Dimension analysis of EQ-5D in patients with acute hepatic porphyria categorized by annualized attack rate to assess any relationship with symptoms occurring between attacks

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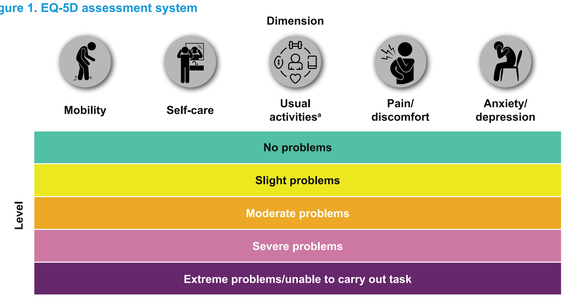
Conclusions

- **These results suggest that patients with AHP experience chronic symptoms, such as pain/discomfort or anxiety/depression, that are not associated with acute AHP attacks or predicted by historical AAR**
- **This analysis builds on earlier findings,[1-4] and suggests the chronic impact of AHP on HRQoL should be assessed regularly to guide treatment management decisions**
- **Additional research is needed to characterize disease burden in patients with lower historical AAR who, to date, have not been included in clinical trials**

Introduction

- Acute hepatic porphyria (AHP) are a group of four rare, genetic, multisystemic disorders caused by defects in the heme biosynthesis pathway[5]
  - The four types of porphyria comprising AHP are acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and δ-aminolevulinic acid dehydratase-deficiency porphyria (ADP)[5]
  - Patients with AHP experience acute attacks, characterized by pain, neurological symptoms, and altered mental status[5]
- AHP severity is typically measured by attack frequency via annualized attack rate (AAR)
- In clinical studies of AHP,[1-4, 6] AAR is defined by requiring hospitalization, urgent care, or intravenous hemin administration
  - Emerging data suggest that patients with AHP also have chronic symptoms that may occur between acute attacks[7,8]
- The EQ-5D is a concise, self-reported, standardized, generic questionnaire designed to evaluate health-related quality of life (HRQoL) across five dimensions[1-4,9]
  - In the EQ-5D, each dimension has five possible severity levels (**Figure 1**)[9,10]
- The objective of this post hoc analysis is to examine if there was any relationship between AAR and the burden of symptoms, occurring between attacks, as assessed by the EQ-5D survey in the ENVISION study

Figure 1. EQ-5D assessment system



[a]The usual activities dimension asks respondents to evaluate the severity of problems in carrying out their usual activities, such as work, study, housework, family, or leisure activities.

Methods

- ENVISION is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study (NCT03338816) investigating the effects of givosiran in patients with AHP[1,2]
  - Baseline was defined as the assessment period before randomization and givosiran dosing (study day −60 to −1)
- During their baseline assessment, patients with AHP aged ≥12 years and with a historical AAR ≥4 completed the EQ-5D survey to describe their health on that day
  - Baseline assessments were performed at a clinic site and thus it was assumed that patients were not experiencing an acute attack during the visit
- Historical AAR was calculated based on the number of attacks requiring hospitalization, urgent care, or hemin administration at home in the 6 months before study randomization
- For this analysis, data from the givosiran and placebo groups were pooled, and patients were categorized into quartiles by historical AAR
- The relationship between EQ-5D dimension level at baseline and historical AAR was determined by Spearman correlation coefficients and logistic regression
  - As these post hoc analyses were not preplanned and were performed in an exploratory manner, data are reported descriptively; *p* values are considered nominal and are included for context

