EXPLORE: A Prospective, Multinational, Natural History Study of Acute Hepatic Porphyrias (AHP) Patients with Recurrent Attacks

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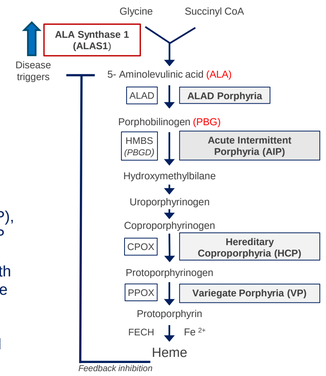
1. Background and Rationale

Acute Hepatic Porphyrias (AHPs)

- Acute hepatic porphyrias (AHPs) are a family of rare, often misdiagnosed, genetic diseases attributed to a mutation of genes encoding enzymes involved in heme biosynthesis[1] (Figure 1).
- 5-aminolevulinic acid synthase 1 (ALAS1), the first and normally rate-controlling enzyme of hepatic heme biosynthesis, is induced by precipitating triggers.[1]
- Neurotoxic heme intermediates, porphobilinogen (PBG) and 5-aminolevulinic acid (ALA), accumulate.
- ALA is thought to be the most likely candidate directly causing neurotoxicity resulting in life-threatening neuropathic attacks with severe neurovisceral pain and chronic debilitating symptoms.[2-4]
- Attacks are identical in patients with acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). HCP and VP may also include skin involvement with or without attacks.[1]
- Prospectively collected data describing severely affected patients with AHP across different countries are lacking, as are data describing the impact of prophylactic therapies.
- EXPLORE sought to characterize the disease activity and clinical management of patients with recurrent attacks of AHP in the US and Europe.

Figure 1: AHP Enzymatic Pathway



2. Methods

Study Design

- EXPLORE is the first prospective, multinational, observational study to characterize the natural history of disease activity and clinical management in symptomatic patients with AHPs (Figure 2). (ClinicalTrials.gov Identifier: NCT02240784)

Figure 2: EXPLORE Study Design

- Eligible patients had a clinical diagnosis of AHP (AIP, HCP, or VP) made by a porphyria specialist, biochemical evidence of porphyria during an attack (≥1 documented urine or plasma PBG level >4x the upper reference limit), and genetic confirmation.
- Eligible patients included males and females ≥18 years of age with ≥3 AHP attacks per year, or who were receiving prophylactic treatment against attacks.
- Attack was defined as acute porphyria symptoms requiring increase in treatment or hospitalization.
- Study assessments included prior medical and porphyria history, characterization of and management of on-study attacks, risk factors associated with attacks, and disease biomarkers.
- Results from the first 12 months of the study are reported here.

3. Results

- 112 patients were enrolled from 20 centers (6 in USA, 14 in Europe).
- 49 (44%) patients were from the USA and 63 (56%) from Europe.
- Patients were followed for a mean (SD) of 11 (3) months and a median (range) of 12 (9-12) months.

Table 1: Demographics and Disease Characteristics

Demographics	N=112
Age, mean (range)	**39.3 (19-70)**
Sex	**N (%)**
Male	12 (11)
Female	100 (89)
Race	**N (%)**
White/Caucasian	95 (85)
Asian	3 (3)
Black/African American	3 (3)
Not Answered	11 (10)

Disease Characteristics	
AHP type	**N (%)**
AIP	104 (93)
VP	5 (4)
HCP	3 (3)
Genotypes represented	**N**
AIP	58
VP / HCP	7

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; HCP, hereditary coproporphyria; VP, variegate porphyria.
*p.R173W and p.W283X were the most common genotypes found (n=4 each).

3. Results (cont)

Table 2: Comorbid Conditions in AHP Patients

- Comorbid conditions involved vascular, renal, psychiatric, and gastrointestinal disorders.

System Organ Class and Preferred Term	n (%)
Vascular disorders	30 (27)
Systemic arterial hypertension	27 (24)
Renal disorders	15 (13)
Renal failure	5 (5)
Chronic kidney disease	3 (3)
Nervous system disorders	35 (31)
Migraine	7 (6)
Peripheral neuropathy	7 (6)
Headaches	5 (5)
Psychiatric disorders	34 (30)
Depression	20 (18)
Insomnia	13 (12)
Anxiety	9 (8)
Gastrointestinal disorders	25 (22)
GERD	9 (8)
Nausea	4 (4)

Figure 3: Baseline AHP Attack Symptoms

- Abdominal pain, nausea, and changes in urine color were experienced by over 80% of the study participants during attacks (Figure 3).

