

Expert Review and Consensus on the Treat-to-Target Management of Hereditary Angioedema: From Scientific Evidence to Clinical Practice

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■ Abstract

Background: Hereditary angioedema with C1 inhibitor deficiency (HAE-C1INH) is a rare disease characterized by swelling episodes. It affects quality of life (QOL) and can be fatal when the upper airways are involved. Treatment is individualized, with therapeutic options including on-demand treatment (ODT) and short- and long-term prophylaxis (STP, LTP). However, available guidelines are not always clear about the selection of treatment, the goals of treatment, or how achievement of these goals is assessed.

Objective: To review available evidence for the management of HAE-C1INH and build a Spanish expert consensus to steer management towards a treat-to-target approach, while addressing some of the less clear aspects of the Spanish guidelines.

Methods: We reviewed the literature on the treat-to-target management of HAE-C1INH, focusing on treatment selection and goals and the tools available to assess whether the goals have been achieved. We discussed the literature based on clinical experience and drew up 45 statements on undefined management aspects. A panel of 53 HAE experts validated the statements through a 2-round Delphi process.

Results: The goals for ODT and STP are to minimize the morbidity and mortality of attacks and to prevent attacks caused by known triggers, respectively, while the main goal of LTP is to decrease the rate, severity, and duration of attacks. Furthermore, when prescribing, clinicians should consider the reduction in adverse effects, while increasing patient QOL and satisfaction. Appropriate instruments for assessing achievement of treatment goals are also indicated.

Conclusions: We provide recommendations on previously unclear aspects of HAE-C1INH management with ODT, STP, and LTP, focusing on clinical and patient-oriented goals.

Key words: Hereditary angioedema. Expert consensus. Treat-to-target. On-demand treatment. Prophylaxis. Treatment. C1 inhibitor.

■ Resumen

Antecedentes: El angioedema hereditario por deficiencia del inhibidor de C1 (AEH-C1INH) es una enfermedad rara que se manifiesta con episodios de hinchazón que afectan la calidad de vida (CdV) y que pueden ser letales en caso de afectar a las vías respiratorias superiores. Las opciones terapéuticas incluyen el tratamiento a demanda y la profilaxis a corto y largo plazo. El tratamiento es individualizado, pero las guías clínicas nacionales e internacionales no son siempre claras en cuanto a la elección del tratamiento, los objetivos y la evaluación de los resultados.

Objetivo: Nuestro objetivo fue revisar la evidencia disponible relativa al manejo del AEH-C1INH y establecer un consenso de expertos españoles orientado a dirigir el manejo del AEH-C1INH hacia una estrategia "treat-to-target" (T2T), y abordar algunos aspectos no resueltos por las guías clínicas españolas.

Métodos: Realizamos una revisión de la bibliografía disponible sobre el manejo del AEH-C1INH según la estrategia T2T, con un especial interés en: 1) la selección y los objetivos del tratamiento, y 2) las herramientas disponibles para conseguir esos objetivos. El comité científico discutió la bibliografía según su propia experiencia profesional y elaboró 45 conclusiones sobre aspectos sin definir relativos al manejo de la enfermedad. Un panel de 53 expertos en AEH validó las conclusiones mediante la metodología Delphi, tras 2 rondas de consulta.

Resultados: Los objetivos del tratamiento a demanda y la profilaxis a corto plazo son, respectivamente, minimizar la morbimortalidad de los ataques y evitar los ataques provocados por estímulos conocidos, mientras que la reducción de la frecuencia, gravedad y duración de los ataques son los principales objetivos de la profilaxis a largo plazo. Más aún, a la hora de prescribir el tratamiento, la reducción de los

efectos adversos y la mejora de la calidad de vida y satisfacción de los pacientes deberían ser considerados. En este documento se indican además las herramientas apropiadas para evaluar la consecución de objetivos.

Conclusiones: Este proyecto ofrece una serie de recomendaciones relativas a aspectos por esclarecer sobre el manejo del AEH-C1INH con tratamiento a demanda y profilaxis a corto y largo plazo, prestando una atención especial a los objetivos clínicos y orientados al paciente.

Palabras clave: Angioedema hereditario. Consenso de expertos. "Treat-to-target". Tratamiento a demanda. Profilaxis. Tratamiento. Inhibidor C1.

Introduction

Hereditary angioedema (HAE) associated with C1-inhibitor deficiency (HAE-C1INH) is a rare disease caused by a mutation in the *SERPING1/C1NH* gene [1,2]. The prevalence of HAE-C1INH is estimated to be between 1.1 and 1.6 per 100 000 individuals [3]. HAE-C1INH is a serious, potentially fatal disease characterized by recurring episodes of swelling and edema in subcutaneous and submucosal tissues [1,2]. Attacks vary in severity, frequency, and location [2,4,5] and may cause asphyxia when the upper airways are involved, especially in pediatric patients [6]. HAE-C1INH negatively affects the health-related quality of life (HRQOL) of patients and caregivers, both in the short and long term [7-9].

