Expert review and consensus on the t2t management of hereditary angioedema: from the scientific evidence to clinical practice

Running title: T2T management of hereditary angioedema

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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 lethal, when involving upper airways. 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 treatment selection, its goals or assessment of goal achievement.

Objective: To review the available evidence for the management of HAE-C1INH and build a Spanish expert consensus to steer HAE-C1INH management towards a treat-to-target (T2T) approach, while addressing some of the unclear aspects of the Spanish guidelines.

Methods: We reviewed the literature on the management of HAE-C1INH with a T2T approach, focusing on: 1) treatment selection and goals; and 2) available tools to assess goal achievement. 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 two-round Delphi process.

Results: The goals for ODT and STP are minimizing the morbidity and mortality of attacks, and preventing 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 events, while increasing patient QoL and satisfaction. Appropriate instruments for assessing goal achievement have also been indicated.

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

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

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RESUMEN

Antecedentes: el angioedema hereditario por deficiencia del inhibidor C1 (AEH-C1INH) es una enfermedad rara que se manifiesta con episodios inflamatorios 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.

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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]. It 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 negatively affects health-related quality of life (HRQoL) of patients and caregivers, both in the short and long term [7-9].

On-demand treatment (ODT) of angioedema attacks along with short- and long-term prophylactic treatment (STP and LTP) aimed at preventing attacks are the three currently available treatment strategies for HAE-C1INH [10-12]. While ODT is recommended for all patients with HAE-C1INH, LTP is usually prescribed to patients with higher disease activity [10, 11, 13]. New therapeutic options have recently become available for HAE-C1INH LTP, such as a subcutaneous (SC) C1-INH concentrate [14], a subcutaneous monoclonal antibody targeting plasma kallikrein (lanadelumab) [15], and an oral kallikrein inhibitor (berotralstat) [16], while other agents are still in development [12]. Treatment guidelines are available for both ODT and prophylaxis in hereditary angioedema [17-21]. However, criteria for LTP initiation, defined LTP therapeutic targets, or treatment switches, and details for preparing patient management plans are still lacking. Furthermore, HAE-C1INH management 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 to ensure optimal treatment. A growing understanding of the disease at a molecular level and the increasing availability of

therapeutic options [12] have, similar to other diseases, opened the door to a paradigm shift from a focus on symptom control to disease control [23]. The treat-to-target (T2T) strategy aims to achieve overall control of symptoms by controlling the underlying condition while sharing decision-making with the patient to improve treatment compliance [24]. It has been successfully applied in various chronic conditions characterized by disease activity flares, such as rheumatoid diseases [25], asthma [26], inflammatory bowel disease [27, 28], and chronic urticaria [29], among others.

Therefore, our aim was to review the available evidence for the management of HAE-C1INH, as well as to build a Spanish expert consensus to steer traditional HAE-C1INH management towards a T2T approach, and to address some of the unclear 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, severity, and quality of life (QoL). The search was carried out in PubMed; the search terms and strategy are detailed in 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 the primary research results reviews, guidelines, and original studies focusing on: 1) management and treatment goals; 2) biomarkers of disease activity; and 3) patient-reported outcomes. Search results were then integrated with references obtained from reviewing the bibliography 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; another 23 references were added manually.

Evidence collated from the literature review was synthesized and presented during a meeting of the steering committee, at which the evidence was discussed. 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 two-round online Delphi consultation on 45 statements relating to the main open topics in HAE management with the participation of 54 HAE experts across Spain. Details are presented in Supplementary Materials.

RESULTS

On-demand treatment

Acute ODT administration after attack onset is part of HAE-C1INH management, and a number of drugs are currently available for this purpose [30]. Different international clinical guidelines and consensuses on HAE-C1INH management recommend several ODTs with confirmed effectiveness and safety in clinical trials and in real-world practice [17, 19, 20, 30] .