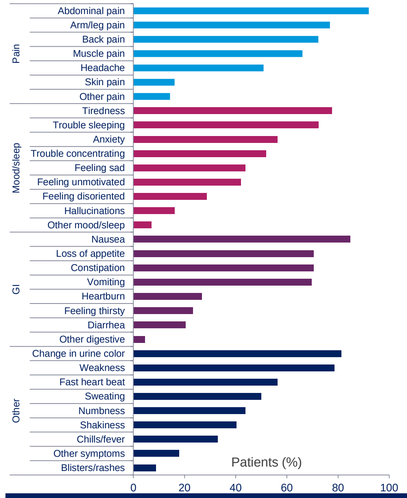


Table 3: Baseline Disease Manifestation and Management

- Of the 122 patients, 89% had ≥3 attacks in the last year.

Patient-Reported Attacks	
Number of attacks within the past 12 months	n (%)
Mean (SD)	9.3 (10.0)
Median (range)	6 (0–54)
Attack frequency over the past 12 months	
0 attacks	8 (7)
1–2 attacks	5 (5)
3–5 attacks	42 (38)
6–10 attacks	21 (19)
>10 attacks	36 (32)
Associated characteristics and symptoms	
Patient knows attack triggers	98 (88)
Prodromal attack symptoms	98 (88)
Hemin use	
Ever taken hemin for attacks	94 (84)
Usual frequency of hemin use per attack	
1 day	15 (13)
2–4 days	60 (54)
>4 days	19 (17)
Ever taken hemin prophylaxis	61 (55)
Frequency of hemin prophylaxis	
Weekly	27 (24)
Monthly	13 (12)
Other	20 (18)
Duration of hemin prophylaxis	
<1 year	15 (13)
1–2 years	8 (7)
>2 years	36 (32)
Experienced side effects from hemin*	55 (59)

Figure 4: Chronic Symptoms Experienced Between AHP Attacks

- 65% of patients with AHPs reported chronic symptoms in between frequent attacks.
- In 46%, chronic symptoms occurred daily (Figure 4).

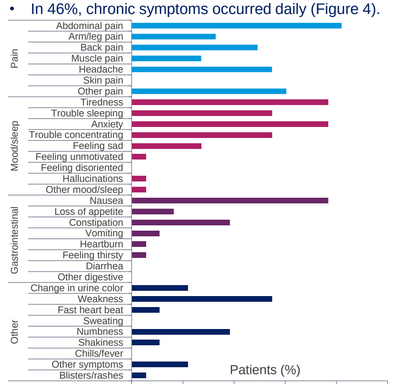


Table 4: On-Study Attack Characteristics

- Over 12 months of follow-up, 97 patients experienced a total of 483 attacks (Table 4).

Characteristic	Attack Rate
Attack duration, days	
Mean (SD); median (range)	7.3 (6.0); 6.1 (1–51)
Attack rate per person-year, mean (SD); median (range)	
Overall	3.7 (5.2); 2.0 (0–37)
By AHP type	
AIP (n=104)	3.8 (5.3); 2.0 (0–37)
VP/HCP (n=8)	1.5 (1.4); 1.3 (0–4)
By region	
US (n=49)	3.2 (3.1); 2.1 (0–16)
Europe (n=63)	4.0 (6.3); 1.0 (0–37)
By patient-reported hemin prophylaxis at baseline	
Yes (n=52)	3.4 (3.7); 2.5 (0–20)
No (n=60)	3.9 (6.2); 1.5 (0–37)
By patient-reported daily symptom status	
Yes (n=52)	3.4 (4.4); 2.0 (0–22)
No (n=57)	4.0 (5.9); 2.0 (0–37)

Quality of Life Baseline Questionnaire: EQ-5D-5L

- At baseline, AHPs were associated with a negative quality-of-life impact, especially as it related to performance of usual activities, due to pain and discomfort and anxiety and/or depression. Hemin prophylaxis did not appear to moderate this impact.

Figure 5: Non-Attack Pain Scores Over 1-Year Follow-Up and at Peak Attack Severity

- Non-attack pain was persistent from baseline through 6 and 12 months of follow-up. Hemin prophylaxis had little effect on chronic pain symptoms over time.
- Patients who had chronic pain at baseline (mean pain score 3.7/10) experienced pain in between attacks that increased during attacks (mean pain score 6.4/10) (Figure 5).