The 3 currently available treatment strategies for HAE-C1INH comprise on-demand treatment (ODT) of angioedema attacks, along with short- and long-term prophylaxis (STP and LTP) aimed at preventing attacks [10-12]. While ODT is recommended for all patients with HAE-C1INH, LTP is usually prescribed to patients with greater disease activity [10,11,13]. New therapeutic options that have recently become available for LTP of HAE-C1INH include subcutaneous C1INH concentrate [14], a subcutaneous monoclonal antibody targeting plasma kallikrein (lanadelumab) [15], and an oral kallikrein inhibitor (berotralstat) [16]. Other agents are still in development [12]. Treatment guidelines are available for both ODT and prophylaxis in HAE [17-21]. However, criteria for initiation of LTP, definitions of LTP targets, treatment switches, and details for preparing patient management plans are still lacking. Furthermore, management of HAE-C1INH varies from country to country depending on drug availability and economic resources [22].

This scenario reveals the need to define appropriate treatment goals and adequate management protocols for assessing the control of HAE-C1INH and optimizing treatment. A growing understanding of the disease at the molecular level and the increasing availability of therapeutic options [12] have led—as in other diseases—to a shift in focus from symptom control to disease control [23]. The treat-to-target strategy aims to achieve overall control of symptoms by controlling the underlying condition while sharing decision-making with the patient to improve adherence [24]. It has been successfully applied in various chronic conditions characterized by disease activity flares, such as rheumatic diseases [25], asthma [26], inflammatory bowel disease [27,28], and chronic urticaria [29].

Therefore, our aims were to review available evidence for the management of HAE-C1INH, to build a Spanish expert consensus that would steer traditional management of HAE-

C1INH towards a treat-to-target approach, and to address some of the less clear aspects of the current guidelines in Spain.

Methods

Literature Review

A structured literature review was carried out to identify, describe, and synthesize relevant information published on guidelines for HAE-C1INH management and instruments for monitoring HAE-C1INH activity, disease control, disease severity, and HRQOL. The search was carried out in PubMed; the search terms and strategy are detailed in the Supplementary Material (Table A 1). The initial review was completed in August 2019 and included references published since 2002. This was subsequently updated in June 2022. Instruments were selected and summarized from primary research results, reviews, guidelines, and original studies focusing on management and treatment goals, biomarkers of disease activity, and patient-reported outcomes. Search results were then integrated with references obtained from reviewing the reference list of selected publications or already known to the authors. The literature review yielded 263 references in total, of which 32 were relevant to this review; a further 23 references were added manually.

Evidence collated from the literature review was synthesized before being discussed during a meeting of the steering committee. Delphi statements were proposed, and the most relevant ones were selected. Subsequently, all committee members reviewed the first version of the Delphi questionnaire and made a final selection of the most relevant items.

Delphi Consultation

To validate the recommendations originating from the literature review, we performed a 2-round online Delphi consultation on 45 statements relating to the main open topics in HAE management with the participation of 54 HAE experts from across Spain. Details are presented in Supplementary Materials.

Results

On-demand Treatment

Acute administration of ODT after onset of an attack is part of HAE-C1INH management, and a number of drugs are currently available for this purpose [30]. International

clinical guidelines and consensus documents on HAE-C1INH management recommend ODTs with confirmed effectiveness and safety in clinical trials and in real-world practice [17,19,20,30].

To date, 4 types of medication containing C1INH are available [12]: intravenous (IV) C1INH concentrates, which include plasma-derived C1INH (pdC1INH), marketed worldwide as Berinert (CSL-Behring) and Cinryze (Takeda Pharmaceutical Company Ltd); recombinant human C1INH (rhC1INH), marketed as Ruconest (Pharming Group NV); and fresh frozen plasma, which contains C1INH but is not authorized in Spain for this indication.

C1INH concentrates are effective in treating acute angioedema attacks [12,18,31], and while evidence regarding the use of fresh frozen plasma to treat angioedema attacks is much less abundant than published data from randomized clinical trials on the other ODTs, fresh frozen plasma remains an option for patients for whom no other acute therapies are readily available [19,20,22].

Targeted therapies include the subcutaneous (SC) bradykinin B2-receptor antagonist icatibant (Firazyr, Takeda Pharmaceutical Company Ltd) and the SC plasma kallikrein inhibitor ecallantide (Kalbitor, Takeda Pharmaceutical Company Ltd) [12,31]. In children, the only approved ODTs for HAE-C1INH are C1INH and icatibant [12].

