Consensus on treatment goals in hereditary angioedema: A global Delphi initiative

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Background: Hereditary angioedema (HAE) is a rare, life-threatening genetic disorder characterized by recurrent episodes of subcutaneous or submucosal angioedema. The ultimate goals of treatment for HAE remain ill-defined.
Objectives: The aim of this Delphi process was to define the goals of HAE treatment and to examine which factors should be considered when assessing disease control and normalization of the patient's life.
Methods: The Delphi panel comprised 23 participants who were selected based on involvement with scientific research on HAE or coauthorship of the most recent update and revision of the World Allergy Organization/European Academy of Allergy and Clinical Immunology guideline on HAE. The process comprised 3 rounds of voting. The final round aimed to aggregate the opinions of the expert panel and to achieve consensus.
Results: Two direct consensus questions were posed in round 2, based on the responses received in round 1, and the panel agreed that the goals of treatment are to achieve total control of the disease and to normalize the patient's life. For the third round of voting, 21 statements were considered, with the participants reaching consensus on 18. It is clear from the wide-ranging consensus statements that the burdens of disease and treatment should be considered when assessing disease control and normalization of patients' lives.
Conclusions: The ultimate goal for HAE treatment is to achieve no angioedema attacks. The availability of improved treatments and disease management over the last decade now makes complete control of HAE a realistic possibility for most patients.
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Key words: *Hereditary angioedema, C1-INH deficiency, treatment goals, quality of life, acute treatment, prophylaxis*

Abbreviations used

AAS:	Angioedema Activity Score
AECT:	Angioedema Control Test
AE-QoL:	Angioedema Quality of Life questionnaire
C1-INH:	C1-inhibitor protein
EAACI:	European Academy of Allergy and Clinical Immunology
ED:	Emergency department
HAE:	Hereditary angioedema
HAE-AS:	Hereditary Angioedema Activity Score
HAE-QoL:	Hereditary Angioedema Quality of Life questionnaire
pdC1-INH:	Plasma-derived C1-inhibitor protein
QoL:	Quality of life
WAO:	World Allergy Organization

Hereditary angioedema (HAE) is a rare, life-threatening genetic disorder characterized by acute and recurrent episodes of subcutaneous or submucosal angioedema. HAE, in most patients, is the result of a deficiency of functional C1-inhibitor protein (C1-INH) and activation of the kallikrein–kinin contact system. This leads to local overproduction of bradykinin, vasodilation, and increased vascular permeability via activation of the bradykinin B2 receptor. Angioedema attacks are unpredictable, painful, and have a significant adverse impact on patient quality of life (QoL).[1,2] Severe attacks require urgent intervention and may also require emergency department (ED) visits or hospitalization. Without appropriate treatment, swelling with airway involvement may ultimately lead to death.[3]

Early diagnosis and appropriate treatment are essential to improve the lives of patients with this disabling disease. Despite advances in disease-specific treatments for HAE over the past decade, patients are still faced with significant disease and treatment burdens. Disease management for patients with HAE is currently achieved through use of on-demand medications and short- and long-term prophylaxis. Current acute treatment options include C1-INH replacement therapy (plasma-derived or recombinant human C1-INH[rhC1-INH] via intravenous administration), the kallikrein inhibitor ecallantide (subcutaneous administration, approved for use in the United States only), and the bradykinin B2 receptor antagonist icatibant (subcutaneous administration). Short-term prophylaxis may be indicated before known triggers of swelling (eg, surgical or dental procedures) and the available options include intravenous plasma-derived C1-INH (pdC1-INH), fresh frozen plasma, and attenuated androgens (eg, danazol, oxandrolone).[4-6]

Several options are approved for long-term prophylaxis. These include C1-INH (via intravenous or subcutaneous administration); subcutaneous lanadelumab, the fully human mAb against plasma kallikrein; attenuated androgens; and antifibrinolytics (eg, tranexamic acid).[7-11] Limitations of existing prophylactic drugs include the side effects associated with androgens and the frequent dosing regimens required with intravenously administered C1-INH (every 3-4 days). Furthermore, the efficacy of antifibrinolytics has been questioned.[4,9] Subcutaneously administered pdC1-INH concentrate and lanadelumab, however, represent significant recent advances toward not only increased efficacy, but also reduced treatment burden resulting from ease of administration and/or decreased frequency of dosing.

