

Therapeutic management of hereditary angioedema due to C1 inhibitor deficiency

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Hereditary angioedema (HAE) due to C1 inhibitor (C1-INH) deficiency is a rare genetic disease characterized by recurrent swellings of the subcutaneous and submucosal tissues that can manifest as cutaneous edema, abdominal pain and laryngeal edema with airway obstruction. These symptoms have a significant impact on patients' quality of life. The reduction in C1-INH function leads to uncontrolled activation of the contact system and generation of bradykinin, the mediator of increased vascular permeability and edema formation. In the past, few treatment options were available; however, several new therapies with proven efficacy have recently become available to treat and prevent HAE attacks, such as plasma-derived and recombinant C1-INHs that replace the deficient protein, bradykinin receptor antagonist (icatibant) that blocks bradykinin activity and kallikrein inhibitor (ecallantide) that prevents bradykinin release. Such therapies can improve disease outcome. This article reviews the therapeutic management of HAE, which involves the treatment of acute attacks and prophylaxis.

KEYWORDS: bradykinin receptor antagonist • C1 inhibitor • hereditary angioedema • kallikrein inhibitor

C1 inhibitor deficiency in hereditary angioedema

Hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency is a rare, life-threatening autosomal dominant disorder with an estimated frequency of 1:50,000 in the global population without racial or gender differences [1]. HAE is caused by mutations in one of the two alleles of the *C1-INH* gene. More than 200 different mutations responsible for HAE have been described [2]; in 85% of patients, they prevent protein synthesis, resulting in quantitative plasma levels of C1-INH below 50% of normal (HAE type I); in the remaining 15%, a dysfunctional protein is produced, resulting in normal or elevated quantitative protein plasma levels and C1-INH plasma activity below 50% of normal (HAE type II). HAE with normal C1-INH protein and function, often referred to as HAE type III, occurs mainly in women and includes HAE associated with mutations in the factor XII gene and other unidentified defects [3–7]; however, HAE type III is not the focus of this review.

The pathophysiologic basis of HAE as a deficiency of C1-INH was discovered independently by Landerman *et al.* [8] and Donaldson and Evans [9]. C1-INH belongs to the protein family of serpins

that regulate the activity of serine proteases by binding to their active site and inactivating their catalytic activity. C1-INH inhibits several target proteases, including proteases of the complement (C1s and C1r and the mannan-binding lectin-associated serine proteases MASP-1 and MASP-2), contact (factor XIIa and kallikrein), coagulation (factor XI and thrombin) and fibrinolytic systems (tissue plasminogen activator and plasmin) [10,11]. The generation of vasoactive peptide bradykinin, resulting from insufficient control of contact system, is the main step in the pathogenesis of angioedema in HAE. Bradykinin, released from high-molecular-weight kininogen cleaved by plasma kallikrein during contact activation, mediates the formation of angioedema by increasing vasopermeability and stimulating vasodilatation (FIGURE 1) [12,13]. During attacks, circulating levels of bradykinin and cleaved high-molecular-weight kininogens are increased, demonstrating that contact system is activated during HAE attacks [14–16].

Clinical features of HAE

HAE is clinically characterized by recurrent episodes of subcutaneous or submucosal edema commonly involving the skin, GI tract, oropharynx and upper respiratory tract. The disease is

