Assessing the Ability of the EQ-5D-5L to Capture Long-Term Health-Related Quality of Life Impacts of Hereditary Angioedema Attacks

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INTRODUCTION

- Hereditary angioedema (HAE) is a rare disorder characterized by recurrent swelling attacks varying in frequency and severity.[1–3]
- HAE attacks typically last between one to five days, with symptoms subsiding gradually, and may occur spontaneously or be precipitated by stimuli such as stress, trauma or estrogen.[2]
- Treatment options for HAE aim to both prevent acute attacks (prophylaxis) and rapidly terminate them when they occur (on-demand treatment).[2]
- Attack features, such as severity, frequency, location and duration, are likely to be key factors impacting health-related quality of life (HRQoL) during and between attacks.

OBJECTIVE

To assess the ability of the EQ-5D-5L instrument to quantify long-term HRQoL impacts of HAE attacks beyond and between attacks.

METHODS

Data Source

- Secondary analysis of APeX-2 (NCT03485911), a phase 3 trial of berotralstat for long-term prophylaxis in HAE in patients aged 12 years and older.
- Trial participants completed the EQ-5D-5L at baseline and study visits every 4 to 12 weeks up to 144 weeks.
- HAE attacks were characterised based on monthly attack frequency (any attack or by location: abdominal-only, peripheral-only, mixed [abdominal and peripheral]), laryngeal[a] (i.e., life-threatening; yes/no), and time since last attack (days).

Statistical Analysis

- Descriptive statistics of EQ-5D-5L index score (utility; 1=Full Health, 0=Dead) and attack characteristics at each study visit were evaluated.
- Cross-sectional Spearman's correlations between the EQ-5D-5L index score and attack characteristics were estimated at each study visit. Correlations were interpreted as weak (<0.3), moderate (≥0.3 to <0.5), or strong (≥0.5).[4]

Modelling Approach

- A longitudinal two-part model was employed consisting of:
  - Model 1: logistic mixed-effects model estimating the odds of being in full health on the EQ-5D-5L
  - Model 2: linear mixed-effects model estimating the EQ-5D-5L index score (utility) if not in full health
- Models included baseline participant characteristics (age, sex, body mass index), treatment arm, and attack characteristics (monthly attack frequency, time since last attack [days], laryngeal attack occurrence [yes/no]).
- For each model part, two separate modelling approaches were conducted: Model A including overall attack frequency (any location), and Model B including attack frequency by location (mixed, abdominal-only, peripheral-only).
- A random intercept for participants was included to account for repeated measurements across visits.
- Overall expected utility was calculated by summing the probability of being in full health/not being in full health (Model 1) times its associated utility (i.e., 1 or estimated utility from Model 2).
- Analyses were conducted in R version 4.5.1,[5] and the R packages *lme4*[6] and *lmerTest*.[7]

[a] Defined as internal swelling symptom (lump in throat, difficulty swallowing, change in voice, difficulty breathing)

RESULTS

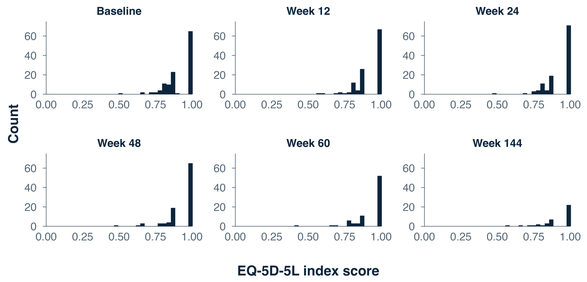
Sample Description

- 121 trial participants were included at baseline.
- Mean age was 41.6 (standard deviation [SD]=15.3) years, and the majority were female (66%).

EQ-5D-5L Index Score

- Mean EQ-5D-5L index score was 0.917 (SD=0.100) at baseline and remained high at subsequent visits.
- At all visits, most participants (54-81%) were in full health on EQ-5D-5L (EQ-5D-5L index score = 1, **Figure 1**).

Figure 1. Histograms of EQ-5D-5L index score at each study visit



HAE Attack Characteristics

- Mean monthly attack frequency (any location) decreased across visits from 3.0 (SD=1.4) at baseline to 0.4 (SD=0.8) at week 60 (**Figure 2**).
  - Mixed attacks were most common, followed by peripheral-only attacks and abdominal-only attacks.