To date, four types of medication containing C1-INH are available [12]: intravenous (IV) C1-INH concentrates, which include the plasma-derived C1-INH (pdC1-INH), marketed worldwide as Berinert (CSL-Behring) and Cinryze (Takeda Pharmaceutical Company Ltd); recombinant human C1-INH (rhC1-INH), marketed as Ruconest (Pharming Group NV); and fresh frozen plasma (FFP) which contains C1-INH, although this is not authorized in Spain in this indication.

C1-INH concentrates are effective in treating acute HAE attacks [12, 18, 31]. Although evidence regarding the use of FFP to treat HAE attacks is much less abundant than the published data

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from randomized clinical trials on the other ODTs, FFP remains an option for many patients for whom no other acute therapies are readily available [19, 20, 22].

Targeted therapies include the 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 HAE1/2 are C1-INH and icatibant [12].

International HAE guidelines recommend that ODT be considered for all HAE attacks, and that patients should be provided with sufficient ODT doses (at least two doses) for treating at least two attacks [18-20]. The administration of ODT can result in a better response when given 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 attack onset was longer when compared with other countries, which likely contributed to a longer duration of attacks and time to attack resolution [32]. This information strongly supports the importance of early ODT to treat attacks in order to improve patient outcomes. Based on this evidence, the expert panel agreed on recommending that all angioedema attacks should be considered as candidates for ODT and treated early after attack onset. Accordingly, all patients diagnosed with HAE-C1INH should always have at least two complete doses of acute HAE medication at their disposal. The goal of acute ODT for angioedema attacks is to prevent worsening of symptoms or suffocation in the event that the upper airways are involved, and to minimize the associated morbidity and mortality while preserving patient QoL [18-20, 30].

The board strongly agrees that the choice of the most appropriate ODT should be made by the clinician and a well-informed patient working together, based on the patient's specific needs and preferences. A close relationship between patients and physicians and detailed discussion of the patient's medical condition, available therapeutic strategies and treatment-associated adverse effects, facilitates shared decision-making on individualized treatment plans. These

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should prioritize the right of patients to be informed and to improve their QoL, disease control and treatment 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-1/2 patients should be trained in home therapy and self-administration of angioedema ODT [18, 20, 35]. Numerous studies have supported the clinical benefits of patient self-treatment with existing therapies, such as C1-INH 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 patients should be trained in self-administration of acute ODT and that the patient's competence in ODT self-administration is periodically evaluated, according to clinical guidelines.

Laryngeal HAE attacks are potentially life-threatening and consequently, those patients who experience 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 a patient with HAE-C1INH and abdominal attack is challenging. Early recognition of a severe acute abdominal attack is crucial to prevent misdiagnosis and unnecessary surgical interventions and also, to provide patients with proper early and effective treatment. An abdominal echography is advisable in case of an abdominal angioedema attack that does not improve after specific angioedema ODT. Abdominal and pelvic ultrasound examination or computed tomography (CT) imaging facilitate the differential diagnosis of the patient suspected of having an abdominal attack due to HAE-C1INH unresponsive to ODT [21, 38-40].

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

Short-term prophylaxis

The main objective of short-term prophylaxis (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 pdC1-INH [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 may provoke angioedema as it may 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 or 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 patients), with higher frequency than other known triggers for which STP is usually recommended (i.e., physical trauma: 5.4% of patients) [41]. Thus, STP should also be considered before or during any stressful life event, such as exams 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 under STP, should have at least two doses of proper angioedema ODT immediately available during and after any medical procedure such as surgical or dental interventions [19].

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

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

Long-term prophylaxis

Therapeutic options for LTP are expanding, but no clear criteria have been established to decide when to initiate this therapy, nor have goals been explicitly set. Several drugs have been approved as LTP in HAE-C1INH. These include oral danazol, which enhances hepatic synthesis of C1 inhibitor and plasma aminopeptidase P (APP) 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 pdC1-INH Cinryze; the SC pdC1-INH Berinert; and the SC monoclonal antibody against plasma kallikrein, lanadelumab (Takhzyro, Takeda Pharmaceutical Company Ltd) [12]. The plasma kallilrein inhibitor berotralstat (Biocryst) was recently approved for LTP [46]. The current international guidelines recommend the use of pdC1-INH, lanadelumab and berotralstat as first-line LTP in HAE-C1INH [18, 20].