The current standard of care in HAE is aimed at reducing the frequency and severity of attacks; however, there are no established guidelines on how control of HAE can be best defined. The existing national and international guidelines, including the World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) and the international/Canadian and US guidelines,[4-6] were developed to provide a framework for the effective management of HAE. They also provide definitions of the aims of acute treatment and prophylaxis. For example, the international/Canadian guidelines state that the aim of acute treatment is to minimize the duration and severity of attacks, and that the aim of long-term prophylaxis is to minimize the frequency and severity of attacks and thus to minimize the impact of HAE on QoL.[6] The US guidelines go further and propose that the overall goal of treatment in HAE is to "restore normal quality of life to the patient."[5]

The existing international and US guidelines for HAE do not, however, explicitly state how control of the disease can best be defined, and they do not define overall "treat-to-target" style goals for HAE. This has perhaps been due to the limited availability of highly effective treatments; however, recent advances in the development of subcutaneous treatments, and in the near-future oral treatments, for long-term prophylaxis now make a treat-to-target approach more feasible for HAE.

Here, we report the results of a Delphi process that aimed to define the ultimate goals of treatment of HAE due to C1-INH deficiency and to examine the factors that should be considered when assessing control of disease and normalization of the

patient's life. To the best of our knowledge, there are no previously reported attempts to reach consensus on treatment goals for this disabling and potentially fatal disease, and it is hoped that the results presented here will be provide benchmarks for assessing disease control.

METHODS

Overview

The Delphi method is a validated approach to evaluate and to refine group opinion. This process uses iterative rounds of questioning, and after each round an independent facilitator provides an anonymized summary of the outcomes. It is expected that with iterative rounds of questioning the group will converge toward an agreed answer. The anonymity of this process is key and enables views to be changed over the course of the process, while ensuring that opinions are considered equally.[12]

Panel selection

To represent intercontinental differences in patient care, 2 co-Chairs were appointed: 1 from Europe (M.M.) and 1 from North America (B.Z.). In consultation with the co-chairs, 25 experts were selected for invitation to the Delphi panel on the basis of involvement with scientific research on HAE or co-authorship of the most recent update and revision of the WAO/EAACI guideline on HAE.[4] The final Delphi panel comprised 23 participants, who were subsequently invited to be authors on the manuscript (2 of the participants died over the course of the Delphi process). This was considered a sufficient number to gain a robust consensus[13] and represented 12 countries (Australia, Brazil, China, Denmark, Germany, Hungary, Italy, Japan, Spain, Switzerland, the United Kingdom, and the United States). No honoraria were paid for participation.

Delphi process

The Delphi process was performed between January 1 and November 30, 2019, using the online survey platform SurveyMonkey (SVMK Inc, San Mateo, Calif). Fig 1 shows an overview of the Delphi process employed to develop consensus statements for treatment goals in HAE due to C1-INH deficiency.[12] The process comprised 3 rounds, the final round of which aimed to aggregate the opinions of the expert panel. The overall aim of this process was to achieve consensus regarding the treatment goals in HAE, without the influence of group pressure or dominant individuals.

ROUND 1

In round 1, free-text responses to 2 open questions on the goals of prophylactic treatment in HAE in routine clinical practice were requested: (1) what should be the goal of treatment in HAE? and (2) what would indicate a patient with HAE whose disease is well controlled? Respondents were asked to consider their clinical experience, the patient management protocols followed in their practice and their broader knowledge. One or more answers could be given, along with any details on cutoff values indicating a successful outcome or level of importance, the respondent's rationale, and considerations for patient subtypes and sex. Discrete items mentioned in the free-text responses were identified and grouped into themes. The following themes were identified: burden of disease, QoL, normal life, and burden of treatment. In round 1, the participants were also invited to comment on the possible impact on clinical practice and on the patient of having consensus on treatment goals in HAE. The following themes were identified: patients, physicians, payers, QoL/normal life, HAE management, and differences in patients' lives.

