EXPLORE: A Prospective, Multinational Natural History Study of Patients With Acute Hepatic Porphyria With Recurrent Attacks

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Background and Objective

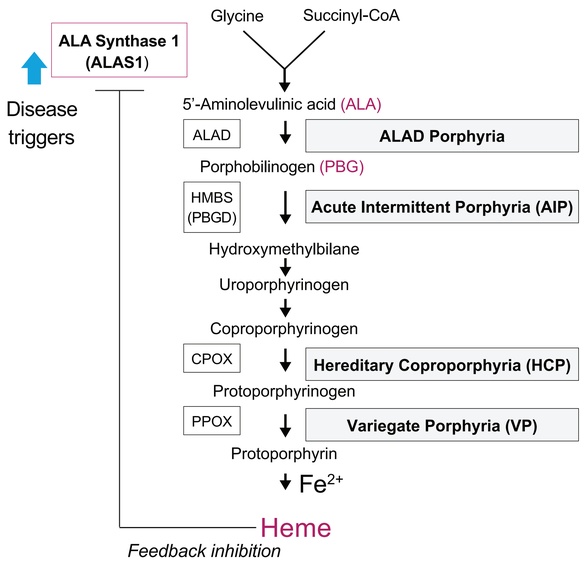
Background

- Patients with acute hepatic porphyrias (AHPs) experience episodic, potentially life-threatening neurovisceral attacks; a proportion of these patients (<10%) go on to develop recurrent attacks. Patients may often have chronic symptoms outside of attack episodes that negatively impact their quality of life (QoL)[1-4]
  - Mutations in genes encoding enzymes that drive heme biosynthesis lead to accumulation of neurotoxic heme intermediates 5'-aminolevulinic acid (ALA) and porphobilinogen (PBG)[1-4] (**Figure 1**)
- Given the nature of attacks and chronicity of disease, it is important to understand the long-term natural history and treatment limitation

Objectives

To characterize the natural history, current management, QoL, and biomarker levels of patients with AHPs

Figure 1: AHPs Enzymatic Pathway



ALAD, ALA dehydratase; CoA, coenzyme A; CPOX, coproporphyrinogen oxidase; HMBS, hydroxymethylbilane synthase; PBGD, PBG deaminase; PPOX, protoporphyrinogen oxidase.

Figure 2: EXPLORE Study Design

[a] Attacks were defined as porphyria symptoms requiring an increase in treatment (hemin, pain medications, carbohydrates) or hospitalization.

Methods

- EXPLORE (NCT02240784)[5] is the first observational, multinational, prospective study designed to characterize the natural history and clinical management of symptomatic patients with AHPs
- The study included male and female patients (≥18 years old) with ≥3 attacks/year or who received prophylaxis (hemin or GnRH)
- Blood and urine were collected to determine ALA and PBG levels as indicators of disease activity (**Figure 2**)
- QoL was evaluated using the EuroQol Five Dimensions Questionnaire 5-Level Scale (EQ-5D-5L)

Results

Patient and Disease Characteristics

- 112 patients (**Table 1**) were enrolled from 14 countries, including 49 (44%) from the US and 63 (56%) from 12 EU countries
- 107 (96%) and 80 (71%) patients completed 6 and 12 months of follow-up, respectively
- Medical conditions associated with AHPs were common (**Table 2**)

Table 1: Demographic and Disease Characteristics

Characteristic	N=112
Mean age, years	39.3
Female, n (%)	100 (89)
Race, n (%)	
White/Caucasian	95 (85)
Hispanic/Latino	5 (4)
Asian	3 (3)
Black/African American	3 (3)
Not answered	11 (10)
AHPs etiology, n (%)	
AIP	104 (93)
VP	5 (4)
HCP	3 (3)

Attack Characteristics Reported at Baseline

- Patients reported a mean of 9.3 attacks in the preceding year before study enrollment
- Pain was the most common symptom, occurring in 111 (99%) patients; tiredness, nausea, change in urine color, and weakness also were common (reported in ≥77% of patients)

Table 2: Most Common Associated Medical Conditions

Condition	N=112
Renal/Vascular Disorders, n (%)	**43 (38)**
Hypertension	26 (23)
Chronic kidney disease	9 (8)
Nervous System Disorders, n (%)	**35 (31)**
Headaches/migraine	12 (11)
Neuropathy/nerve pain	10 (9)
Psychiatric/Sleep Disorders, n (%)	**33 (29)**
Depression	19 (17)
Insomnia	13 (12)
Anxiety	9 (8)
Gastrointestinal Disorders, n (%)	**25 (22)**
Gastroesophageal reflux disease	9 (8)