LTP initiation and switch criteria

Long-term prophylaxis (LTP) is a standard treatment aimed at preventing HAE attacks when the 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 QoL 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 guidelines and the HAE Association (HAEA) guidelines recommend that patients and physicians participate in shared decision-making on whether to initiate LTP [18-20].

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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, patient comorbidities, QoL, expectations and preferences, and the accessibility to healthcare 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 under LTP, changes in medication or dosing should also be considered. In accordance with the current HAE and WAO/EAACI guidelines, the expert panel recommends regular assessment of the efficacy and tolerability of LTP to adjust or switch the prophylactic treatment according to the disease severity and the patient's response to therapy [18, 20].

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

LTP goals and outcome measurement

HAE treatment goals are to achieve overall disease control and normalize the patient's life [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 global goal.

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First of all, it should be noted that, according to the principle of shared decision-making, LTP goals should be established by the clinician and the patient working together. Not all patients may 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. (2017)[48]. Severity of attacks is not easily evaluated, as it is the result of different parameters [48, 49]. Patient-reported outcome measures (PROMs) such as visual analogue scales referring to a single sign/symptom or the whole complex of signs/symptoms of an attack are often employed 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) [50], shows a global score that incorporates the number of anatomical locations affected during an acute attack ("symptoms complex", e.g., hands and abdomen) and the patient's own evaluation of swelling severity at each site (e.g., none to severe). Thus, the MSCS measures the attack severity 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 due to the difficulty in calculating the score.

HAE-C1INH disease severity has been defined as the patient's overall disease experience. It includes the previous problems imposed by the disease since its onset, the current burden of disease, and the 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 airways attack and death by asphyxiation [48]. The 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

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(HAE-AS) can be used as a tool to assess overall disease activity [51]. It consists of 12 items, which show one-dimensionality. The raw score is transformed into a linear measure with a scale from 0 to 30 which shows good internal consistency, satisfactory reliability for group comparisons, and good discriminative validity by age, sex and disease severity [51]. The Angioedema Activity Score (AAS) for recurrent angioedema is a more general available tool [52].

It is also important to measure disease control at specific time points. The Angioedema Control Test (AECT) 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 treatment initiation, considering treatment adjustments to achieve maximum effectiveness

Health-related quality of life

There are basically two instruments available for HRQoL evaluation in patients with recurrent angioedema: the Angioedema Quality of Life (AE-QoL) tool [54, 55] oriented to adult patients with any type of recurrent angioedema, and the specific Hereditary Angioedema Quality of Life (HAE-QoL) tool validated for HAE-C1INH [56]. There is another specific instrument, the HAEA-QoL, which was developed specifically for use in the USA [57]. The AE-QoL consists of 17 questions distributed onto 4 domains (functioning, fatigue/mood, fear/shame, and nutrition), and presents a 4-week recall period and a score that ranges from 0 to 100. The HAE-QoL consists of 25 questions distributed onto 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 to monitor the HRQoL of these patients. As HAE-QoL has a 6-month recall period, it should be performed at least every six months, which is a reasonable timeframe considering Spanish follow-up protocols.