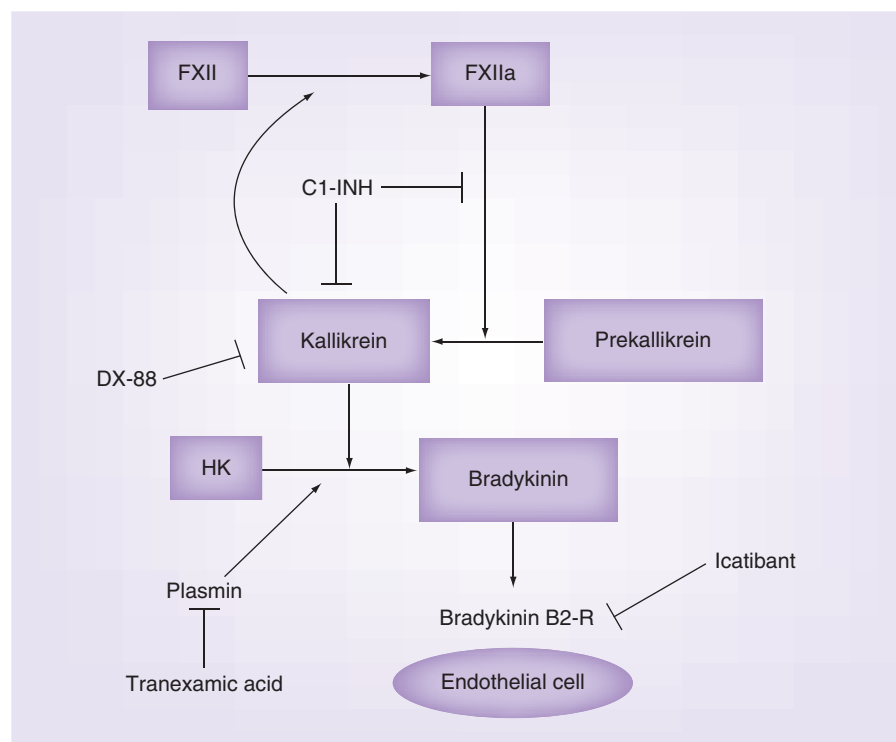


Figure 1. Pathogenesis of angioedema due to C1-INH deficiency showing mechanisms of action of therapeutic agents. Upon activation of the contact system, FXII and prekallikrein are activated to FXIIa and kallikrein, respectively. Kallikrein then cleaves HK, releasing bradykinin, which binds to bradykinin type 2 receptors on endothelial cells, increasing vascular permeability with edema formation. Plasma-derived and recombinant C1-INH inhibit both FXIIa and kallikrein. DX-88 inhibits kallikrein, icatibant blocks binding of bradykinin to bradykinin type 2 receptors on endothelial cells, and tranexamic acid acts by inhibiting release of bradykinin from HK by plasmin (arrows: activation; bar-ended arrows: inhibition).
C1-INH: C1 inhibitor; FXII: Factor XII; FXIIa: Factor XIIa; HK: High-molecular-weight kininogen.

disabling and laryngeal edema can lead to asphyxiation and death if left untreated [17]. HAE presents a significant psychological, social and economic burden for affected individuals [18]. HAE patients typically begin to present angioedema symptoms in childhood and often suffer increased attacks around the time of puberty. Affected individuals will continue to experience recurrent attacks of angioedema lasting 3–5 days before a complete recovery [19]. The most common HAE symptoms are cutaneous swellings (usually of the extremities, trunk, genitals or face) without urticaria or pruritus and abdominal pain due to edema of the mucosa of the GI tract with consequent subocclusion of the gut. Almost all HAE patients (>90%) report cutaneous and abdominal edema episodes [20]. About half of all patients experience laryngeal edema, although these episodes occur rarely compared with the frequency of cutaneous and abdominal episodes [21]. Attacks often result in hospitalization, may lead to inappropriate abdominal surgery and can be fatal when involving the airway.

Therapeutic management of HAE

The potentially life-threatening nature of HAE and its significant burden on patients underscore the importance of increasing

physicians' awareness of this rare disorder and appropriate treatment of acute attacks, as well as strategies to prevent them. In recent years, the results of controlled clinical trials with existing and new drugs for HAE have been published and new treatments have reached the market. This article reviews the therapeutic management of HAE, which involves acute treatments of attacks, long-term prophylaxis to reduce the frequency and severity of attacks in patients who are not adequately controlled with acute treatments, and short-term prophylaxis for patients undergoing stresses or procedures likely to precipitate an attack (TABLE 1). As the frequency and severity of HAE attacks vary significantly from patient to patient, HAE is best managed using an individualized treatment plan that takes into consideration specific patients' needs. Patients typically receive treatment for acute attacks in a medical setting, but this approach is not ideal, carrying delays in providing appropriate therapy. Home-based self-treatment can help reduce the time between attack onset and initiation of treatment, resulting in significant shortage of angioedema duration and quality of life improvement [22,23].