International HAE guidelines recommend that ODT be considered for all HAE attacks, and that patients should be provided with at least 2 doses [18-20]. ODT can result in a better response when administered early during the attack [12]. However, data obtained from real-world studies have shown that, in real practice in Spain, the time to treatment with ODT after onset was longer than in other countries, likely contributing to a longer duration of attacks and time to resolution [32]. This information strongly supports the importance of early ODT to treat attacks in order to improve patient outcomes. Therefore, the expert panel recommended

that all angioedema attacks be considered candidates for ODT and treated early after onset. Accordingly, all patients diagnosed with HAE-C1INH should always have at least 2 complete doses of acute HAE medication at their disposal. The goals of acute ODT for angioedema attacks are to prevent worsening of symptoms or suffocation if the upper airways are involved and to minimize associated morbidity and mortality while preserving patient HRQOL [18-20,30].

The panel strongly agreed that the most appropriate ODT should be chosen by the clinician and a well-informed patient working together, based on the patient's specific needs and preferences. Shared decision-making on individualized treatment plans is facilitated by a close relationship between patients and physicians and detailed discussion of the patient's medical condition, available therapeutic strategies, and treatment-associated adverse effects. These should prioritize the right of patients to be informed and to improve their HRQOL, disease control, and adherence [33,34]. Preventive measures such as home care and self-administration of ODT should be part of individualized treatment plans. Self-administration is crucial for early treatment of acute angioedema attacks. International guidelines recommend that all HAE-C1INH patients should be trained in home therapy and self-administration of ODT for angioedema [18,20,35]. Numerous studies have supported the clinical benefits of patient self-treatment with existing therapies, such as C1INH concentrates [33,36]. In addition, costs related to the management of acute HAE attacks may be substantially reduced by training patients to self-administer acute therapy at home [37]. The expert panel highly recommends that all HAE-C1INH patients should be trained in self-administration of acute ODT and that the patient's competence in self-administration is periodically evaluated, according to clinical guidelines.

Laryngeal angioedema attacks are potentially life-threatening, and, consequently, those patients who experience

Table 1. Summary of the Recommendations Agreed by the Panel of Experts for On-demand Treatment (ODT).

Recommendation	Supporting literature
The goal of ODT for angioedema attacks should be to minimize associated morbidity and mortality.	[18-20,30]
The most appropriate ODT should be chosen by the clinician and a well-informed patient working together, based on his/her specific needs and preferences.	[33,34]
All angioedema attacks are candidates for ODT.	[18-20]
All angioedema attacks should be treated as early as possible.	[12]
All patients diagnosed with HAE-C1INH should have 2 complete doses of angioedema-specific medication at their disposal at all times.	[18-20]
The patient should be adequately trained in the self-administration of angioedema ODT.	[18,20,35]
The patient's competence in self-administration of ODT should be periodically evaluated.	[35]
A patient with an upper airway angioedema attack should attend the emergency room after treatment in order to monitor the degree of airway involvement.	[18,20,38]
The need for naso- or orotracheal intubation or tracheotomy should always be considered in case of an upper airway angioedema attack.	[18,20,33]
Abdominal ultrasound scan is advisable in the case of an abdominal angioedema attack that does not improve after specific ODT for angioedema.	[21,38-40]

an upper airway angioedema attack should seek emergency care after treatment in order to monitor the degree of airway involvement and to reduce the risk of asphyxia [18,20,38]. The need for naso- or orotracheal intubation or tracheotomy should always be considered early in progressive upper airway edema if respiratory distress does not improve after the administration of ODT [18,20,33].

In the emergency department, the diagnosis of HAE-C1INH with abdominal involvement is challenging. Early recognition of a severe acute abdominal attack is crucial to prevent misdiagnosis and unnecessary surgical interventions and to provide patients with proper early and effective treatment. Abdominal ultrasound is advisable in the case of an abdominal angioedema attack that does not improve after specific ODT for angioedema. Abdominal and pelvic ultrasound examination or computed tomography imaging facilitate the differential diagnosis of the patient suspected of having an abdominal attack that does not respond to ODT for HAE-C1INH [21,38-40].

Based on the evidence discussed and experience from clinical practice, the expert committee agreed on a series of recommendations (Table 1) (Delphi scores are available in Supplementary Material Table A2).

Short-term Prophylaxis

The main objective of STP is to reduce the risk of angioedema attacks and of associated morbidity and mortality when exposure to a potential or known trigger can be anticipated. The recommended option for STP is IV pdC1INH [18-21]. Data on potential triggers for HAE attacks come mostly from small retrospective studies or patients' reported experiences [2,38,41,42]. It is known that the mechanical impact on the upper airway due to surgical or dental procedures, intubation, and other interventions can provoke angioedema and be associated with upper airway swelling. Thus, the upper airway of HAE-C1INH patients undergoing procedures that require intubation should be monitored after extubation [43].

Based on the current inability to link the risk of an attack to a specific procedure, it is recommended that STP be administered at least prior to medical, surgical,

and dental procedures to prevent associated breakthrough attacks [18-21]. Emotional distress has been reported as the most common trigger for HAE attacks (in 23.2% of HAE-C1INH patients), with higher frequency than other known triggers for which STP is usually recommended (ie, physical trauma [5.4% of patients]) [41]. Thus, STP should also be considered before or during any stressful life event, such as examinations or important life or work events that may worsen HAE-C1INH activity, to avoid triggering angioedema attacks [35]. As discussed above, all patients, including those taking STP, should have at least 2 doses of proper angioedema ODT immediately available during and after any medical procedure such as surgical or dental interventions [19].

