Development of a Conceptual Model Supporting a Clinical Outcome Assessment Strategy for Acquired Angioedema due to C1 Inhibitor Deficiency

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Andrea Zanichelli[1,2], Danny M. Cohn[3], Delphine Gobert[4], Marc A. Riedl[5], Sarah Clifford[6], Beverly Romero[6], Kelsie Brewer[6], Swaha Pattanaik[6], Maggie Chen[7], Joan Mendivil[8]

[1]Universita degli Studi di Milano, Dipartimento di Scienze Biomediche per la Salute, Milan, Italy; [2]IRCCS, Policlinico San Donato, Centro Angioedema, UO Medicina, Milan, Italy; [3]Amsterdam UMC, University of Amsterdam, Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands; [4]Sorbonne Université, Médecine Interne, AP-HP, Centre de référence des angiœdèmes à kinines, Hôpital Saint-Antoine, France; [5]University of California San Diego, Division of Allergy and Immunology, La Jolla, CA, USA; [6]Sprout Health Solutions, Los Angeles, CA, USA; [7]Pharvaris Inc, Lexington, MA, USA; [8]Pharvaris GmbH, Zug, Switzerland

Key takeaways

These findings inform a new patient-centered conceptual model for acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH). Cognitive interviews showed that the patient global impression and assessment items were relevant and easy to interpret by patients.

Gap

- **No approved therapies for AAE-C1INH attacks**
- **No validated patient-reported outcome tools for AAE-C1INH**

Real-world study

- **A conceptual disease model for AAE-C1INH was developed**
- **100% of participants correctly interpreted PGI-C to assess AAE-C1INH attack symptoms**

AAE-C1INH; acquired angioedema due to C1 inhibitor deficiency, PGI-C, Patient Global Impression of Change.

Background

- **Acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH):** a rare disease mediated by bradykinin and characterized by unpredictable, painful swelling attacks.[1-3]
- **Treatments:** there are no approved therapies for AAE-C1INH attacks.[1-2]
- **Patient-reported Outcome (PRO) tools:** while several PRO measures have been developed to measure symptoms and impacts of hereditary angioedema (HAE),[4-7] there are no PRO tools validated for use in AAE-C1INH.
- **Study:** to address this knowledge gap, we report the results of a combined concept elicitation and cognitive interview study assessing the real-world patient experience with AAE-C1INH.

Objectives

- To develop a conceptual model of AAE-C1INH that could reveal important disease concepts supporting a clinical outcome assessment strategy.
- To evaluate patients' comprehension and interpretation of Patient Global Impression of Change (PGI-C), PGI-Severity (PGI-S), Patient Global Assessment of Change (PGA-C), and PGA-Status (PGA-S), and explore patients' perceptions of meaningful change using these measures.

Methods

Concept elicitation (CE)

- **Aim:** develop a conceptual model of AAE-C1INH based on the interview data and provide a high-level visual of patients' experiences living with AAE-C1INH.
- **Approach:** semi-structured interview guide, including open-ended questions to elicit patients' descriptions of AAE-C1INH manifestations and their impact:
  - experiences of attack events
  - attacks experienced in various locations of the body
  - overall daily life impacts of living with AAE-C1INH.
- **Analysis:** CE data were coded and analyzed using principles of thematic analysis[8-9] with additional features drawn from grounded theory.[10-11] This approach conforms to best practices in the clinical outcome assessment field.[12]
  - A saturation grid of concepts related to AAE-C1INH attacks as reported by patients was developed.[13]
  - Analyzed interview data were used to develop a conceptual model of AAE-C1INH, which is a visual model of the relationship between the signs and symptoms of AAE-C1INH and their impact on daily life activities and overall health-related quality of life.

Cognitive interviews

- **Aim:** explore and confirm the relevance of adapting PRO items validated for HAE, another bradykinin-mediated disease with similar clinical manifestations, for AAE-C1INH.
- **Approach:** structured questions to assess the understanding and relevance of PGI-C, PGI-S, PGA-C, and PGA-S.
- **Analysis:** cognitive interview data were analyzed with a content analysis approach, with a focus on item-level analysis and the identification of issues associated with interpretation, recall, and clarity. Relevance to the patient experience of AAE-C1INH was also assessed along with the participants' perceptions of meaningful changes in symptoms and impacts in relation to the measures.