Round 2

In round 2, respondents were asked to rank the appropriateness and importance of 14 considerations/factors (informed by the analysis and interpretation of round 1 responses) using a 5-point Likert scale (appropriateness: 0 = not appropriate, 1 = slightly appropriate, 2 = moderately appropriate, 3 = appropriate, and 4 = very appropriate; importance: 0 = not important, 1 = slightly important, 2 = moderately important, 3 = important, and 4 = very important). The statements fell into 2 broad categories: (1) measures of disease control and (2) instruments for assessing patient well-being. Factors that ranked highly in terms of appropriateness and importance were selected for inclusion in round 3. Following assessment of round 1 responses, 2 direct consensus questions were also posed in round 2: (1) regardless of what current treatment options can achieve, do you agree that an ultimate goal of HAE treatment should be to achieve total control of the disease? and (2) regardless of what current treatment options can achieve, do you agree that an ultimate goal of HAE treatment should be to normalize the patient's life? Consensus was defined *a priori* as agreement by at least 75% of respondents.[14]

Round 3

Finally, in round 3, to gain consensus on the parameters to be taken into consideration when assessing whether a patient's HAE was well controlled or their life normalized (in relation to HAE), respondents were asked whether they agreed or disagreed with 21 statements. As above, consensus was defined *a priori* as agreement by at least 75% of respondents; percentage agreement was not taken as an indicator of the strength of a particular consensus statement.

RESULTS

Overview of the Delphi process

The expert panel consisted of 23 participants, most of them allergists or immunologists, with a median (minimum, maximum) of 24 (12, 45) years of experience in the treatment of patients with HAE and a median of 93 (6, 500) patients with HAE in each practice. The response rates in this Delphi process were 96%, 91%, and 83% for rounds 1, 2, and 3, respectively. Of significant note, consensus regarding the ultimate goals of treatment of HAE was reached in the second round of voting. Respondents overwhelmingly agreed that the ultimate goals of HAE treatment are to achieve total control of the disease and to normalize the patient's life. Furthermore, 90% of respondents agreed that it is important/very important to minimize the burden of treatment.

For round 3 of voting, 21 statements were considered, with the participants reaching consensus on 18 (86%) (Table I). The panel did not agree that the mean length of attack-free period should be considered when assessing control of HAE or that the average time from onset of attack to complete resolution of symptoms should be considered when assessing control of HAE or normalization of the life of a patient with HAE (Table II).

Consensus statements for treatment goals in HAE

Consensus statements and their respective percentage agreements are summarized in Table I. It is apparent from the agreed