Results

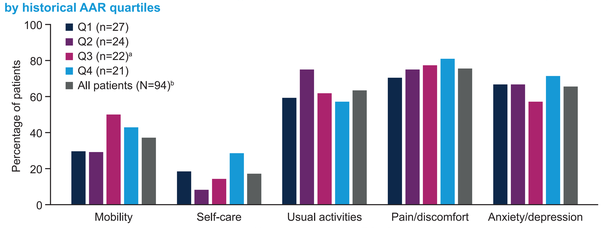
- In total, 94 patients (89% [84/94] women) were included in this analysis (**Table 1**)
  - Patients had a mean age of 39 (standard deviation 11.4) years and a median historical AAR of 8.0 (range 0.0-46.0)
  - At baseline, 52% (49/94) of patients reported prior chronic symptoms between attacks (defined as symptoms of porphyria when not having an attack daily or on most days before the study)
- Using the EQ-5D survey, the most frequently reported dimensions for which patients reported any problems (defined as 'slight problems' or worse [**Figure 1**]) were pain/discomfort (75.5% [71/94]), anxiety/depression (65.6% [61/93]), and usual activities (63.4% [59/93]) (**Figure 2**)
  - Mobility (37.2% [35/94]) and self-care (17.2% [16/93]) problems were reported less frequently (**Figure 2**)
- The affected distributions for each dimension were generally similar across the historical AAR quartiles (**Figure 2**)

Table 1. Demographics and clinical characteristics of patients stratified by historical AAR quartiles

Characteristic/demographic	Q1 (n=27)	Q2 (n=24)	Q3 (n=22)	Q4 (n=21)	All patients (N=94)
Age at screening, years, mean (SD)	40 (12.0)	37 (8.8)	39 (13.5)	39 (11.2)	39 (11.4)
Female, n (%)	25 (93)	22 (92)	21 (96)	16 (76)	84 (89)
Years since diagnosis, median (range)	4.3 (0.2, 35.3)	4.4 (0.1, 38.5)	8.7 (0.2, 34.2)	9.4 (0.7, 43.3)	6.6 (0.1, 43.3)
Historical AAR,[a] median (range)	4.0 (0.0, 4.0)	6.0 (6.0, 8.0)	12.0 (10.0, 16.0)	24.0 (18.0, 46.0)	8.0 (0.0, 46.0)
History of hemin prophylaxis, n (%)	8 (30)	11 (46)	11 (50)	10 (48)	40 (42.6)
History of symptoms between attacks,[b] n (%)	13 (48)	15 (63)	12 (55)	9 (43)	49 (52)
Urinary ALA,[c,d] mmol/mol					
Mean (SD)	13.6 (9.2)	16.6 (10.7)	22.6 (17.9)	22.7 (16.3)	18.5 (14.1)
Range	0.7, 40.1	2.2, 42.7	2.8, 88.9	6.0, 82.0	0.7, 88.9
Urinary PBG,[c,e] mmol/mol					
Mean (SD)	35.0 (22.4)	44.0 (25.2)	53.5 (34.1)	60.2 (33.4)	47.3 (29.9)
Range	0.4, 80.4	1.5, 103.8	0.4, 150.0	8.9, 147.2	0.4, 150.0

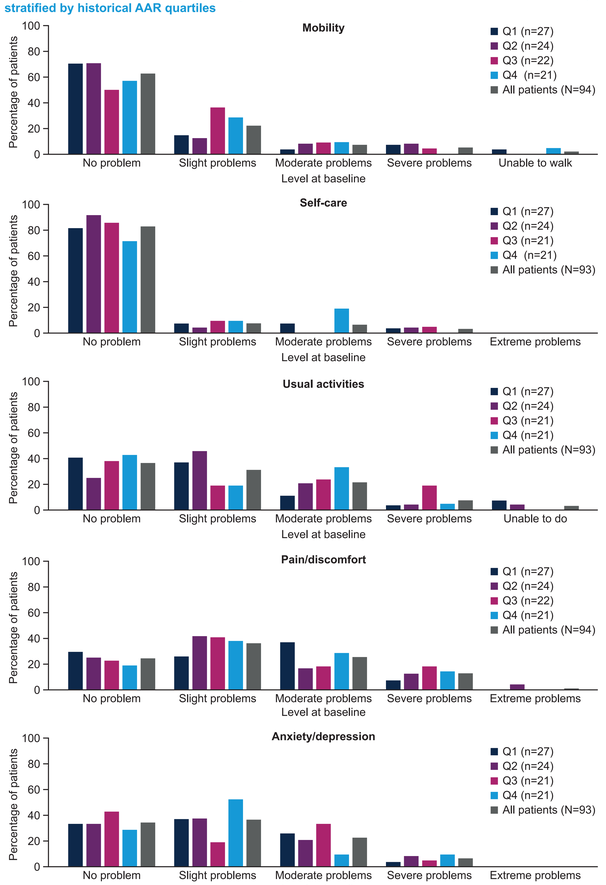
[a]Historical AAR was calculated based on the number of attacks requiring hospitalization, healthcare facility visit, or hemin use at home in the 6 months before randomization. [b]Defined as symptoms of porphyria when not having an attack daily or on most days before the study. [c]Normalized to creatinine. [d]Median ALA in healthy individuals: 0.46 mmol/mol. [e]Median PBG in healthy individuals: 0.02 mmol/mol.
AAR, annualized attack rate; ALA, δ-aminolevulinic acid; PBG, porphobilinogen; Q, quartile; SD, standard deviation.