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A recently published study evaluated the validity of use of the generic 36-item Short-Form Health Survey (SF-36v2) to evaluate the QoL in HAE-C1INH patients [58]. The conclusion was that it could be useful to assess HRQoL with some content validity limitations. We consider that, while this questionnaire may be helpful in comparative studies between different pathologies, it is not the best tool to monitor 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 QoL perception 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 room/hospital resources, and improved self-administration of SC C1-INH (SC) along with independence from assistance [64]. Patients also expressed increased confidence, optimism, and normalcy along with reduced absence from work/school activities, increased productivity, improved sleep and energy, healthier family relationships, and improved cognition. In the interviews, all AE-QoL items spontaneously emerged from patients, while other numerous identified concepts were not addressed by the AE-QoL, including increased awareness of potential attack triggers (e.g., stress/anxiety, sports), reduced attack frequency, improvements in ability to perform day-to-day tasks and social plans, and a lower burden from medical visits.

Although clinical guidelines indicate that follow-up of LTP should include HRQoL evaluation at each visit (recommended minimum one visit per year), the specific HRQoL improvement in the PROMs that should be taken into consideration when contemplating switching therapy are 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, the clinician should consider adjusting or switching treatment.

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Adverse events

One of the potential limitations of current tools for QoL assessment is that the convenience or side effects of treatments are not considered, even though they may have an important impact on patient QoL. 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 or side effects is a factor that influences the selection of LTP therapy. The choice of LTP should be agreed between physician and patient considering the risks of experiencing treatment-associated adverse effects, especially in fertile women and in case of pregnancy or lactation [18, 20, 67]. In this sense, we recommend that AEs associated with LTP are regularly monitored at every follow-up visit. Current clinical guidelines advocate regular assessment of efficacy, safety, and adherence of patients to LTP medications [18]. Some therapies require closer surveillance (as occurs with the prophylactic use of anabolic androgens, which are associated with important side effects) in order to re-evaluate their risk-benefits. At least 6-monthly follow-up visits and control tests are recommended, as well as in the case of using 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 lanadelumab or SC pdC1-INH, and venous complications from the administration of IV C1-INH concentrates [20].

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

All recommendations that reached consensus on LTP goals, follow-up, HRQoL, and adverse events are listed in Table 4 (Delphi scores available in Supplementary Material Table A 5).

General aspects of HAE-C1INH treatment

Patient satisfaction

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

This expert panel supports the periodical assessment of patient satisfaction with treatment using the Treatment Satisfaction Questionnaire for Medication (TSQM) 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 and access to treatment

The costs of suitable treatments for ODT or LTP are indeed an important barrier for HAE patients and physicians when accessing care. Several European countries have limited the access of patients to IV/SC pdC1-INH prophylaxis or lanadelumab and to self-administration of treatments in order to save costs [72]. In this respect, it is important to highlight the substantial direct and indirect costs associated with HAE in terms of utilization of healthcare resources and work productivity [8, 44]. In this context, drug development has improved QoL and has helped to significantly reduce the burden of HAE, utilization of emergency and medical resources, absenteeism from work and school, and deaths, all of which translates into a lower overall cost to the public healthcare system [37, 73].

Based on what this expert board considers an inherent responsibility from the physician's point of view, agreement was reached in that all approved therapeutic options should be equally accessible to all patients, independently of their place of residence. In this scenario, clinicians

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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 [74].

Importance of the patient diary

It is recommended that patients, especially those under LTP, document all characteristics of their HAE attacks, as this information may help both patients and clinicians to assess the efficacy of treatment and improve disease management [18, 20, 75]. International guidelines and consensus documents advise patients to record all data regarding their disease activity in a diary to be reviewed at each follow-up consultation [18, 20]. The expert committee agreed on recommending that patients keep a diary that collects the characteristics of each angioedema attack, including location, severity, duration, ODT administration, 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.

General recommendations agreed upon are listed in Table 5 (Delphi scores available in Supplementary Material Table A 6).

DISCUSSION

According to the systematic review performed, there are 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 the new drugs with high efficacy and fewer side effects, but at a

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higher cost. However, there is a lack of specific goals for LTP, which we attempted to address in this Delphi consensus.

This 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 a patient diary to track the attacks and response to treatments in the follow-up of the progression and severity of disease.