Acute treatment for HAE attacks

Acute treatment aims to resolve angioedema symptoms as quickly as possible, reducing morbidity and mortality

of HAE. Attacks should be treated at onset, as soon as the patient recognizes the first signs of angioedema. Since all HAE treatments are aimed at reducing disease-related disability, it may be reasonable not to treat attacks that are known to be nondisabling. Based on this principle, the 2010 International Consensus Algorithm for the diagnosis, therapy and management of hereditary angioedema recommends prompt treatment for all acute attacks with the exception of cutaneous attacks that do not affect the face or neck. According to the algorithm, peripherally located angioedema may easily remain mild without affecting the patient's life and therefore may be left untreated. However, attack-related disability is strongly dependent on individual variables, such as type of daily activities, anxiety and so on, and once again the decision for treating peripheral attacks should be mainly on evaluation of the patient after an appropriate and extensive education for complete understanding of the symptoms [24].

Because HAE is mediated by bradykinin rather than histamine, therapies used to manage allergic angioedema, such as antihistamines and corticosteroids, are ineffective in the treatment of HAE attacks. The use of epinephrine has been reported to

Table 1. Therapeutic options for the treatment of hereditary angioedema.

Drug	Indications	Recommended dose/ route of administration	Self-administration option	Mechanism of action
Plasma-derived, pasteurized, nanofiltered C1-INH concentrate (Berinert®, CSL Behring GmbH, Marburg, Germany)	Acute HAE attacks in children and adults	20 U/kg bodyweight by iv. infusion	Yes [†]	Replaces plasma C1-INH activity
Recombinant human C1-INH concentrate (Ruconest®, Pharming Group NV, Leiden, The Netherlands)	Acute HAE attacks in adults	50 U/kg bodyweight for patients <84 kg; 4200 U for patients ≥84 kg by iv. infusion	No	Replaces plasma C1-INH activity
Plasma-derived, pasteurized, nanofiltered C1-INH (Cinryze®, ViroPharma Inc., PA, USA)	Acute HAE attacks in children and adults. Preprocedural prevention of HAE attacks in adolescents and adults. Routine prevention of attacks	1000 U + 1000 U after 1 h if required by iv. infusion. 1000 U by iv. infusion within 24 h of a medical procedure. 1000 U every 3 or 4 days by iv. infusion	Yes [†]	Increases plasma C1-INH activity
Icatibant (Firazyr®, Shire plc., St Helier, Jersey)	Acute HAE attacks in adults	30 mg by sc. injection	Yes [†]	Blocks bradykinin B2 receptor
Ecallantide (Kalbitor®, Dyax Corp., MA, USA)	Acute HAE attacks in adults	30 mg by 3 sc. injections (10 mg)	No	Inhibits plasma kallikrein
Attenuated androgens (danazol, stanozolol)	Long-term and short-term prophylaxis of acute HAE attacks	Danazol: 50–200 mg/day Stanozolol: 1–2 mg/day	Yes	Increases hepatic synthesis of C1-INH
Antifibrinolytics (tranexamic acid)	Long-term and short-term prophylaxis of acute HAE attacks. Acute HAE attacks	Adults: 1 g three-times daily, children: 50–75 mg/kg three-times daily; adults: 1 g every 4 h, children: 20 mg/kg every 4 h	Yes	Inhibits fibrinolysis, thereby plasmin on kallikrein activation and subsequent bradykinin generation

[†]After appropriate training by a healthcare professional.

C1-INH: C1 inhibitor; HAE: Hereditary angioedema; iv.: Intravenous; sc.: Subcutaneous.

slow angioedema progression in some patients, but there is no evidence of sustained efficacy and this should not be included in the therapeutic armamentarium of HAE.

Disease-specific treatments for HAE are designed to reduce the elevated bradykinin levels that characterize this disorder. Currently available HAE therapies tackle bradykinin generation or activity by increasing plasma C1-INH activity (e.g., C1-INH concentrates), directly inhibiting kallikrein (e.g., ecallantide) or inhibiting the interaction of bradykinin with its B2 receptors (e.g., icatibant). If disease-specific treatments are not available, fresh frozen plasma can be administered.