The expert committee stressed that HAE-C1INH should not induce patients to delay or avoid emergency interventions, irrespective of whether STP is not immediately available or has been administered less than 1 hour before any procedure [44,45].

All recommendations on STP agreed by the Delphi expert panel are detailed in Table 2 (Delphi scores are available in Supplementary Material Table A3).

Long-term Prophylaxis

Therapeutic options for LTP are expanding, although no clear criteria have been established on when to initiate this therapy, nor have goals been explicitly set. Several drugs have been approved as LTP in HAE-C1INH. These include the following: oral danazol, which enhances hepatic synthesis of C1 inhibitor and plasma aminopeptidase P activity; tranexamic acid, which competitively inhibits plasminogen activation (although its efficacy is considered low in real life, and thus its use is reserved for specific females or children); the IV pdC1INH Cinryze; the SC pdC1INH Berinert; and the SC monoclonal antibody against plasma kallikrein, lanadelumab (Takhzyro, Takeda Pharmaceutical Company Ltd) [12]. The plasma kallikrein inhibitor berotralstat (Biocryst) was recently approved for LTP [46]. Current international guidelines recommend pdC1INH, lanadelumab, and berotralstat as first-line LTP in HAE-C1INH [18,20].

Table 2. Summary of Recommendations for Short-term Prophylaxis (STP).

Recommendation	Supporting literature
The objective of STP should be to prevent angioedema attacks associated with known triggers, such as medical, surgical, and dental procedures and stressful life events.	[17-20]
STP should be administered before medical or surgical procedures to prevent angioedema attacks.	[18-21]
STP should be administered before dental procedures with a risk of triggering angioedema attacks.	[18-21]
STP may be administered before or during any stressful life event that may worsen HAE-C1INH activity to prevent angioedema attacks.	[35]
Despite previous administration of STP, at least 2 doses of angioedema on-demand treatment should be available during and after medical, surgical, or dental procedures.	[19]
An urgent surgical intervention should never be delayed, even if STP has been administered less than 1 hour before.	[44,45]
The upper airway must be monitored after extubation in the case of procedures that required intubation.	[43]

Initiation of LTP and Criteria for Switching

LTP is a standard treatment aimed at preventing angioedema attacks when ODT is not sufficient to achieve adequate disease control. The main goal of LTP is to achieve full control of the disease by reducing the frequency and severity of attacks, as well as the impact of disease on the HRQOL of patients and the burden and toxicity of treatments. The World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines, International/Canadian Hereditary Angioedema Guidelines, and the HAE Association (HAEA) guidelines recommend that patients and physicians share decision-making on whether to initiate LTP [18-20]. However, there are still no clear indications on the right time at which to start treatment. The expert panel agreed that the need to start LTP should be reviewed at each follow-up visit, according to the criteria reported in Table 3. In the shared decision-making on LTP, the benefits and potential risks of LTP medications should be discussed in detail with patients so they can participate with physicians in choosing the most appropriate LTP and make well-informed choices. Treatment planning must consider a series of individualized factors such as disease activity, burden, and control, in addition to patient comorbidities, HRQOL, expectations, preferences, and accessibility to health care and emergency resources (Table 3). In this sense, the overall criteria followed for the indication of HAE medications, including LTP, are the same in adults as in children [19,20]. The committee also agreed that the choice of LTP is influenced by the desired effectiveness of medication.

In patients receiving LTP, changes in medication or dosing should also be considered. In accordance with the current HAEA and WAO/EAACI guidelines, the expert panel recommends regular assessment of the efficacy and tolerability of LTP to adjust or switch prophylaxis according to disease severity and the patient's response to therapy [18,20].

Table 3. Criteria for Initiating Long-term Prophylaxis (LTP) According to the Degree of Importance Attributed by the Delphi Panel.

Criterion	Importance (range, 1-9)
Number of monthly angioedema attacks	9
Severity of angioedema attacks	
Location of angioedema attacks	
Disease activity	8
Disease control	
Quality of life	
Limitation of activities of daily living	
Accessibility to on-demand medication	
Distance from the closest health center	
Expected adherence to LTP	7
Duration of angioedema attacks	
Satisfaction of the patient with on-demand treatment	
Explicit desire of the patient	

However, it is important that patients receiving LTP have rapid access to an acute ODT plan agreed with physicians, as prophylaxis does not eliminate the risk of angioedema and attacks may still occur [18,19].

Goals of LTP and Measurement of Outcomes

The goals of HAE treatment are to achieve overall disease control and restore the patient's life to normal [18,20,47]. This translates into pursuing zero attacks, for which LTP is the key. However, zero attacks remains a difficult goal to achieve. Thus, we analyzed the different components of this overall goal.