Table 1. Description of PRO assessment questions

Assessment	Description of PRO assessments	Meaningful change interpretation
Patient Global Impression of Change (PGI-C)	Asks participants to assess the amount of change experienced in their AAE-C1INH attack symptoms from the time they first took the study medication until "right now," using a seven-point response scale ranging from "much better" to "much worse"	Asks participants to discuss, hypothetically, what levels of change they would perceive as meaningful at various timepoints post-treatment
Patient Global Impression of Severity (PGI-S)	Asks participants to assess the current severity of their AAE-C1INH with a five-point response scale ranging from "none" to "very severe"	Asks participants to complete a baseline "pre-treatment" version of the PGI-S, and then to discuss, hypothetically, what levels of change they would perceive as meaningful at various timepoints post-treatment
Patient Global Assessment of Change (PGA-C)	Asks participants to assess the overall change in the impact on their health-related quality of life related to AAE-C1INH since starting the study medication, with a five-point response scale ranging from "much better" to "much worse"	Asks participants to consider a hypothetical 12-week clinical trial and to provide a hypothetical response about the level of change in health-related quality of life they would perceive as meaningful at the end of the 12-week clinical trial
Patient Global Assessment of Status (PGA-S)	Asks participants to assess the current impact of AAE-C1INH on their overall health-related quality of life with a five-point response scale ranging from "no impact" to "very severe impact"	Asks participants to consider a hypothetical 12-week clinical trial and to provide a baseline response (representing a hypothetical status at the start of the trial) and how much change from baseline on the PGA-S at the end of the trial they would need to experience to consider that change to be meaningful

PRO, patient-reported outcome.

Results

Participants

- Due to the rarity of AAE-C1INH and other recruitment challenges, eight adults in the United States with AAE-C1INH and no prior or concomitant diagnosis of other angioedema types were enrolled and completed the study.

Table 2. Participant demographics, disease characteristics, and treatments

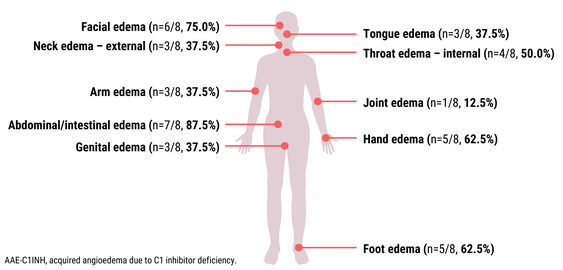
	Number of participants (%) (N=8)
Mean age (range); SD	67.6 years (48–77); 9.2
Sex, n (%)	
Female	7 (87.5%)
Male	1 (12.5%)
Race/Ethnicity, n (%)	
White	8 (100%)
Mean age at symptom onset (range); SD	55.9 years (48–68); 7.1
Mean age at diagnosis (range); SD	57 years (48–68); 9.4
Mean number of attacks in past 12 weeks (range); SD	5.5 (0–30); 10.0
Treatments for AAE-C1INH – Prescribed[a], n (%)	
Icatibant (30 mg/3 mL, as needed)	7 (87.5%)
Berotralstat (150 mg, once a day)	2 (25.0%)
Lanadelumab (300 mg/2 mL, every 2 weeks)	2 (25.0%)
C1 esterase inhibitor-human (unknown dosage, before dental procedures)	1 (12.5%)
Danazol (unknown dosage, before dental procedures)	1 (12.5%)
C1 esterase inhibitor-recombinant (2100 units, before medical procedures)	1 (12.5%)
Underlying conditions, n (%)	
Monoclonal gammopathy of undetermined significance (MGUS)	3 (37.5%)
Myasthenia gravis	1 (12.5%)
Breast cancer (in remission)	1 (12.5%)
Chronic lymphocytic leukemia (CLL)	1 (12.5%)
Lymphoma w/u negative	1 (12.5%)
Lymphoproliferative b cell disorder	1 (12.5%)

AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency; SD, standard deviation. [a]Prescribed off-label by physicians.

Attack areas

- In total, participants discussed 10 unique attack areas with mean (SD) number of attacks in the past 12 weeks 5.5 (10.0).

Figure 1. AAE-C1INH attack areas described by participants



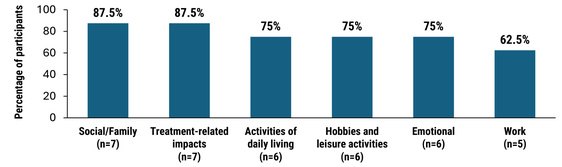
AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency.

Results

Impacts on daily life

- In addition to the symptoms, characteristics, and impacts experienced due to specific attack areas and events, participants also noted a broad range of daily life impacts.