Soon after this expert committee completed the two Delphi rounds, an international panel of specialists on HAE published another consensus document using the Delphi approach that defined two 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 were assessed related to these two overall goals, and consensus was reached for 18.

In our Delphi, 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 HAE control and normalization of the patient's life.

The international consensus published by Maurer et al. (2021) [47] proposed the following features as indicators of HAE-C1INH control and QoL normalization: need for rescue medication, number of attacks, number of both 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

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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 HAE-C1INH control 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 a reduction in the attack rate as a main variable to evaluate disease management and control. However, as additional parameters, we proposed the change in the patient's disease activity and HRQoL score, patient satisfaction score regarding treatment, and the use of an *ad hoc* checklist to evaluate treatment-associated AEs.

From our experts' point of view, it is crucial that patients feel empowered to control their own disease and to provide their own perception on the degree of control of their disease and HRQoL. In this sense, 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 that records all the features of their attacks and responses to treatments may be a helpful tool to monitor disease severity and to design 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, 76].

One of the most important statements agreed 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 an important gap in our daily practice.

Finally, just one of the proposed statements submitted to Delphi consultation failed to reach consensus in either of the two rounds: *"The level of LTP response considered adequate is assessed based on the type of LTP administered"*. This statement considered the fact that some specialists have to choose less effective and/or safe "conventional" treatments (e.g., attenuated androgens, tranexamic acid) instead of the most recently approved LTP medications (e.g., SC pdC1-INH, lanadelumab, berotralstat), due to the limitations of the existing local treatment algorithms and direct drug costs. Thus, specialists often adjust the therapeutic goals for their patients to the expected effectiveness of the chosen treatment, while trying to keep the patient within proper safety margins (e.g., 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 not actually agreeing with it. Therefore, rejecting this item might be understood as HAE experts preferring not to maintain this standard practice and instead to assess therapeutic effectiveness in terms of achieving the ideal patient goal from a T2T perspective.

We constructed recommendations based fundamentally on the experts' opinion and the updated review of available evidence. Indeed, recommendations based on high-quality evidence are already incorporated into clinical guidelines, in which a series of other topics still remain undetermined. The aim of this exercise was to gather and share the Spanish experience in real-world clinical practice in areas where the management guidelines are less clear and to reinforce the adherence to certain recommendations that are poorly applied in this setting. Our aim was to provide a practical framework that may help Spanish clinicians to improve HAE-C1INH management in their daily practice.

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CONCLUSIONS

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

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CONFLICTS OF INTERESTS

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 is a researcher from the IdiPAZ program for promoting research activities.

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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 from 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 is a researcher from the VHIR program for promoting research activities**.**

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REFERENCES

1. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy. 2014;69(5):602-16.
2. Caballero T, Baeza ML, Cabanas R, Campos A, Cimbollek S, Gomez-Traseira C, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part I. Classification, epidemiology, pathophysiology, genetics, clinical symptoms, and diagnosis. J Investig Allergol Clin Immunol. 2011;21(5):333-47; quiz follow 47.
3. Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. Orphanet J Rare Dis. 2018;13(1):73.
4. Davis-Lorton M. An update on the diagnosis and management of hereditary angioedema with abnormal C1 inhibitor. J Drugs Dermatol. 2015;14(2):151-7.
5. Caballero T. Angio-oedema due to hereditary C1 inhibitor deficiency in children. Allergol Immunopathol (Madr). 2013;41(1):45-53.
6. Farkas H. Management of upper airway edema caused by hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):19.
7. Caballero T, Prior N. Burden of Illness and Quality-of-Life Measures in Angioedema Conditions. Immunol Allergy Clin North Am. 2017;37(3):597-616.
8. Caballero T, Aygoren-Pursun E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. Allergy Asthma Proc. 2014;35(1):47-53.
9. Bygum A, Aygoren-Pursun E, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Burden of Illness in Hereditary Angioedema: A Conceptual Model. Acta Derm Venereol. 2015;95(6):706-10.
10. Caballero T, Baeza ML, Cabañas R, Campos A, Cimbollek S, Gómez-Traseira C, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. J Investig Allergol Clin Immunol. 2011;21(6):422-41; quiz 42-3.
11. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy. 2012;67(2):147-57.
12. Caballero T. Treatment of Hereditary Angioedema. J Investig Allergol Clin Immunol. 2021;31(1):1-16.
13. Craig T, Aygören-Pürsün E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012;5(12):182-99.
14. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376(12):1131-40.
15. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-21.
16. Zuraw B, Lumry WR, Johnston DT, Aygören-Pürsün E, Banerji A, Bernstein JA, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. J Allergy Clin Immunol. 2021;148(1):164-72.e9.