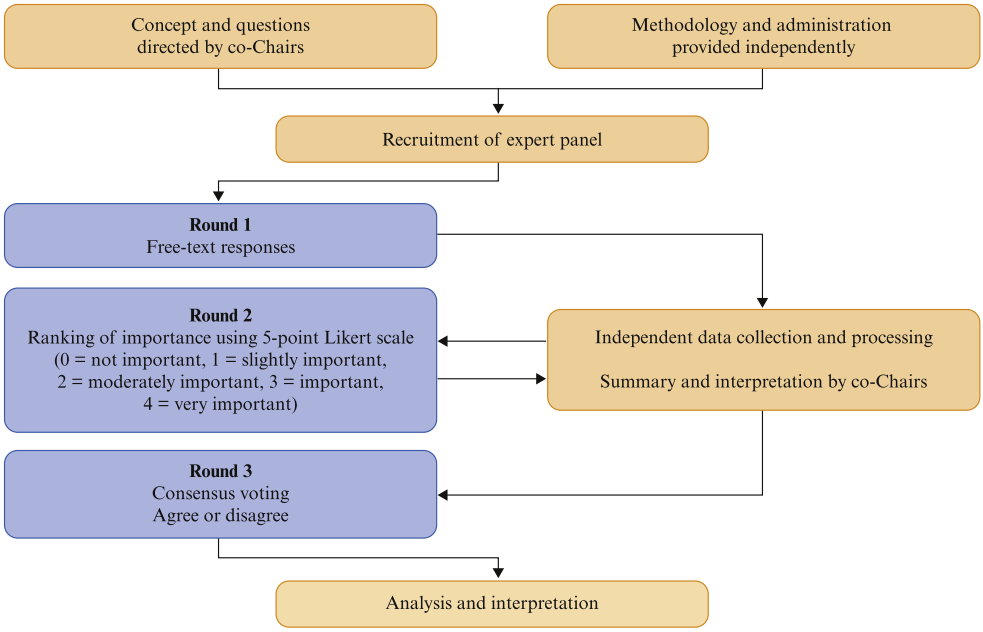

FIG 1. Overview of Delphi process employed to achieve consensus on treatment goals in HAE.

TABLE I. Summary of consensus statements (% agreement)

Ultimate treatment goals in HAE
One of the ultimate goals of HAE treatment should be to achieve total control of the disease (95%).
One of the ultimate goals of HAE treatment should be to normalize the patient's life (100%).
Consensus statement: control of HAE
The requirement for rescue medication in a given time period should be considered when assessing whether a patient's HAE is well controlled (100%).
The number of attacks experienced by a patient in a given time period should be considered when assessing whether a patient's HAE is well controlled (95%).
The ability of a treatment for HAE to achieve good control can be assessed by taking into account the proportional reduction in the number of attacks (95%).
The number of ED visits or hospitalizations should be considered when assessing whether a patient's HAE is well controlled (95%).
The number of days of sick leave in a given time period should be considered when assessing whether a patient's HAE is well controlled (89%).
The number of hours of activity impairment in a given time period should be considered when assessing whether a patient's HAE is well controlled (84%).
None of the available tools on their own are ideal for assessing whether a patient's HAE is well controlled (84%).
Consensus statement (normalization of a patient's life)
The number of ED visits or hospitalizations should be considered when assessing whether the life of a patient with HAE is normalized (95%).
The number of attacks experienced by a patient in a given time period should be considered when assessing whether the life of a patient with HAE is normalized (89%).
The patient's requirement for rescue medication in a given time period should be considered when assessing whether the life of a patient with HAE is normalized (89%).
The ability of a treatment for HAE to enable a patient with HAE to achieve a normal life can be assessed by taking into account the proportional reduction in the number of attacks (84%).
The number of hours of activity impairment in a given time period should be considered when assessing whether the life of a patient with HAE is normalized (84%).
The mean length of attack-free period should be considered when assessing whether the life of a patient with HAE is normalized (84%).
None of the available tools on their own are ideal for assessing whether the life of a patient with HAE is normalized (79%).
The number of days of sick leave in a given time period should be considered when assessing whether the life of a patient with HAE is normalized (79%).
Consensus statement (control of HAE/normalization of a patient's life)
Patients with HAE should provide input on how they or their treating physician should assess whether HAE is well controlled or their life is normalized (100%).
Patients with HAE will benefit from the development of novel tools that help them to assess whether their HAE is well controlled or whether their life is normalized (89%).
Physicians who treat HAE patients will benefit from the development of novel tools that help them to assess whether a patient's HAE is well controlled or whether the life of a patient with HAE is normalized (89%).

TABLE II. Summary of statements for which consensus was not reached (% agreement)

Statement for which consensus was not reached (control of HAE/normalization of a patient's life)
The average time from onset of attack to complete resolution of symptoms should be considered when assessing whether a patient's HAE is well controlled (63%).
The mean length of attack-free period should be considered when assessing whether a patient's HAE is well controlled (68%).
The average time from onset of attack to complete resolution of symptoms should be considered when assessing whether the life of a patient with HAE is normalized (53%).

statements that the burden of disease and treatment should be the primary considerations when assessing control of HAE and normalization of the patient's life in relation to HAE.