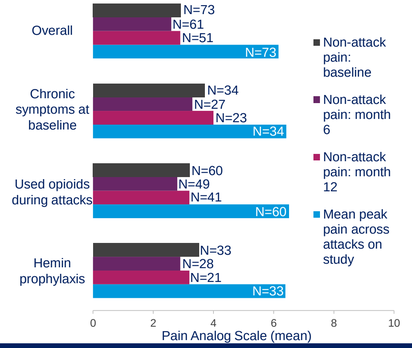


Table 5: On-Study Attack Treatment

- Treatment most commonly included the administration of hemin; treatment was most frequently administered at a healthcare facility (Table 5).

	USA	Europe	Total
Total attacks, n	176	307	483
Attack treatment			
Treatment location, n (%)			
Home	48 (27)	100 (33)	148 (31)
Healthcare facility	127 (72)	207 (67)	334 (69)
Unknown	1 (0.6)	0	1 (0.2)
Treatment type, n (%)			
Included hemin	125 (71)	207 (67)	332 (69)
Included opioids	84 (48)	168 (55)	252 (52)
Included carbohydrates NSAIDs, or other	75 (43)	129 (42)	204 (42)

Table 6: On-Study ALA and PBG Levels

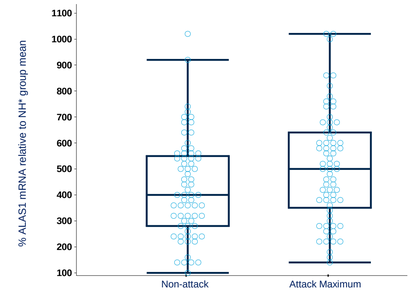
- Urinary ALA and PBG levels were significantly elevated in between attacks relative to normal values, and increased further during attacks (Table 6).

Biomarkers	ULN	Non-Attack, Mean (range)	Attack Maximum, Mean (range)
ALA (mmol/mol Cr)	<3.1	27.1 (1.0-211.0)	51.2 (1.0-1020.0)
PBG (mmol/mol Cr)	<1.2	27.3 (0.0-158.0)	55.5 (0.0-858.0)

On-Study Disease Biomarkers

- Liver ALAS1 mRNA expression, detected via circulating extracellular RNA Detection (cERD),[5] was significantly elevated relative to normal healthy values and increased further during attacks (Figure 6).

Figure 6: ALAS1 mRNA by Urine cERD



*Normal healthy (NH) values derived from healthy individuals not in study
Baseline ALAS1 mRNA for patients with AIP was 4.7; for patients with HCP/VP, it was 2.0.

4. Summary

Baseline Findings

- AHPs were associated with significant medical comorbidities, including neurological (31%), psychiatric (30%), vascular (27%), GI (22%), and renal (13%) disorders.
- Patients had a mean attack frequency of 9.3 over the preceding 12 months; 32% of patients reported >10 attacks in the previous 12 months.
- 65% endorsed chronic symptoms in between acute attacks, most commonly pain, fatigue, anxiety, and nausea; 46% had symptoms on a daily basis.
- Quality of life was most negatively impacted in the domains of usual activities, pain, and anxiety/ depression.
- Patients had induced ALAS1 mRNA expression and high ALA and PBG levels at baseline compared to normal healthy individuals.

On-Study Findings

- During attacks of porphyria, increases beyond those found at baseline, were observed in ALAS1 mRNA expression and ALA and PBG levels.
- The annualized attack rate (AAR) was 3.7 overall, with mean attack of 7.3 days. AAR was similar in groups reporting hemin prophylaxis at baseline vs not (3.4 vs 3.9, respectively).
- AIP diagnosis, experiencing ≥3 attacks, and hemin use for attacks were factors associated with higher risk of attack development on univariate analysis.
- The majority of attacks were treated in healthcare facilities (69%) and involved hemin (69%) and narcotics (52%).
- Patients reported chronic pain between attacks that increased during attacks, regardless of opioid or hemin prophylaxis treatment.

5. Conclusions

- EXPLORE represents the first international natural history study in patients with hepatic porphyria characterized by recurrent attacks that investigated AHP-associated disease characteristics and clinical management.
- These results underline the unmet need for new therapeutic options to prevent attacks of porphyria, as well as to reduce or ameliorate the chronic symptoms associated with AHPs.
- Additional observations from EXPLORE are expected in the future.

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