C1-INH concentrates

Administration of plasma-derived C1-INH (pdC1-INH) has been used for decades as a treatment of acute angioedema attacks in HAE patients [25]. This approach is based on the rationale that increasing functional C1-INH levels in the circulation in HAE patients may restore normal homeostatic control of plasma cascade systems, such as complement and contact systems, and stop the formation of vasoactive peptides that mediate

angioedema. The preparations suitable for replacement therapy include human pdC1-INH concentrate and recombinant human C1-INH (rhC1-INH). Currently, two preparations of pdC1-INH concentrate, tested in clinical trials, are commercially available: Berinert® (CSL Behring GmbH, Marburg, Germany) and Cinryze® (ViroPharma Inc., PA, USA). A third pdC1-INH preparation, Ceter® (Sanquin, Amsterdam, The Netherlands), registered in 1997 in a few European countries, was never tested in clinical trials. The rhC1-INH Ruconest® (Pharming Group NV, Leiden, The Netherlands and marketed by Swedish Orphan Biovitrum), similarly to plasma-derived products, exerts its action by supplying the deficient C1-INH protein.

Berinert was first licensed in Germany in 1979 and is currently approved in several countries, including the EU and the USA. In Europe, Berinert is indicated for the treatment of acute episodes of HAE in adults and pediatric patients. In the USA, it is licensed for the treatment of acute abdominal, facial or laryngeal attacks of HAE in adults and in adolescents [26]. Berinert has been safely administered to children, as well as to pregnant women and nursing mothers with HAE [27–29].

This product is administered intravenously, with a recommended dose of 20 U/kg bodyweight. The efficacy of the 20-U/kg dose was established in a recent placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group study in 124 adult and pediatric patients with HAE [30]. Subjects treated with a 20-U/kg dose of Berinert had a significant reduction in time to onset of relief versus placebo (median: 0.5 vs 1.5 h; $p = 0.0025$), particularly for severe HAE attacks (0.5 vs 13.5 h). A total of 1 h after treatment, >75% of the patients in the 20-U/kg group reported onset of symptom relief compared with 40% of the patients in the placebo group. Median time to complete resolution of symptoms was also significantly lower in the 20-U/kg group (4.9 vs 7.8 h with placebo; $p = 0.0237$) [30]. The most commonly reported adverse events were nausea, diarrhea, abdominal pain and muscle spasms, which occurred at lower rates in the 20-U/kg group versus the placebo group. In an open-label extension of this study evaluating the efficacy of Berinert for repeated HAE attacks, 57 patients were treated for 1085 attacks over a 24-month period. Median time to onset of symptom relief was 0.46 h for all types of attacks and the median time to complete resolution of symptoms was 15.5 h; the dosage of 20 U/kg of C1-INH concentrate was sufficient in 1073 out of 1085 HAE attacks [31].

This product is now approved for self-administration by intravenous infusion after consultation with a physician and adequate training in self-infusion techniques. Self-administration has recently become common practice in HAE: extensive data on this approach are limited to one center [32], and indicate that the advantages of self-administration include decreased frequency and severity of swelling attacks, increased quality of life and fewer days of absence from work or school. Quality of life measures were reported to be significantly improved after initiation of C1-INH home therapy in a trial of seven patients trained to self-administer treatment for acute HAE attacks [33]. No cases of laryngeal edema were observed under home self-administration of C1-INH. In this study, there was a significant reduction in the time spent in hospital in a group of 20 pediatric patients who switched from physician-based therapy to home therapy with C1-INH [32]. Tourangeau *et al.* compared the outcomes of 39 HAE patients treated with C1-INH at a medical clinic with those self-administering C1-INH at home. All efficacy outcomes were superior in the home treatment group; the mean duration of swelling attacks was dramatically shortened (34 vs 8 h, respectively). Improvements were also evident considering the number of hospital visits, the requirement for narcotic pain medications, the missed work time and sleep disruption. It was noticed that the home treatment group experienced more adverse events, but they were infrequent and mild in severity [34].