Figure 2. Impacts on daily life in eight participants with AAE-C1INH

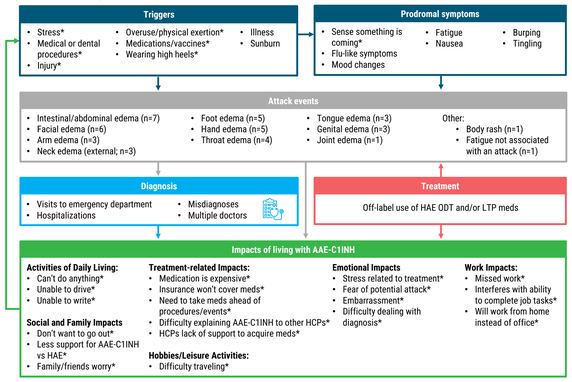


AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency.

Conceptual model

- Analyzed interview data were used to develop a conceptual model of AAE-C1INH.
- The concepts listed in this model are not exhaustive. Particularly, the impacts of living with AAE-C1INH mentioned below were by two or more participants.

Figure 3. Conceptual model of AAE-C1INH

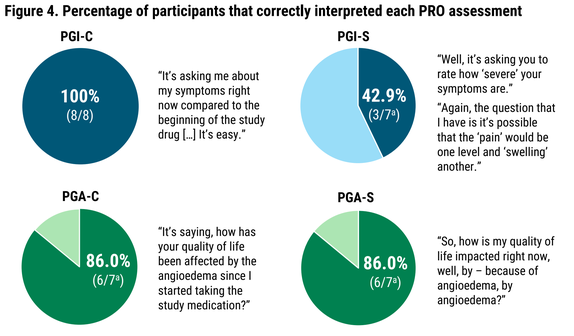


*Indicates mention by ≥2 people.
AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency; HAE, hereditary angioedema; LTP, long-term prophylaxis; ODT, on-demand treatment.

Evaluation of PRO assessments

- The majority of participants correctly interpreted the PGI-C, PGA-C, and PGA-S (**Figure 4**), and more than half found all 4 items easy to answer (**Figure 5**).
- Four participants had some difficulty interpreting the PGI-S, such as understanding "right now" and determining what severity level to select.
- At 4 hours post-treatment, participants perceived "better" and "1 level of change," a meaningful change for PGI-C and PGI-S, respectively (**Figure 6**).

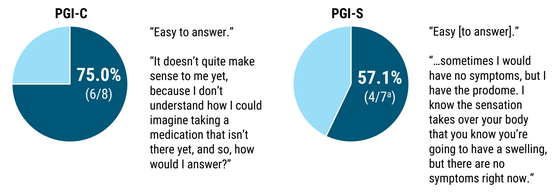
Figure 4. Percentage of participants that correctly interpreted each PRO assessment



PGA-C, Patient Global Assessment of Change; PGA-S, Patient Global Assessment of Status; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome. [a]One participant was unable to complete PGI-S, PGA-C, PGA-S assessments due to time constraints.

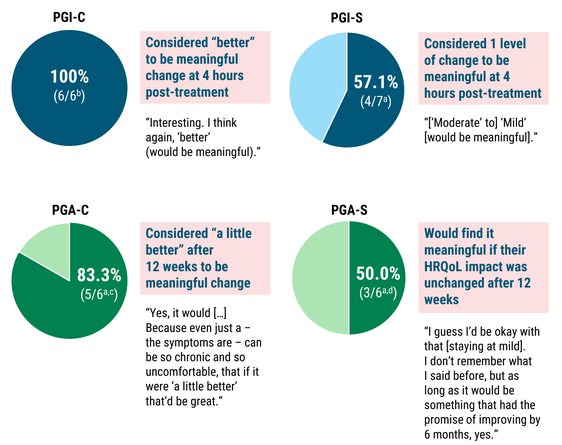
Results

Figure 5. Percentage of participants that found each PRO assessment easy to answer



PGA-C, Patient Global Assessment of Change; PGA-S, Patient Global Assessment of Status; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome. [a]One participant was unable to complete PGI-S, PGA-C, PGA-S assessments due to time constraints.

Figure 6. Participant perception of meaningful change in each PRO assessment



HRQoL, health-related quality of life; PGA-C, Patient Global Assessment of Change; PGA-S, Patient Global Assessment of Status; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome. [a]One participant was unable to complete PGI-S, PGA-C, PGA-S assessments due to time constraints. [b]Two participants were not asked about whether "better" would be a meaningful change because they believed only "much better" would be meaningful. [c]One participant was unable to complete PGA-C due to time constraints. [d]One participant inaccurately interpreted the response scale and was therefore excluded.

References

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