doi: 10.18176/jiaci.0875

17. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575-96.
18. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-90.
19. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol. 2019;15:72.
20. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-50.e3.
21. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300-13.
22. Jindal AK, Bishnoi A, Dogra S. Hereditary Angioedema: Diagnostic Algorithm and Current Treatment Concepts. Indian Dermatol Online J. 2021;12(6):796-804.
23. Berger WE. New approaches to managing asthma: a US perspective. Ther Clin Risk Manag. 2008;4(2):363-79.
24. van Vollenhoven R. Treat-to-target in rheumatoid arthritis - are we there yet? Nat Rev Rheumatol. 2019;15(3):180-6.
25. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15.
26. Nannini LJ. Treat to target approach for asthma. J Asthma. 2020;57(6):687-90.
27. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A Treat-to-Target Update in Ulcerative Colitis: A Systematic Review. Am J Gastroenterol. 2019;114(6):874-83.
28. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015;110(9):1324-38.
29. Lima H, Gooderham M, Dutz J, Lynde C, Chapdelaine H, Ellis A, et al. Management of chronic spontaneous urticaria (CSU): a treat to target approach using a patient reported outcome. Allergy Asthma Clin Immunol. 2017;13:38.
30. Longhurst H. Optimum Use of Acute Treatments for Hereditary Angioedema: Evidence-Based Expert Consensus. Front Med (Lausanne). 2017;4:245.
31. Valerieva A, Nedeva D, Yordanova V, Petkova E, Staevska M. Therapeutic management of hereditary angioedema: past, present, and future. Balkan Med J. 2021;38(2):89-103.
32. Guilarte M, Sala-Cunill A, Baeza ML, Cabañas R, Hernández MD, Ibañez E, et al. Hereditary angioedema due to C1 inhibitor deficiency: real-world experience from the Icatibant Outcome Survey in Spain. Allergy, Asthma & Clinical Immunology. 2021;17(1):137.
33. Katelaris CH. Self-Management Plans in Patients with Hereditary Angioedema: Strategies, Outcomes and Integration into Clinical Care. J Asthma Allergy. 2020;13:153-8.
34. Riedl MA, Neville D, Cloud B, Desai B, Bernstein JA. Shared decision-making in the management of hereditary angioedema: An analysis of patient and physician perspectives. Allergy Asthma Proc. 2022.
35. Longhurst HJ, Farkas H, Craig T, Aygören-Pürsün E, Bethune C, Bjorkander J, et al. HAE international home therapy consensus document. Allergy Asthma Clin Immunol. 2010;6(1):22.
36. Shapiro RS, Zacek L. Training hereditary angioedema patients to self-administer intravenous C1 esterase inhibitor concentrate. J Infus Nurs. 2014;37(4):284-90.