Cinryze was recently approved in the EU for acute treatment of HAE attacks in adolescents and adults [35]. This product is administered by intravenous injection, and the recommended dose for acute attacks in both adolescents and adults is 1000 U administered at the first sign of the onset of an acute attack. A second 1000-U dose may be administered if the patient does not respond adequately after 60 min. In the treatment of laryngeal edema, this second dose can be given earlier.

The approval of Cinryze for the acute treatment of HAE attacks is based on a randomized, double-blind, placebo-controlled, parallel-group study of 71 subjects and an open-label trial involving 101 patients [36]. In the double-blind controlled study, patients received Cinryze ($n = 36$) or placebo ($n = 35$) within 4 h after onset of an acute attack; 68 patients were evaluable. Symptom severity was assessed every 15 min until the beginning of unequivocal relief, defined as three consecutive reports of symptom improvement at the attack site. The median time to beginning of unequivocal relief of the defining symptom of the HAE attack was 2 h in the Cinryze group versus >4 h in the placebo group ($p = 0.02$). The median time to complete resolution of the HAE attack was 12.3 h with Cinryze versus 25.0 h with placebo ($p = 0.004$). In the study, 60% of the patients in the Cinryze arm and 42% of those in the placebo arm ($p = 0.062$) had onset of unequivocal relief for the defining symptom within 4 h.

In an open-label trial assessing the efficacy of Cinryze for repeated attacks, 101 patients were treated with this product for a total of 609 acute attacks. The subjects received 1000 U of Cinryze intravenously for an attack at any anatomic location and could receive a second 1000-U dose if improvement had not occurred within 60 min. Improvement was defined by patient report. In this study, unequivocal relief of the defining symptom was achieved for 87% of attacks within 4 h of Cinryze dosing. For 95% of attacks, clinical relief was achieved, improvement was observed and/or subjects were discharged within 4 h. Importantly, the efficacy of Cinryze did not decrease with the number of attacks treated. For subjects with more than one attack, the proportion of attacks responding within 4 h after Cinryze dosing and the time to response were comparable regardless of the number of attacks treated. In addition, none of the 84 separate laryngeal HAE attacks required intubation following treatment with Cinryze.

The data on Cinryze self-administration or home treatment are limited. In a database review of 516 patients receiving this product, 47% were treated at home, 23% in an infusion center and 28% in a physician's office. Of those treated at home, 42% were self-administering treatment, 16% were administered treatment by a family member and 23% received treatment from a home healthcare worker [37]. The decision to use home treatment for an individual patient should be made by the treating physician after the patient and/or caregiver has received appropriate training in self-infusion techniques.

Ruconest, a rhC1-INH extracted from the milk of transgenic rabbits, is approved in Europe for the acute treatment of HAE attacks in adults only [38]. As with the plasma-derived C1-INH concentrates, Ruconest is administered intravenously. However, this product must be administered by a healthcare professional experienced in treating patients with HAE; self-administration is not recommended. The recommended dose of Ruconest is 50 U/kg bodyweight for adult patients weighing less than 84 kg. For those weighing 84 kg or more, the recommended dosage is 4200 U or two vials. A single dose of 2100 U is sufficient to elicit a clinical response in most patients, but a second

2100-U dose may be administered if the clinical response is insufficient. The efficacy and safety of Ruconest have been evaluated in two independent randomized, double-blind, placebo-controlled studies conducted in Europe and North America. In these studies, 70 patients received treatment with Ruconest 50 or 100 U/kg ($n = 41$) or saline placebo ($n = 29$). Both the 100- and 50-U/kg doses resulted in a statistically significant reduction in the median time to first symptom relief versus placebo ($p < 0.001$ and $p = 0.013$, respectively) and in the time to minimal symptoms versus placebo ($p < 0.001$ and $p = 0.001$, respectively). A third controlled study for efficacy of rhC1-INH was completed recently and top-line results released to the press confirm previous efficacy data. In all studies, the product was well tolerated with no evidence for clinical relapse; headache and vertigo were the only adverse events determined to be related to this treatment. The manufacturing process for Ruconest involves expressing the human C1-INH protein in the milk of transgenic rabbits. One healthy volunteer with undisclosed rabbit allergy experienced anaphylaxis after administration of Ruconest, suggesting that this treatment is unsuitable for patients with proven rabbit allergy. Patients should be screened by skin-prick testing or serum-specific IgE to rabbit epithelium prior to prescribing this product [39]. No evidence of IgG or IgE antibody formation to rabbit, milk or C1-INH has been seen in repeat dosing studies. There are no data in pregnancy or in breastfeeding.

