Analyzing symptom relief definitions in HAE using AMRA and PGI-C/PGI-S

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Introduction

- Hereditary angioedema (HAE) is a rare genetic disease that predominantly occurs due to a deficiency or dysfunction in C1-inhibitor (C1-INH) protein.[1]

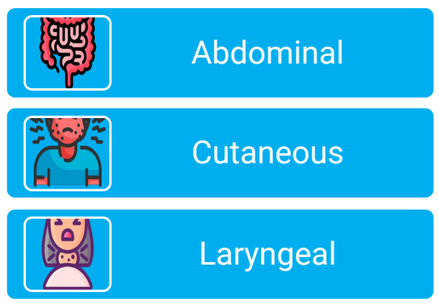
Types of HAE

Type 1 HAE
- Deficient C1-INH

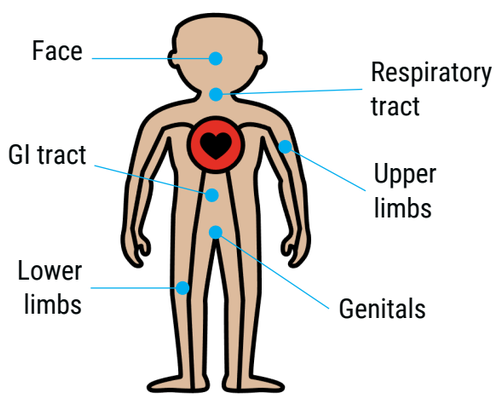
Type 2 HAE
- Dysfunctional C1-INH

HAE with normal C1-INH
- C1-INH at normal levels and functioning properly

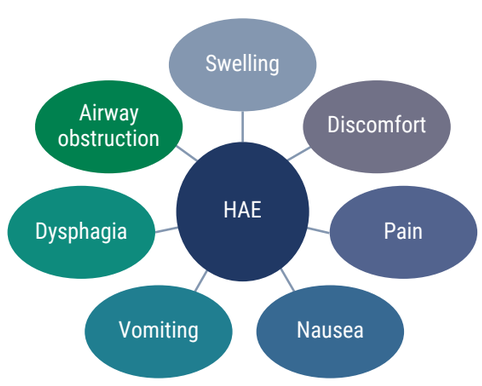
Locations of HAE attacks



Organs/body systems affected



Symptoms



- Patient-reported outcome (PRO) instruments are tools used in clinical trials that allow researchers to assess the patient experience of their disease.[2]
- The Angioedema syMptom Rating scAle (AMRA) is a numeric rating scale derived from the visual analogue scale (VAS) that is used to assess symptoms of HAE attacks.[3]
  - AMRA-3 is a 3-item scale that measures skin pain, skin swelling, and abdominal pain.
- The Patient Global Impression (PGI) scales were designed to capture the patient perception of change in clinical status (PGI-C) and of disease severity (PGI-S).[4-5]
- A need exists to explore the relationship between the AMRA-3 and PGI-C/PGI-S assessments because they are used to support endpoints in pivotal clinical trials of novel, oral, on-demand treatments.

Methods

- A mixed-methods study was performed in the United States to assess the content validity and psychometric properties of AMRA-3.
- Data collection involved participants completing the following PRO assessments via a mobile app during an HAE attack: AMRA-3, PGI-C, and PGI-S.
  - Post-treatment assessments were collected at baseline at the onset of attack, every 30±15 min from 0.5–2 h, every 1±0.5 h from 3–6 h, and at 8±1.5, 12±2.5, 24±9.5, and 48±14.5 h.
- Qualitative interviews were conducted with a subset of individuals who took part in the real-time data collection.
- Median time to symptom relief was calculated by Kaplan-Meier (KM) estimate (95% CI) for the following measures:
  - Median time to reduction in the AMRA-3 composite score from pre-treatment (20%, 30%, and 50% thresholds) in 2 consecutive timepoints.
  - PGI-C reaching at least "a little better" in 2 consecutive timepoints (on a 7-point scale of "much better," "better," "a little better," "same," "a little worse," "worse," and "much worse").
  - PGI-C reaching at least "better" in 1 timepoint.
  - PGI-S 1-level reduction in severity from baseline (on a 5-point scale of "very severe," "severe," "moderate," "mild," and "none").