First, it should be noted that, according to the principle of shared decision-making, LTP goals should be established by the clinician and the patient together. Not all patients prioritize the same goals. One goal for LTP is, undoubtedly, to reduce the rate of angioedema attacks, whereas independent goals may be to decrease the rate of severe angioedema attacks and/or their duration.

The assessment of disease severity/activity and attack severity in HAE-C1INH was reviewed by Bygum et al [48] in 2017. Severity of attacks is not easily evaluated, as it comprises various parameters [48,49]. Patient-reported outcome measures (PROMs) such as visual analog scales referring to a single sign/symptom or the whole complex of signs/symptoms of an attack are often used in clinical trials and in routine practice, as they are easy to use [48,49]. A validated PROM taking into account the global severity of the attack, the Mean Symptom Complex Severity (MSCS) score [50], provides a global score that incorporates the number of anatomical locations affected during an acute attack ("symptoms complex", eg, hands and abdomen) and the patient's own evaluation of severity of swelling at each site (eg, none to severe). Thus, the MSCS measures the severity of an attack at a specified time point, prior to administration of a study medication or during a time period after drug administration [48]. However, its use is very limited owing to the difficulty in calculating the score.

The severity of HAE-C1INH has been defined as the patient's overall disease experience. It includes previous problems imposed by the disease since onset, current disease burden, and long-term risks and prognosis, including fear of the emergence of potential problems [48]. There is no validated score to measure disease severity. It has been suggested that all patients have severe disease as they are at risk for an upper airway attack and death by asphyxiation [48]. Disease activity was found to be a more appropriate variable to use and has been defined as "the sum of the current problems (over a specified period of time) that a patient has experienced with his or her disease" [48]. The Hereditary Angioedema-Activity Scale (HAE-AS) can be used to assess overall disease activity [51]. It consists of 12 one-dimensional items. The raw score is transformed into a linear measure on a scale of 0 to 30. The HAE-AS has good internal consistency, satisfactory reliability for group comparisons, and good discriminative validity by age, sex, and disease severity [51]. The Angioedema Activity Score for recurrent angioedema is a more widely available tool [52].

It is also important to measure disease control at specific time points. The Angioedema Control Test is the most suitable instrument for this evaluation [53].

The LTP response with respect to any of the aforementioned goals should be assessed between 3 and 6 months after initiation of treatment, and adjustments to treatment should be considered to achieve maximum effectiveness.

Health-Related Quality of Life

The 2 main instruments available for evaluating HRQOL in patients with recurrent angioedema are the Angioedema Quality of Life (AE-QoL) tool [54,55], which is oriented toward adult patients with any type of recurrent angioedema, and the specific Hereditary Angioedema Quality of Life (HAE-QoL) tool, which has been validated for HAE-C1INH [56]. Another specific instrument, the HAEA-QoL, was developed specifically for use in the USA [57]. The AE-QoL consists of 17 questions in 4 domains (functioning, fatigue/mood, fear/shame, and nutrition) and covers a 4-week recall period. The score ranges from 0 to 100. The HAE-QoL consists of 25 questions distributed into 7 domains spanning all areas in which HAE patients are affected by their disease (treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, and mental health). Both are validated instruments for monitoring the HRQOL of affected patients. As HAE-QoL has a 6-month recall period, it should be performed at least every 6 months, which is a reasonable timeframe considering Spanish follow-up protocols.

A recently published study evaluated the validity of use of the generic 36-item Short-Form Health Survey (SF-36v2) to evaluate HRQOL in HAE-C1INH patients [58]. The authors concluded that this tool could be useful for assessing HRQOL, with some content validity limitations. We consider that, while this questionnaire may be helpful in studies comparing different diseases, it is not the best tool for monitoring disease follow-up.

Several studies have shown that LTP improves HRQOL in HAE patients, as assessed with both the AE-QoL and/or HAE-QoL questionnaires [16,59-63]. A qualitative study showed that patients reporting no or almost no attacks improved perception of HRQOL in terms of no longer having feelings of HAE-inflicted limitations, less HAE-related anxiety/worry and depression, improved ability to travel, reduced use of emergency department/hospital resources, and improved self-administration of subcutaneous pdC1INH, along with independence from assistance [64]. Patients also expressed increased confidence, optimism, and normalcy, together with reduced absence from work/school, increased productivity, improved sleep and energy, healthier family relationships, and improved cognition. In the interviews, all AE-QoL items emerged spontaneously from patients. However, numerous identified concepts were not addressed by the AE-QoL, including increased awareness of potential attack triggers (eg, stress/anxiety, sports), reduced attack frequency, improvements in ability to perform day-to-day tasks and make social plans, and a lower burden from medical visits.