Figure 2. Mean and observed range of attack characteristics across study visits

Relationship Between HAE Attacks and EQ-5D-5L Index Score

- HAE attack characteristics were weakly (r<0.3) correlated with the EQ-5D-5L index score, with no significant correlations (**Figure 3**).
- The two-part model showed mostly small and non-significant relationships between attack characteristics and the EQ-5D-5L index score (**Figure 4**).
- The overall expected utilities ranged between -0.002 to 0.000, reflecting the small effects of attack characteristics on the EQ-5D-5L index score.

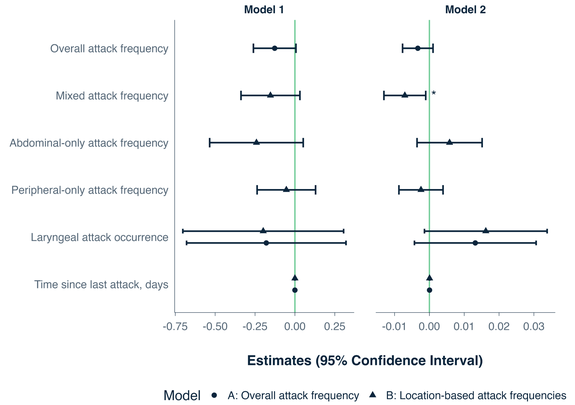
Model 1 (odds of full health):

- Higher attack frequencies, laryngeal attack occurrence, and shorter time since last attack were associated with decreased odds of being in full health on the EQ-5D-5L index score, however, all associations were statistically non-significant (p>0.05)

Model 2 (utility if not in full health):

- There were small and inconclusive effects of HAE attack characteristics on utility if not in full health
- Only increased mixed location attack frequency was associated with a small disutility (-0.007, 95% CI -0.013, -0.001) for participants not in full health, all other associations were statistically non-significant (p>0.05).

Figure 4. Two-part model: Model 1 = Odds ratio for full health; Model 2 = Effect of attack characteristics on EQ-5D-5L index score conditional on not being in full health



Notes: Statistical significance: *p<0.05
Models included age, sex, BMI, planned trial arm, laryngeal attack occurrence, time since last attack (days) and either A) overall attack frequency or B) location-based attack frequencies (mixed, abdominal-only, peripheral-only)
Number of observations: 1631 (Model 1) / 579 (Model 2)

Figure 3. Spearman rank correlation between EQ-5D-5L index score and HAE attack characteristics

	Baseline	Week 12	Week 24	Week 48	Week 60	Week 144
Overall attack frequency	-0.11	-0.03	0.01	-0.17	-0.02	-0.14
Mixed attack frequency	-0.28	-0.13	-0.00	-0.25	-0.02	-0.43
Abdominal-only attack frequency	-0.03	-0.07	-0.09	-0.05	-0.01	-0.12
Peripheral-only attack frequency	0.17	0.10	0.08	-0.02	-0.01	-0.00
Laryngeal attack occurrence	-0.22	-0.16	-0.00	-0.05	0.02	
Time since last attack, days	0.15	0.08	0.13	0.25	-0.04	0.15

Visit

Correlation -1.0 -0.5 0.0 0.5 1.0

Notes: No laryngeal attack occurred Week 144

Limitations and future research

- This was an exploratory secondary analysis of clinical trial data, where the trial itself was not designed to investigate the effects considered in this analysis.
- The focus of the analysis was to evaluate long-term HRQoL impacts of HAE attacks. Though not assessed here, the EQ-5D-5L may be more sensitive to short-term impacts of HAE attacks, due to its short reference period ('health today'). Future work could explicitly address the sensitivity of the EQ-5D-5L over different time windows in HAE.

CONCLUSIONS

1. This study showed weak associations between HAE attack characteristics and EQ-5D-5L index scores between attacks in patients with HAE aged 12 years and older.
2. Throughout the trial, participants reported high EQ-5D-5L index scores (mostly full health), even compared to the US general population.[8]
3. The generic EQ-5D-5L appears insufficiently sensitive to detect longer-term HRQoL impacts associated with HAE attacks beyond and between attacks.

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