- Patients receiving prophylactic hemin had 4.0 attacks per person-year (**Table 3**)
- For treatment of attacks, 76/102 (75%) patients were hospitalized and 42% were treated with hemin

Table 3: Attack Characteristics

Characteristic	N=112
Attack rate per person-year	
Overall	4.9
Chronic symptoms[a]	
Yes (n=52)	5.1
No (n=57)	4.8
Current hemin prophylaxis	
Yes (n=52)	4.0
No/unknown (n=60)	5.5
Mean (range) attack duration, days	7.05 (1.3–33.2)
Attacks requiring treatment,[b] %	77
Attack triggers/prodromal attack symptoms, %	88

[a]Excludes 3 patients with unknown chronic symptomatology.
[b]Treatment in healthcare facility or with hemin.

Table 4: Paired Urinary ALA/PBG Samples

Mean Biomarker Level[a] (range)	Non-attack	Attack Max	Attack Max Fold Above Non-attack
ALA mmol/mol Cr (n=65)	29.8	64.1	3.4
PBG mmol/mol Cr (n=66)	31.3	57.6	3.5

[a]Upper limit of normal: ALA <3.9 mmol/mol Cr; PBG <1.6 mmol/mol Cr.

Chronic Disease Characteristics

- Chronic symptoms were reported by 73 (65%) patients
  - Abdominal pain was the most frequently reported symptom, occurring in 21% of patients
  - Other common symptoms (reported in ≥19%) included tiredness, anxiety, and nausea
  - 46% of patients experienced symptoms daily
- During time not in attack (n=100), patients reported diminished QoL (mean EQ-5D-5L summary index, 0.78), which is similar to patients with heart disease (0.79),[6] ulcerative colitis (0.77),[7] and chronic obstructive pulmonary disease (0.79)[8]
  - Moderate to extreme impact on QoL was common, including pain/discomfort in 39 (39%) patients, anxiety/depression in 28 (28%) patients, and effects on usual activities in 25 (25%) patients

ALA/PBG Levels

- Mean ALA and PBG levels at screening (while patients were not having an attack) were markedly increased to 8x and 20x the upper limit of normal, respectively (**Table 4**)
- These elevations are approximately double those seen in high excreters of ALA/PBG without recognized symptoms of AHPs[9]

Summary

- EXPLORE is the first international, natural history study in symptomatic patients with AHPs and recurrent attacks
- Porphyria attacks are severe and disabling events that typically require hospitalization and treatment
  - In patients treated with hemin prophylactically, attacks may continue or recur
- Patients with AHPs experience symptoms during attacks and chronically, resulting in diminished QoL
  - Chronic symptoms occurred frequently, including daily in 46% of patients
- Study limitations include a small proportion of patients with recurring attacks
- In some patients who suffer frequent attacks, AIP is not just an "intermittent" disease as its name implies, but also has chronic manifestations that impact patients' lives and their ability to function
- Given morbidity and mortality, there remains an unmet need for novel therapies to prevent attacks and decrease the frequency of chronic symptoms

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DISCLOSURES: JRB: Recordati Rare Diseases – advisory committees or review panels; Brin and Brin, Mitsubishi Tanabe Pharma – consulting; Alnylam Pharmaceuticals, American Porphyria Foundation, Clinuvel, NIH 5U54 DK083909 – grant/research support. **MB:** Alnylam Biopharma – consulting. **DCR:** Alnylam Pharmaceuticals – advisory committees or review panels. **RJD:** Recordati Rare Diseases – advisory committees or review panels; Alnylam Pharmaceuticals – consulting, grant/research support, and patent held/filed. **PV:** Orphan Europe – advisory committees or review panels; Alnylam Pharmaceuticals – consulting. **KEA:** Alnylam Pharmaceuticals – advisory committees or review panels; Alnylam Pharmaceuticals, Mitsubishi Tanabe Pharma America – consulting; Alnylam Pharmaceuticals, Recordati Rare Diseases – grant/research support. **RK:** Clinuvel – consulting; Orphan Europe – speaking and teaching; Orion Corporation – stock shareholder. **HLB:** Clinuvel, Recordati Rare Chemicals – advisory committees or review panels; Alnylam Pharmaceuticals, Clinuvel, Mitsubishi Tanabe Pharma – consulting; Gilead Sciences – grant/research support. **MC:** Sanofi Genzyme, Celgene – advisory committees or review panels; Novartis – board membership. **AA and KM:** Alnylam Pharmaceuticals – consulting. **AC, CHS, WQ, CP, and AS:** Alnylam Pharmaceuticals – employment. **LG, DMB, US, JDP, JGL, JCD, CP, HN, MB, PS, EM, JW, PM, ES, PH, SS, FA, and AI** have nothing to disclose.