Although clinical guidelines indicate that follow-up of LTP should include an evaluation of HRQOL at each visit (recommended minimum 1 visit per year), the specific improvement in HRQOL seen through the PROMs that should be taken into consideration when contemplating switching therapy is not clearly specified. Nevertheless, this

expert committee suggested that the LTP response should be considered appropriate when HAE-QoL or AE-QoL scores improve; consequently, if the improvement in the LTP response in terms of the HAE-QoL or AE-QoL score is not sufficient, then the clinician should consider adjusting or switching treatment.

Adverse Effects

One of the potential limitations of current tools for assessment of HRQOL is that the convenience or adverse effects of treatments are not considered, even though they may have a considerable impact on patient HRQOL. There is a need for larger studies that help to differentiate between disease symptoms and treatment-associated adverse events [65,66].

We concur that the probability of experiencing certain AEs influences the selection of LTP. The choice of LTP should be agreed between physician and patient, considering the risks of treatment-associated adverse effects, especially in fertile women and in pregnancy and breastfeeding [18,20,67]. In this sense, we recommend that adverse effects associated with LTP are regularly monitored (ie, at follow-up visits). Current clinical guidelines advocate regular assessment of efficacy, safety, and adherence to LTP medications [18]. Some therapies require closer surveillance (as occurs with the prophylactic use of anabolic androgens, which are associated with major adverse effects) in order to re-evaluate their risk-benefit. At least 6-monthly follow-up visits and control tests are recommended. The same is true for prophylactic antifibrinolytics. Although other HAE medications do not need specific monitoring, minor medication-associated AEs should be reviewed at every follow-up visit, including injection site reactions with SC lanadelumab or SC pdC1INH and venous complications from the administration of IV C1INH concentrates [20].

We also suggest an ad hoc checklist-based evaluation at each follow-up consultation of HAE-associated adverse events that may trigger specific medical concerns (Supplementary table A4) for prompt detection of any change in situation during treatment.

All recommendations for which consensus was reached (LTP goals, follow-up, HRQOL, and adverse effects) are listed in Table 4 (Delphi scores available in Supplementary Material Table A5).

General Aspects of HAE-C1INH Treatment

Patient Satisfaction

Treatment options have traditionally been limited in the setting of HAE-C1INH. Patient satisfaction is becoming more important, however, as new therapeutic options become available [12]. This is particularly relevant, as patient satisfaction with treatment is consistently associated with better adherence and, accordingly, better clinical outcomes, improved HRQOL, and reduced management costs [68,69].

This expert panel supports the periodical assessment of patient satisfaction with treatment using the Treatment

Table 4. Summary of Recommendations for Long-term Prophylaxis (LTP).

Recommendation	Supporting literature
LTP indication and switch criteria	
LTP requirements should be considered at each follow-up visit.	
The decision to initiate LTP should be shared between the physician and the patient.	[18-20]
The selection of the most appropriate LTP treatment should be shared between the clinician and a properly informed patient.	
The criteria for indicating LTP are the same in adults and children.	[19,20]
The desired effectiveness will influence the selection of LTP type	Steering committee consensus
If the response to treatment is insufficient, then treatment should be adjusted or switched.	[18,20]
LTP goals and outcome measurement	
LTP goals should be established by the clinician and the patient working together.	Steering committee consensus
A goal of LTP is to reduce the angioedema attack rate.	[18-20]
LTP response is assessed based on the decrease in the angioedema attack rate.	Steering committee consensus
A goal of LTP is to reduce the rate of severe angioedema attacks.	[18-20]
A goal of LTP is to reduce the duration of angioedema attacks.	Steering committee consensus
The Hereditary Angioedema-Activity Score [51] should be used as a tool to assess overall disease activity, and the AngioEdema Control Test for the assessment of disease control [53]	Steering committee consensus
The LTP response with respect to any of the aforementioned goals should be assessed between 3 and 6 months after starting treatment.	Steering committee consensus
Health-related quality of life (HRQOL)	
HRQOL should be assessed at least every 6 months.	Steering committee consensus
HRQOL should be assessed using specific questionnaires: Hereditary Angioedema-Quality of Life (HAE-QoL) [56] or the Angioedema-Quality of Life (AE-QoL) [55].	[18-20]
The LTP response should be considered appropriate when HAE-QoL or AE-QoL scores improve.	Steering committee consensus
If the LTP response in terms of the HAE-QoL score is not sufficient, adjusting or switching treatment should be considered.	Steering committee consensus
Adverse effects (AEs)	
AEs associated with LTP should be monitored at every follow-up visit.	Steering committee consensus
AEs associated with LTP should be monitored using an ad hoc checklist.	Steering committee consensus
The probability of experiencing certain AEs will influence the choice of LTP.	Steering committee consensus

Satisfaction Questionnaire for Medication in its original or abbreviated versions [70,71]. Consequently, patient satisfaction should be included as a criterion when considering whether to maintain or switch treatment.