Figure 2. Proportion of patients reporting any problems in each EQ-5D dimension at baseline, stratified by historical AAR quartiles



[a]N=21 in Q3 for domains of self-care, usual activities, and anxiety/depression. [b]N=93 in 'all patients' for domains of self-care, usual activities, and anxiety/depression.
AAR, annualized attack rate; Q, quartile.

Figure 3. Proportion of patients reporting each level of each individual EQ-5D dimension at baseline, stratified by historical AAR quartiles



AAR, annualized attack rate; Q, quartile.

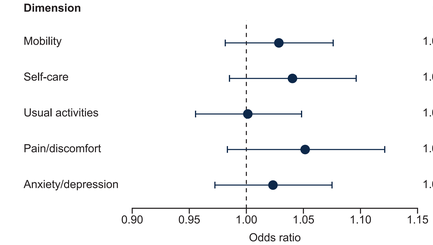
- The proportion of patients reporting each level for each dimension was similar across the historical AAR quartiles (**Figure 3**)
- No firm correlations were observed between EQ-5D levels and historical AAR for any dimension, with Spearman correlation coefficients all close to zero (nominal *p* values all >0.05; **Table 2**)
- There were no apparent differences in the odds of reporting a problem in any EQ-5D dimension as a function of historical AAR, with all odds ratios tending to 1; nominal *p* values were all >0.05 (**Figure 4**)

Table 2. Analysis of baseline EQ-5D dimension levels and historical AAR

Dimension	Spearman correlation coefficient	Nominal *p* value
Mobility	0.1240	0.2339
Self-care	0.1151	0.2720
Usual activities	0.0478	0.6494
Pain/discomfort	0.0720	0.4906
Anxiety/depression	−0.0073	0.9447

Individual dimension levels were coded as 1 (no problems), 2 (slight problems), 3 (moderate problems), 4 (severe problems), or 5 (extreme problems/unable to carry out task) for the Spearman correlation calculation.
Spearman correlation coefficient can range from −1 to +1; values close to 0 indicate no relationship.
AAR, annualized attack rate.

Figure 4. No relationship between historical AAR[a] and report of any problems across individual EQ-5D dimensions



[a]Effect on odds ratios is per 1 unit increase in historical AAR. Odds ratios, 95% CIs, and *p* values were calculated from a logistic regression model predicting individual EQ-5D levels of 2-5 (slight to extreme problems) vs level of 1 (no problems).
AAR, annualized attack rate; CI, confidence interval.

REFERENCES

1. Kuter DJ *et al. J Hepatol* 2023;79:1150-8.
2. Balwani M *et al. N Engl J Med* 2020;382:2289-301.
3. Gouya L *et al. Hepatology* 2020;71:1546-58.
4. Cassiman D *et al. J Inherit Metab Dis* 2022;45:1163-74.
5. Wang B *et al. Hepatol Commun* 2019;3:193-206.
6. Guida CC *et al. Mol Genet Metab Rep* 2024;40:101111.
7. Wheeden K *et al. Adv Ther* 2022;39:4330-45.
8. Simon A *et al. Patient* 2018;11:527-37.
9. Devlin NP *et al.* 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK565678/ (Accessed October 22, 2024)
10. Herdman M *et al. Qual Life Res* 2011;20:1727-36.

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