doi: 10.18176/jiaci.0875

37. Blasco AJ, Lázaro P, Caballero T, Guilarte M. Social costs of icatibant self-administration vs. health professional-administration in the treatment of hereditary angioedema in Spain. Health Economics Review. 2013;3(1):2.
38. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004;114(3 Suppl):S51-131.
39. Poza Cordón J, de María Pallarés P, Caballero Molina T. Ultrasound findings in an abdominal crisis of a patient with hereditary angioedema. Rev Esp Enferm Dig. 2020;112(5):418.
40. Cheng BT, Silverberg JI, Samet JD, Fishbein AB. Burden of emergency department utilization and abdominal imaging for hereditary angioedema. J Allergy Clin Immunol Pract. 2020;8(4):1443-6.e2.
41. Caballero T, Maurer M, Longhurst HJ, Aberer W, Bouillet L, Fabien V. Triggers and Prodromal Symptoms of Angioedema Attacks in Patients With Hereditary Angioedema. J Investig Allergol Clin Immunol. 2016;26(6):383-6.
42. Craig T. Triggers and short-term prophylaxis in patients with hereditary angioedema. Allergy Asthma Proc. 2020;41(Suppl 1):S30-s4.
43. Floyd E, Goldstein NA, Joks R, Mascaro M, Liaw C, Dickson B, et al. An Extubation Protocol for Angioedema. OTO Open. 2017;1(1):2473974x17691230.
44. Aygören-Pürsün E, Martinez Saguer I, Kreuz W, Klingebiel T, Schwabe D. Risk of angioedema following invasive or surgical procedures in HAE type I and II--the natural history. Allergy. 2013;68(8):1034-9.
45. Longhurst H, Cicardi M. Hereditary angio-oedema. Lancet. 2012;379(9814):474-81.
46. Gao Y, Hwang J, Hwang G, Craig T. A review of oral kallikrein inhibitor berotralstat for hereditary angioedema. Drugs Today (Barc). 2022;58(2):59-67.
47. Maurer M, Aygören-Pürsün E, Banerji A, Bernstein JA, Balle Boysen H, Busse PJ, et al. Consensus on treatment goals in hereditary angioedema: A global Delphi initiative. J Allergy Clin Immunol. 2021.
48. Bygum A, Busse P, Caballero T, Maurer M. Disease Severity, Activity, Impact, and Control and How to Assess Them in Patients with Hereditary Angioedema. Front Med (Lausanne). 2017;4:212.
49. Caballero T. Efficacy assessments in randomized controlled studies of acute therapy for hereditary angioedema. J Clin Immunol. 2012;32(6):1204-12.
50. Vernon MK, Rentz AM, Wyrwich KW, White MV, Grienenberger A. Psychometric validation of two patient-reported outcome measures to assess symptom severity and changes in symptoms in hereditary angioedema. Qual Life Res. 2009;18(7):929-39.
51. Forjaz MJ, Ayala A, Caminoa M, Prior N, Pérez-Fernández E, Caballero T; DV-HAE-QoL Study Group. HAE-AS: A Specific Disease Activity Scale for Hereditary Angioedema With C1-Inhibitor Deficiency. J Investig Allergol Clin Immunol. 2021;31(3):246-52.
52. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development, validation, and initial results of the Angioedema Activity Score. Allergy. 2013;68(9):1185-92.
53. Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Validation of the Angioedema Control Test (AECT)-A Patient-Reported Outcome Instrument for Assessing Angioedema Control. J Allergy Clin Immunol Pract. 2020;8(6):2050-7.e4.
54. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy. 2012;67(10):1289-98.
55. Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. Allergy. 2016;71(8):1203-9.