Cost of and Access to Treatment

The costs of suitable treatments for ODT and LTP are a major barrier for HAE patients and physicians when accessing care. Several European countries have limited access to prophylaxis with IV/SC pdC1INH or lanadelumab and to self-administration of treatments in order to reduce direct drug costs [72]. In this respect, it is important to highlight the substantial direct and indirect costs associated with HAE in terms of utilization of health care resources and work productivity [8,73]. Drug development has improved HRQOL and helped to significantly reduce the burden of HAE, use of emergency and medical resources, absenteeism from work and

school, and mortality, all of which decrease the overall cost to the public health system [37,74].

Based on what the expert panel considers an inherent responsibility from the physician's point of view, agreement was reached that all approved therapeutic options should be equally accessible to all patients, independently of their place of residence. In this scenario, clinicians could guarantee and provide patients with treatment options to improve disease management and reduce the need for emergency care. Unfortunately, in Spanish clinical practice, it is not always possible to prescribe the best available therapeutic option, as treatment costs often influence the choice of therapy to comply with local hospital protocols and budgetary restrictions [75].

Importance of the Patient Diary

It is recommended that patients, especially those receiving LTP, document all characteristics of their HAE

Table 5. Recommendations for General Aspects of HAE-C1INH Treatment.

Recommendation	Supporting literature
Patient satisfaction with treatment	
Patient satisfaction with treatment should be assessed periodically.	Steering committee consensus
Patient satisfaction should be considered a criterion for considering the maintenance/switching of treatment.	
Patient satisfaction should be assessed by the Treatment Satisfaction Questionnaire for Medication in its original version (14 items) [70,71] or abbreviated version (9 items) [70]	
Cost and accessibility of treatment	
Cost of treatment influences choice of treatment.	Steering committee consensus
All patients should have access to all treatments independently of their place of residence.	
Patient diary	
Patients should keep a diary to record the characteristics of each angioedema attack (location, severity, duration, on-demand treatment administration, and response to on-demand treatment), whether short-term prophylaxis was administered and reason, or if the patient is receiving long-term prophylaxis.	[18,20,75]
Analysis of the patient diary may help optimize treatment and identify unknown triggers.	Steering committee consensus

attacks, as this information can help both patients and clinicians to assess the efficacy of treatment and improve disease management [18,20,76]. International guidelines and consensus documents advise patients to record all data regarding their disease activity in a diary, which should be reviewed at each follow-up consultation [18,20]. The expert committee agreed to recommend that patients keep a diary of the characteristics of each angioedema attack, including location, severity, duration, ODT, and response to ODT. Information should also include whether STP was administered and the reasons for its initiation, or if the patient was receiving LTP. Analysis of the patient diary may help to optimize treatment and identify unknown triggers.

The general recommendations agreed upon are listed in Table 5 (Delphi scores available in Supplementary Material Table A6).

Discussion

Our systematic review revealed several international guidelines with recommendations on the management of HAE-C1INH. Nevertheless, adherence to these guidelines varies from country to country, mostly depending on drug availability and local protocols. The approval of new drugs for LTP is changing the treatment landscape and guideline recommendations, prioritizing new drugs with high efficacy and fewer adverse effects, albeit at a higher cost. However, there is a lack of specific goals for LTP, which we attempted to address in our Delphi consensus.

The consensus highlights the need for an integrated HAE-C1INH management plan that includes ODT, STP, and LTP. Our aim was also to define the main treatment goals for ODT (minimizing the morbidity and mortality associated with angioedema attacks), STP (preventing angioedema attacks associated with known triggers), and LTP (reducing

the rate of angioedema attacks and severe angioedema attacks and attack duration). We also provided the criteria for LTP indications and a checklist for the follow-up of treatment-associated AEs. Moreover, we addressed the importance of patient satisfaction regarding treatment, treatment costs and accessibility, and the importance of the patient diary for tracking the attacks and response to treatments in the follow-up of disease progression and severity.

Soon after this expert committee completed the 2 Delphi rounds, an international panel of specialists on HAE published another Delphi-based consensus document that defined 2 general objectives in the management of HAE-C1INH: achievement of total disease control and restoration of a normal life for the patient [47]. In this consensus, 21 statements related to these 2 overall goals were assessed, and consensus was reached for 18.

In our Delphi process, a panel of HAE experts evaluated a total of 45 statements aimed at facilitating discussion of the most suitable treatment according to each patient's profile and needs, trying to define the specific goals for ODT, STP, and LTP as a means for achieving overall control of HAE and restoration of a normal life.

The international consensus published in 2021 by Maurer et al [47] proposed the following features as indicators of control of HAE-C1INH and normalization of HRQOL: need for rescue medication, number of attacks, number of emergency room visits and hospitalizations, days of sick leave due to HAE-C1INH, and hours of activity impairment due to HAE-C1INH in a given time period. The authors also stated that the estimation of the proportional reduction in the number of HAE-C1INH attacks in a given period of time should be used to evaluate the ability of a treatment to maintain control of HAE-C1INH and restore normal life. In addition, the duration of attack-free intervals was proposed as a measure to assess whether normal life had been restored, although the authors did not agree on the use of this variable to evaluate HAE-C1INH control.

