96%), including opioids (62%)
  - Most patients (85%) also had chronic symptoms

Table 2. History of Attacks, Prophylaxis, and Chronic Symptoms in Patients with AHP: Subgroups of Patients with <3 Attacks without Prophylaxis or ≥3 Attacks or Prophylaxis and Total Population[a]

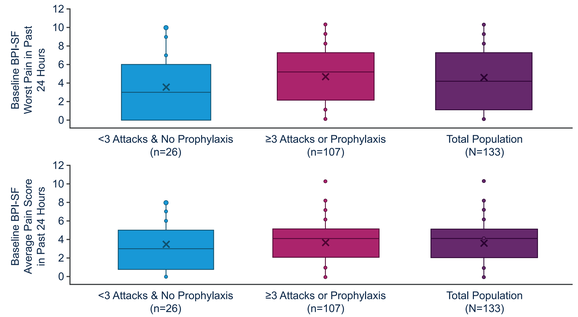
Characteristic	<3 Attacks/Year without Prophylaxis (n=26)	≥3 Attacks/Year or Prophylaxis (n=110)	Total Population (N=136)
Number of attacks within previous 12 mo, median (range)	1.0 (0–2)	4.0 (0–52)	3.0 (0–52)
Prophylaxis within previous 12 mo, n (%)	0	62 (56.4)[b]	62 (45.6)[b]
Hemin	0	56 (50.9)[b]	56 (41.2)[b]
GnRH	0	17 (15.5)	17 (12.5)
Symptoms associated with attacks within previous 12 mo, n (%)[c]			
Pain	26 (100.0)	97 (88.2)	123 (90.4)
Mood/sleep	25 (96.2)	92 (83.6)	117 (86.0)
Digestive/bladder	23 (88.5)	95 (86.4)	118 (86.8)
Nervous system	22 (84.6)	89 (80.9)	111 (81.6)
Other	19 (73.1)	87 (79.1)	106 (77.9)
Patients reporting chronic symptoms within previous 12 mo, n (%)	22 (84.6)	79 (71.8)[b]	101 (74.3)[b]

AHP, acute hepatic porphyria; GnRH, gonadotropin-releasing hormone.
[a]Subgroups defined as follows: <3 attacks/year without prophylaxis = patients who had <3 attacks and were not on hemin or GnRH prophylaxis within 12 months before enrollment; ≥3 attacks/year or prophylaxis = patients who had ≥3 attacks or were on hemin or GnRH prophylaxis within 12 months before enrollment. [b]Missing responses for 7 patients. [c]Responses were check all that apply.

Pain

- In patients with <3 attacks without prophylaxis at baseline, mean worst pain and average pain scores on the BPI-SF were 3.5 and 3.3, respectively (**Figure 1**)
  - Among those taking pain medications regularly (n=18), patients on average reported having only 44% of their pain relieved within the previous 24 hours
- In patients with ≥3 attacks or prophylaxis at baseline, mean worst pain and average pain scores on the BPI-SF were 4.5 and 3.7, respectively (**Figure 1**)

Figure 1. Pain Intensity at Baseline as Assessed with BPI-SF Scores for Subgroups of Patients with <3 Attacks without Prophylaxis or ≥3 Attacks or Prophylaxis and for Total Population[a]

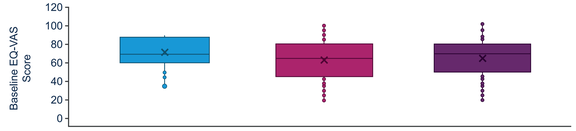


BPI-SF, Brief Pain Inventory–Short Form. Horizontal line within box indicates median. Bottom and top edge of box indicates Q1 and Q3, respectively. × indicates mean. Vertical lines indicate range of observed values.
[a]Data shown are for patients with available data.

Quality of Life

- Mean EQ-VAS score was 71.8 in the subgroup with <3 attacks without prophylaxis and 62.9 in the subgroup with ≥3 attacks or prophylaxis (**Figure 2**)

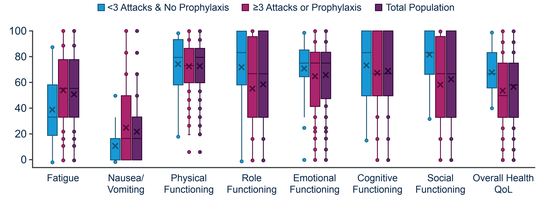
Figure 2. Mean EQ-VAS Scores at Baseline for Subgroups of Patients with <3 Attacks without Prophylaxis or ≥3 Attacks or Prophylaxis and for Total Population[a,b]



EQ-VAS, EuroQol visual analog scale; QoL, quality of life. Horizontal line within box indicates median. Bottom and top edge of box indicates Q1 and Q3, respectively. × indicates mean. Vertical lines indicate range of observed values.
[a]Data shown are for patients with available data. [b]On the EQ-VAS, a standard vertical 20-cm visual analog scale, individuals self-rate their current overall health-related QoL from 0 ("the worst imaginable health state") to 100 ("the best imaginable health state").[14]

- Mean EORTC QLQ-C30 overall health/QoL scores were 68 and 54, respectively (**Figure 3**)

Figure 3. Mean EORTC QLQ-C30 Total and Subscale Scores at Baseline for Subgroups of Patients with <3 Attacks without Prophylaxis or ≥3 Attacks or Prophylaxis and for Total Population[a,b]



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; QoL, quality of life. Horizontal line within box indicates median. Bottom and top edge of box indicates Q1 and Q3, respectively. × indicates mean. Vertical lines indicate range of observed values.
[a]Data shown are for patients with available data. [b]Scale range for EORTC QLQ-C30 is 0–100. On its fatigue and nausea/vomiting symptoms subscales, higher scores indicate worse symptoms; on its functioning subscales, higher scores indicate better functioning.

Limitations

- Number of attacks was self-reported by patients and was not verified by a clinician or confirmed with testing of ALA and porphobilinogen levels
- Patients may have had symptoms similar to those of attack symptoms but unrelated to AHP, resulting in overestimates of number of attacks

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Abbreviations: AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; BPI-SF, Brief Pain Inventory–Short Form; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; EQ-VAS, EuroQol visual analog scale; GnRH, gonadotropin-releasing hormone; QOL, quality of life; SD, standard deviation.

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