doi: 10.18176/jiaci.0875

56. Prior N, Remor E, Pérez-Fernández E, Caminoa M, Gómez-Traseira C, Gayá F, et al. Psychometric field study of hereditary angioedema quality of life questionnaire for adults: HAE-QoL. J Allergy Clin Immunol Pract. 2016;4(3):464-73. e4.
57. Busse PJ, Christiansen SC, Birmingham JM, Overbey JR, Banerji A, Otani IM, et al. Development of a health-related quality of life instrument for patients with hereditary angioedema living in the United States. J Allergy Clin Immunol Pract. 2019;7(5):1679-83.e7.
58. Palao-Ocharan P, Prior N, Pérez-Fernández E, Caminoa M, Caballero T; DV-HAE-QoL Study Group. Psychometric study of the SF-36v2 in hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE). Orphanet J Rare Dis. 2022;17(1):88.
59. Lumry WR, Miller DP, Newcomer S, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy Asthma Proc. 2014;35(5):371-6.
60. Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2018;6(5):1733-41.e3.
61. Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet J Rare Dis. 2021;16(1):86.
62. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy. 2021;76(4):1188-98.
63. Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygören-Pürsün E, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. Clinical and translational allergy. 2021;11(4):e12035-e.
64. Anderson J, Levy DS, Lumry W, Koochaki P, Lanar S, Henry Li H. Letting the patients speak: an in-depth, qualitative research-based investigation of factors relevant to health-related quality of life in real-world patients with hereditary angioedema using subcutaneous C1 inhibitor replacement therapy. Allergy Asthma Clin Immunol. 2021;17(1):60.
65. Bork K, Anderson JT, Caballero T, Craig T, Johnston DT, Li HH, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. Allergy, Asthma & Clinical Immunology. 2021;17(1):40.
66. Jean-Baptiste M, Itzler R, Prusty S, Supina D, Martin ML. The symptom experience of hereditary angioedema (HAE) patients beyond HAE attacks: literature review and clinician interviews. Orphanet Journal of Rare Diseases. 2022;17(1):232.
67. Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: Implications for future therapies. Allergy Asthma Proc. 2018;39(1):74-80.
68. Iuga AO, McGuire MJ. Adherence and health care costs. Risk management and healthcare policy. 2014;7:35-44.
69. Dubina MI, O'Neill JL, Feldman SR. Effect of patient satisfaction on outcomes of care. Expert Rev Pharmacoecon Outcomes Res. 2009;9(5):393-5.
70. Bharmal M, Payne K, Atkinson MJ, Desrosiers M-P, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;7:36-.
71. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.
72. Longhurst H, Farkas H. Biological therapy in hereditary angioedema: transformation of a rare disease. Expert Opin Biol Ther. 2020;20(5):493-501.

doi: 10.18176/jiaci.0875

73.Lumry WR. Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front Med (Lausanne). 2018;5:22.
74.AEDAF. Encuestas sobre el acceso a los medicamentos para AEH AEDAF; 2022.
75.Paige D, Maina N, Anderson JT. Hereditary angioedema: Comprehensive management plans and patient support. Allergy Asthma Proc. 2020;41(Suppl 1):S38-s42.
76.Radojicic C. Guidelines for management of hereditary angioedema: What is new? What is missing? Allergy Asthma Proc. 2022;43(1):12-9.

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TABLES

Table 1. Summary of the recommendations agreed by the panel of experts for "on-demand" treatment (ODT).

Recommendation	Supporting literature
1. The goal of ODT for angioedema attacks should be to minimize associated morbidity and mortality.	[18-20, 30]
2. 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]
3. All angioedema attacks are candidates for ODT.	[18-20]
4. All angioedema attacks should be treated as early as possible.	[12]
5. All patients diagnosed with HAE-C1INH should have 2 complete doses of angioedema-specific medication at their disposal at all times.	[18-20]
6. The patient should be adequately trained in the self-administration of angioedema ODT.	[18, 20, 35]
7. The patient's competence in ODT self-administration should be periodically evaluated.	[35]
8. 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]
9. The need for naso- or orotracheal intubation or tracheotomy should always be considered in case of an upper airway angioedema attack.	[18, 20, 33]
10. An abdominal echography is advisable in case of an abdominal angioedema attack that does not improve after specific angioedema ODT.	[21, 38-40]

Table 2. Summary of recommendations for short-term prophylaxis (STP).

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

Table 3. Criteria for initiating long-term prophylaxis according to the degree of importance attributed by the Delphi panel

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

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Table 4. Summary of recommendations for long-term prophylaxis (LTP)

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

Table 5. Recommendations for general aspects of HAE-C1INH treatment.

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