We also selected reduced attack rate as a key variable for evaluating disease management and control. However, as additional parameters, we proposed change in disease activity and HRQOL score, patient satisfaction score regarding treatment, and the use of an ad hoc checklist to evaluate treatment-associated adverse effects.

From our experts' point of view, it is crucial that patients feel sufficiently empowered to control their disease and provide their perception of the degree of control of their disease and HRQOL. Therefore, this expert panel stressed the importance of prioritizing the patient's own therapeutic goals and shared decision-making on treatment options. Keeping an accurate diary to record all the features of their attacks and response to treatment may be a helpful tool for monitoring disease severity and designing the best individualized treatment plans. None of the currently available tools for measuring disease burden or activity alone is sufficient for the assessment of disease control or HRQOL. The development of new tools to assess patient-reported outcomes would surely cover this unmet need for both patients and physicians [20,47,77].

One of the most important statements agreed on by our expert committee was that all approved therapeutic options should be equally accessible to all patients, independently of their place of residence, as this is currently a major gap in our daily practice.

Finally, consensus was not reached for only 1 of the proposed statements submitted to Delphi consultation in either of the 2 rounds, namely, "*The level of LTP response considered adequate is assessed based on the type of LTP administered*". This statement addressed the fact that some specialists have to choose less effective and/or safe "conventional" treatments (eg, attenuated androgens, tranexamic acid) instead of the more recently approved LTP medications (eg, SC pdC1INH, lanadelumab, and berotralstat) owing to the limitations of the existing local treatment algorithms and direct drug costs. Thus, specialists often adjust the therapeutic goals to the expected effectiveness of the chosen treatment, while trying to keep the patient within proper safety margins (eg, not trying to reach zero attacks with attenuated androgens, but prescribing the minimal effective dose that will keep the number of attacks very low) [2]. Our failure to reach an agreement on this item might be due either to a lack of understanding of the issue or to the panelists simply not agreeing with it. Therefore, rejecting this item might be understood as HAE experts preferring not to maintain standard practice and instead to assess therapeutic effectiveness in terms of achieving the ideal patient goal from a treat-to-target perspective.

We constructed our recommendations based on expert opinion and the updated review of available evidence. Indeed, recommendations based on high-quality evidence are already incorporated into clinical guidelines, in which various other topics remain undetermined. The aims of this exercise were to gather and share Spanish experience in real-world clinical practice in areas where the management guidelines are less clear and to reinforce adherence to specific recommendations that are poorly applied in this setting. We also aimed to provide a practical framework that may help Spanish clinicians to improve management of HAE-C1INH in their daily practice.

Conclusions

We provide a validated, evidence-based list of statements and recommendations on the management of HAE, focusing on therapeutic goals in clinical- and patient-oriented terms and aiming to fill existing gaps on certain aspects of HAE management.

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Conflicts of Interest

Teresa Caballero is a member of advisory boards for Astria, BioCryst, CSL Behring, Novartis, Octapharma, Pharming, and Takeda; she is a member of speakers bureaus for CSL Behring, Novartis, and Takeda; she has received grants or honoraria from BioCryst, CSL Behring, Novartis, Pharming, and Takeda and funding to attend conferences and educational events from CSL Behring, IONIS, Novartis, Pharming, and Takeda; she is a clinical trial/registry investigator for BioCryst, CSL Behring, Novartis, Pharming, and Takeda and a researcher in the IdiPAZ program for promoting research activities.

Ramón Lleontart has received honoraria from BioCryst, CSL Behring, KalVista, Novartis, and Takeda; he has received funding to attend conferences and educational events from CSL Behring, Novartis, Pharming, and Takeda and is a clinical trial/registry investigator for BioCryst, CSL Behring, Novartis, Pharvaris, KalVista, and Takeda.

María Pedrosa has received grants or honoraria from CSL Behring, Novartis, Pharming, and Takeda; she has received funding to attend conferences and educational events from CSL Behring, Novartis, Pharming, and Takeda and is a clinical trial/registry investigator for CSL Behring, Pharming, and Takeda; she is also a researcher in the IdiPAZ program for promoting research activities.

Lucía Ferrer has received honoraria and funding to attend conferences and educational events from Takeda and is a researcher from IIS (Aragon Health Research Institute)

Mar Guilarte has received honoraria for educational purposes from CSL Behring, Novartis, and Takeda; she has participated in advisory boards organized by CSL Behring, Novartis, and Takeda and has received funding to attend conferences and educational events from CSL Behring, Novartis, Pharming, and Takeda; she is a clinical trial/registry investigator for BioCryst, CSL Behring, Novartis, Pharming,

Pharvaris, and Takeda and a researcher in the VHIR program for promoting research activities.

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