Results

- A total of 35 participants recorded at least 1 treated attack in the mobile app (**Table 1**).
  - Mean age was 40 years (range: 16–70 years) with 34 adult participants (age, yrs: ≥18) and 1 adolescent participant (age, yrs: ≥16–<18). In total, 74% of participants were female.
  - Most participants (86%) were diagnosed with type 1 HAE.
- A total of 133 HAE attacks were recorded, of which 98 were non-laryngeal.

Conclusions

These results suggest that the median time to symptom relief using AMRA-3 20% reduction from pre-treatment and PGI-C "a little better" on 2 consecutive timepoints are comparable, whereas AMRA-3 50% reduction from pre-treatment, PGI-C "better," and PGI-S 1-level improvement take longer and are within the same range.

Results (continued)

Table 1. Baseline demographic and clinical characteristics

	Total sample			Interview sub-sample
	Adults (n=34)	Adolescents (n=1)	Total (N=35)	Adults (n=20)
Age (years), mean (min, max)	41.0 (18, 70)	16.0 (16, 16)	40.3 (16, 70)	43.4 (31, 51)
Sex, female, n (%)	25 (73.5)	1 (100)	26 (74.3)	16 (80.0)
Ethnicity/Origin: non-Hispanic, non-Latino, or non-Spanish origin, n (%)	33 (97.1)	1 (100)	34 (97.1)	20 (100)
Race, White, n (%)	29 (85.3)	1 (100)	30 (85.7)	19 (95.0)
Age at diagnosis (years), mean (min, max)	25.0 (1, 65)	13.0 (13, 13)	24.6 (1, 65)	28.3 (1, 65)
Age at first attack (years), mean (min, max)	16.8 (2, 55)	11.0 (11, 11)	16.6 (2, 55)	19.0 (5, 55)
Type of HAE, n (%)				
Type 1	29 (85.3)	1 (100)	30 (85.7)	16 (80.0)
Type 2	1 (2.9)	0 (0)	1 (2.9)	1 (5.0)
HAE with normal C1-INH	4 (11.8)	0 (0)	4 (11.4)	3 (15.0)

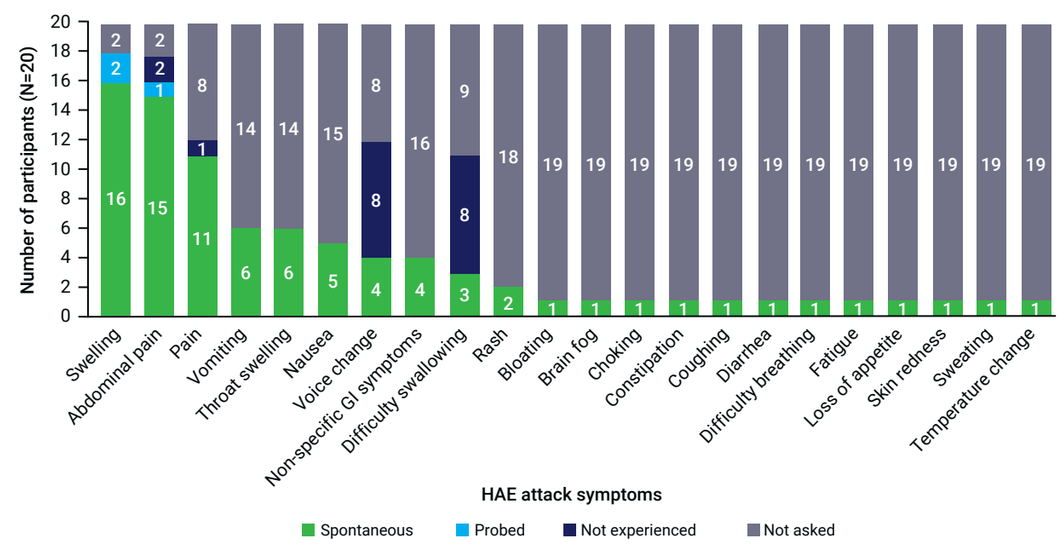
Table 2. On-demand treatments used for non-laryngeal HAE attacks