Examining the results in more detail, the participants agreed that the requirement for rescue medication and the number of attacks in a given time period, in addition to the proportional reduction in the number of attacks with treatment, should be taken into account when assessing whether HAE is well controlled. In addition to the factors listed above, it was agreed that the number of hours of activity impairment, the number of days of sick leave in a given time period, and the mean length of attack-free periods should be taken into consideration when assessing whether the life of a patient with HAE is normalized.

Furthermore, when assessing patient QoL or control of HAE, the panel agreed that the number of ED visits and hospitalizations should be taken into consideration. In alignment with the patient-centered approach to HAE management suggested in the WAO/EACCI, US, and international/Canadian guidelines, the participants unanimously agreed that patients with HAE should provide input on how they or their treating physician should assess whether HAE is well controlled or their life is normalized.

DISCUSSION

This expert panel agrees and recommends that the ultimate goals of treatment in HAE are to achieve total control of the disease and to normalize patients' lives. This translates to no attacks, which we recognize is not always possible. If complete control cannot be achieved, the goal is to reduce the number of attacks and to improve the patient's QoL.

Since 2008, several new treatments for long- and short-term prophylaxis for HAE due to C1-INH deficiency have become available (pdC1-INH [intravenous and subcutaneous formulations]/subcutaneous lanadelumab and intravenous pdC1-INH, respectively).[7] Recent studies demonstrating efficacy of recombinant human C1-INH, which is not currently approved for prophylaxis, have also been reported.[15] The efficacy of these prophylactic drugs has been well documented. For example, treatment with subcutaneous pdC1-INH (60 IU/kg twice weekly) has been shown to result in a 95% reduction in median attack frequency relative to control.[16] In an open-label extension study, 62% of patients receiving subcutaneous pdC1-INH (60 IU/kg) did not use any rescue medication during the following 12 months.[17] For lanadelumab, patients receiving 300 mg every 2 weeks experienced an 87% mean reduction in attack frequency compared with those receiving placebo.[18] Furthermore, interim results from an open-label extension study to examine the long-term efficacy of lanadelumab demonstrated that the maximum attack-free period was 6 months or longer in 78% of patients and at least 12 months in 58% of patients.[19] These advances in disease-specific treatments now make complete control of HAE symptoms feasible for some patients. There are currently no licensed drugs approved with proven treatment effects for HAE with normal C1-INH.[20] However, a number of recent studies suggest that there is some overlap in treatment options for HAE due to C1-INH deficiency and for HAE with normal C1-INH associated with increased production in bradykinin due to, for example, variants in the plasminogen gene or the *F12* gene.[21-23]

Beyond complete disease control, it is apparent from the agreed consensus statements that the burdens of disease and treatment should be the primary considerations when assessing effective disease control and normalization of the patient's life. The number of factors considered appropriate underlines the importance of taking a holistic, patient-centered, shared decision-making approach when assessing control of HAE; shared decision making is proposed to have several benefits including improved disease management, better outcomes and treatment adherence, and reduced costs.[24-26] The number of agreed consensus statements may also reflect variability in access to highly effective therapies and specialized disease management across different countries.

Statements for which consensus was not reached included the mean length of the attack-free period (disease control only) and the time from onset of an attack to complete resolution of symptoms (for both disease control and normalization of the patient's life). In the case of the mean length of the attack-free period, the expert panel clearly viewed the assessment of disease control and normalization of the patient's life differently; this may be because the attack-free period will impact normal activity including, for example the patient's ability to work or socialize. Furthermore, it may be that consensus was not reached for these statements because greater emphasis was placed on the overall number of attacks rather than the duration of an attack or the length of the attack-free period. However, it is worth noting that these factors are related and, for example, a reduction in the number of attacks experienced by a patient will likely be associated with an increase in the attack-free period.

