Session 5
PCR238

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

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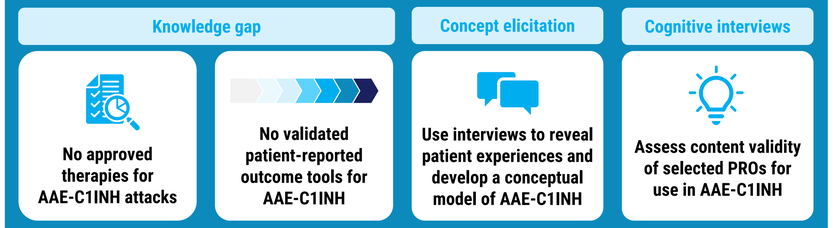
Key takeaways

The results of this qualitative interview study will inform the creation of a conceptual disease model for acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH) and may confirm the relevance and appropriateness of selected PROs for use in clinical trials of investigational treatments for AAE-C1INH.



AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency; PRO, patient-reported outcome.

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]
- **PRO tools:** while several patient-reported outcome measures (PROs) 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 design 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/Severity (PGI-C/S) and Patient Global Assessment of Change/Status (PGA-C/S) and explore patients' perceptions of meaningful change using these measures.

Methods

Participants

- **Target enrollment:** up to 10 US participants with AAE-C1INH.
  – IRB approval was obtained in November 2024 and study recruitment commenced thereafter.
- **Eligibility:** inclusion and exclusion criteria shown in **Table 1**.

Table 1. Eligibility criteria

Inclusion Criteria	Exclusion Criteria

• Adults aged ≥18 years at the time of providing written informed consent/assent
• Diagnosis of AAE-C1INH based upon all of the following:
  • Documented clinical history consistent with AAE-C1INH (subcutaneous or mucosal, nonpruritic swelling without accompanying urticaria)
  • Diagnostic testing results to confirm AAE-C1INH
  • C1INH functional level <40% of the normal level
  • No family history of an angioedema diagnosis
  • And at least one of the following:
  • Age ≥40 years at reported onset of first angioedema symptoms
  • C1q below the lower limit of the normal range
  • Serological confirmation of anti-C1-inhibitor antibodies
• At least one AAE-C1INH attack in the last 3 months (12 weeks)
• Stable underlying disease of AAE-C1INH (e.g., lymphoproliferative disease, immune complex disorders, monoclonal gammopathy of undetermined significance) – specifically, treatment for the underlying disease causing AAE-C1INH has not changed for the last 3 months and can be reasonably expected to remain unchanged for the next 6 months
• *Extended criterion*:
  • Participants with C1-INH functional level >40% may be allowed at the discretion of the study team
  • Participants with unstable underlying disease may be permitted into the study at the discretion of the study team
	• Any prior or concomitant diagnosis of angioedema other than AAE-C1INH
	• Does not:
	  • wish to or unable to take part in a 90-minute interview
	  • read, write, or speak English fluently
	  • have access to the internet
	  • have access to a computer or tablet
	  • wish to have the interview audio-recorded

Methods

Concept elicitation

- **Aim:** reveal patients' daily life experiences with AAE-C1INH.
- **Approach:** semi-structured interview guide, including open-ended questions to elicit patients' descriptions of AAE-C1INH manifestations and their impact.

Cognitive interviews

- **Aim:** explore the relevance and assess content validity of selected PROs for use in AAE-C1INH.
- **Approach:** structured questions to assess the understanding and relevance of a selection of patient-reported outcome items.
- **Data collection:** participants were asked to complete and discuss up to six different measures.

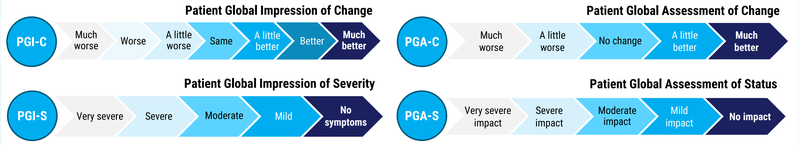
Table 2. Description of PRO assessments

Assessment*	Description	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 "no symptoms" 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 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

*All scales were adapted for AAE

- PGI-C, PGI-S, PGA-C, and PGA-S were assessments that interviewers aimed to have all participants complete.

Figure 1. PROs evaluated during cognitive interviews



Analysis

- Descriptive statistics were used to summarize the sociodemographic and clinical data collected during screening.
- Concept elicitation and cognitive interview data were analyzed using a mixed thematic and content analysis approach.

Concept elicitation

- Concept elicitation data was 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 (COA) 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 more proximal signs and symptoms of AAE-C1INH with the more distal impacts on daily life activities and overall health-related quality of life.

Cognitive interviews

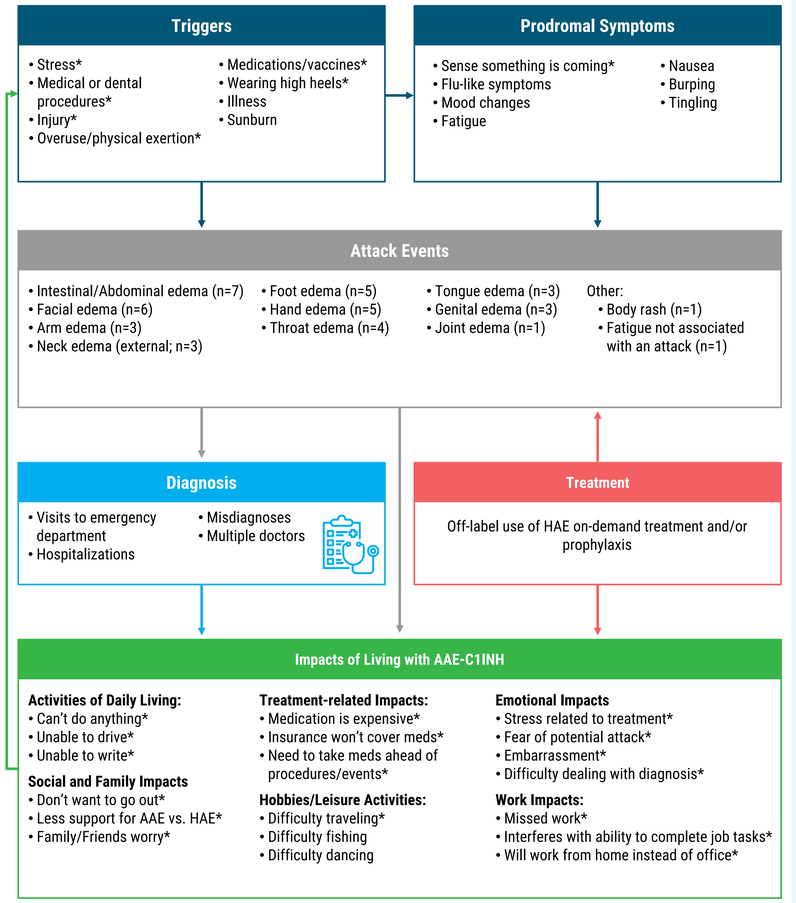
- Cognitive interview data were analyzed with a content analysis approach, with a focus on item-level analysis and the identification of issues associated with interpretation, recall, and clarity.
- Relevance to the patient experience of AAE-C1INH was also assessed.

Results

Conceptual model

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

Figure 2. Conceptual model of AAE-C1INH



AAE, acquired angioedema; HAE, hereditary angioedema. *Indicates mention by 2 or more people

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