	Number (%) of attacks[a]		
Treatment	**Treatment taken at attack onset**	**Additional dose**	**Additional new treatment**
Icatibant (branded or generic)	59 (60.2)	8 (8.2)	0
Plasma-derived C1-INH concentrate	22 (22.5)	0	0
Recombinant C1-INH concentrate	9 (9.2)	2 (2.0)	0
Other[b]	9 (9.2)	4 (4.1)	6 (6.1)

[a]These percentages are calculated based on the total 98 non-laryngeal attacks represented in this table. Participants could take multiple medications for each attack at attack onset, as additional doses, or as additional new treatments. [b]Other treatments used include tranexamic acid (n=6), diphenhydramine (n=1), and lanadelumab (n=1), with 1 not stated.

- The main symptoms reported by participants during qualitative interviews were swelling, abdominal pain, and pain, substantiating the content validity of AMRA-3 (**Figure 1**).

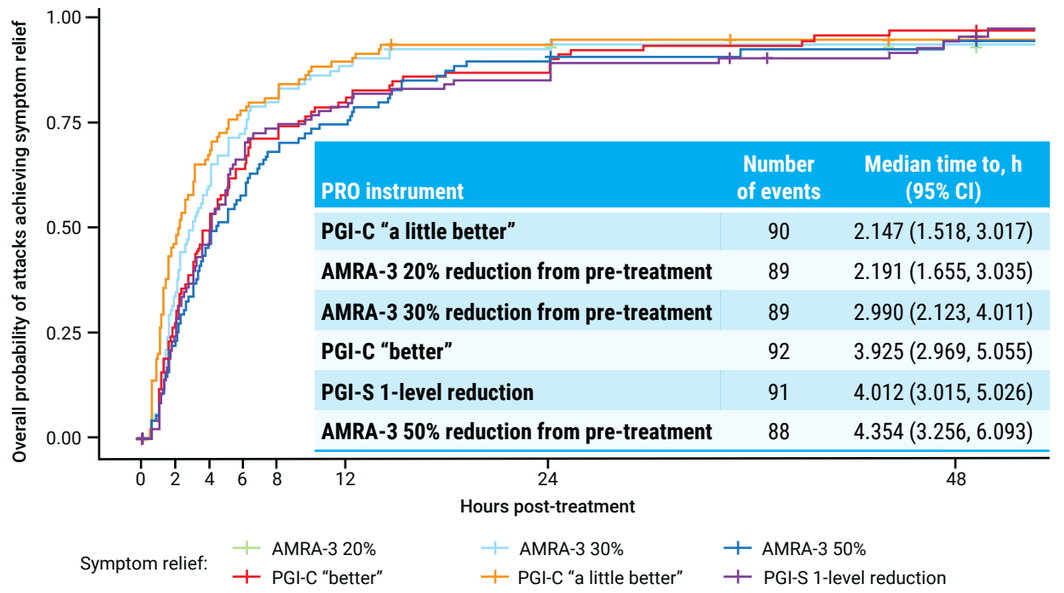
Figure 1. Symptoms reported by participants[a]



[a]These data are from the sub-sample of participants who completed the qualitative interviews.

- Symptom relief was achieved earliest by the defined measure PGI-C "a little better" (**Figure 2**).

Figure 2. Kaplan-Meier plot of non-laryngeal attacks achieving symptom relief



PRO instrument	Number of events	Median time to, h (95% CI)
PGI-C "a little better"	90	2.147 (1.518, 3.017)
AMRA-3 20% reduction from pre-treatment	89	2.191 (1.655, 3.035)
AMRA-3 30% reduction from pre-treatment	89	2.990 (2.123, 4.011)
PGI-C "better"	92	3.925 (2.969, 5.055)
PGI-S 1-level reduction	91	4.012 (3.015, 5.026)
AMRA-3 50% reduction from pre-treatment	88	4.354 (3.256, 6.093)

References

1. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Fijen L, et al. *Allergy*. 2022;77:2222-4. **3.** McMillan CV, et al. *Patient*. 2012;5:113-26. **4.** Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Heath, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, 1976. **5.** Cohn DM, et al. *Clin Transl Allergy*. 2023;e12288.

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