In addition to achieving complete disease control, the panel also recognized the importance of normalizing the patient's life. The impact of HAE on health-related QoL has been well documented,[27-29] with the burden of disease including debilitating physical, psychological, and social effects. Reiterating the importance of the patient perspective when assessing QoL and disease control, and in alignment with the current WAO/EAACI, US, and international guidelines, all participants agreed that patient input should be sought on how they or their physician should assess disease control and QoL. It is important to note,

however, that this does not take precedence over other considerations or agreed consensus statements. Furthermore, in this study the percentage agreement was not taken as an indicator of the strength of that consensus statement.

Highlighting an important gap in the tools available to physicians, particularly for the assessment of disease control, the respondents agreed that the available tools for assessing disease burden or activity alone were not sufficient to assess disease control or patient well-being. Furthermore, it was agreed that both patients and physicians would benefit from the development of new tools to assess disease burden, activity, and control (consensus statements across all 3 categories) (Table I).

It is important to note that the existing WAO/EAACI guideline recommends that patients are evaluated for long-term prophylaxis at each visit and that the disease burden experienced by the patients and their preferences are taken to into consideration; a robust set of validated and easy to use tools for the measurement of disease control, disease activity, and QoL are necessary to achieve this goal. Validated disease-specific patient-reported outcome measures for assessing disease burden include the Angioedema Quality of Life questionnaire (AE-QoL) and Hereditary Angioedema Quality of Life questionnaire (HAE-QoL).[30-34] Comparative studies assessing the utility of AE-QoL and HAE-QoL are, however, lacking. An additional patient-reported outcome measure, the US HAE Association Quality of Life questionnaire, is under development for patients in the United States.[35] Validated tools for the assessment of disease activity include the Angioedema Activity Score (AAS)[36,37] and the HAE Activity Score (HAE-AS)[38]; however, at present, studies comparing AAS and HAE-AS are lacking. Disease activity has been proposed as an important determining factor for the need for long-term prophylaxis and so these may prove useful tools for the assessment of treatment needs. One noteworthy difference is that HAE-AS considers the number of attacks by location, which is of importance when assessing disease activity for HAE. However, both AAS and HAE-AS use a daily diary and as a result may be more appropriate for a clinical trial setting than everyday clinical practice. In addition, the interpretation of the results of patient-reported outcome measures assessing both disease burden and activity can be challenging and requires experience.

A tool that measures disease control, the Angioedema Control Test (AECT), has recently been developed, validated, and published, thus addressing the gap identified in this project.[39,40] The AECT, although not disease-specific, is validated for recurrent angioedema including HAE, has similarities to other established control tests (eg, asthma and urticaria control test), and is designed to guide treatment decisions. The AECT does not assess the location of an attack and focuses on the frequency, impact, and unpredictability of attacks, in addition to how well the condition is controlled by therapy. The major advantages of the AECT are its brevity and ease of use, resulting in a straightforward tool to evaluate disease control and the need for long-term prophylaxis at each visit in line with the recommendation in the WAO/EAACI guideline. However, it is important to note disease activity and QoL should also be monitored. To achieve the goals set out by this study, validated tools, which enable comprehensive assessment of disease activity, disease control, and patient well-being are essential. Further work is required to improve the dissemination and implementation of these tools and to provide validated versions for use in pediatric patients.

Conclusions

This report is the first international Delphi initiative to develop a formal definition of treatment goals in HAE. The overarching conclusion is that the ultimate goal for treatment of HAE is to achieve no angioedema attacks. The availability of improved disease-specific treatments and disease management means that complete control of HAE is now becoming a realistic possibility for some patients. It is recognized that total control is not always possible, and as a result it is essential to take a holistic view, considering factors such as the number of attacks, the need for rescue medication, and the number of hours of activity impairment when assessing whether a patient's HAE is well controlled or whether their life is normalized. Finally, it is hoped that the definitions of treatment goals in HAE outlined here will provide benchmarks for assessing both disease control and treatment efficacy.

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Key messages

- **A Delphi process was used to explore the ultimate goals of treatment of HAE and to examine the factors that should be considered when assessing disease control.**
- **A panel of experts agreed that the ultimate goal of treatment in HAE is to achieve no angioedema attacks.**
- **The definitions of treatment goals outlined here will provide benchmarks for assessing disease control in HAE.**

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