Safety of C1-INH concentrates

pdC1-INHs carry the usual concerns for transmission of blood-borne infections. The safety of new-generation pdC1-INH products is excellent due to selection of donors, testing each donation for the absence of known relevant blood-borne viruses, and to sophisticated purification and viral inactivation procedures (cryoprecipitation, pasteurization and nanofiltration) during manufacture [40]. Blood-borne pathogen surveillance (hemovigilance) samples should be collected at baseline, and testing for hepatitis viruses, HIV, HTLV and parvovirus should be carried out annually. As pdC1-INH products may be required at any time on an emergency basis after diagnosis, hemovigilance is best performed at diagnosis. Vaccination to hepatitis B is recommended for patients receiving pdC1-INH concentrates [26].

The prescribing information of Berinert and Cinryze mention the risk of thrombosis following administration of these pdC1-INH products [26,35]. Interaction of C1-INH with fibrinolytic proteases has been put forward as a theoretical potential risk for thromboembolic side effects of treatment with pdC1-INH concentrates. Reports for thrombotic events in association with Berinert are limited to off-label use at extremely high (500 U/kg) doses [41]. Cinryze has been reported to be thrombogenic in an animal model [101]. In an open-label trial investigating the use of Cinryze for prevention of HAE attacks, five serious thrombotic events (including myocardial infarction, deep vein thrombosis, pulmonary embolism and two events of cerebrovascular accident) occurred. These subjects had underlying risk factors for thrombotic events [35]. A retrospective data analysis provided an insight into the Adverse Events Reporting System database of the US FDA

regarding potential signals of thrombotic events associated with the use of C1-esterase inhibitor products in patients with HAE in the USA [42,102]. Cinryze used for long-term prophylaxis has been associated with ten distinct cases of thrombotic events (deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, transient ischemic attack, embolic stroke and myocardial infarction); no thrombotic events were found with Berinert. While previous reports of Cinryze-associated thrombotic events were found in patients using off-label C1-esterase inhibitor products at high doses [35], the thrombotic events identified in this study were associated with the recommended dosage of 1000 U intravenously every 3–4 days. It seems possible that Cinryze-associated thrombotic events were due to the use of permanent intravenous infusion devices. Drug-related thromboembolic complications have not been observed during the clinical development of Ruconest.

Icatibant

Icatibant (marketed as Firazyr®, Shire plc., St Helier, Jersey) is a potent, specific and selective bradykinin B2 receptor antagonist that is similar in structure to bradykinin but is resistant to enzymatic cleavage [43]. Icatibant is approved in the EU and in the USA for the treatment of acute HAE attacks in adults only. No data on the efficacy and safety of icatibant in children (0–18 years of age) are available [44]. Icatibant is administered as a 30-mg subcutaneous injection and may be self-administered by the patient after adequate training in self-injection technique.

The efficacy and safety of icatibant have been evaluated in three randomized, double-blind, controlled Phase III trials (FAST-1, FAST-2 and FAST-3) in HAE patients ≥ 18 years of age presenting with moderate to very severe cutaneous and/or abdominal symptoms [44,45]. FAST-1 and FAST-3 were placebo-controlled trials and FAST-2 was an active-controlled trial (tranexamic acid). In the FAST-1 and FAST-2 trials, the primary end point was the median time to clinically significant relief ($\geq 30\%$) of the index symptom (cutaneous pain, cutaneous swelling or abdominal pain), as measured on a 10-cm visual analog scale. In FAST-1, icatibant was not found to be significantly different from placebo with regard to the primary end point (2.5 vs 4.6 h, respectively; $p = 0.14$); however, in FAST-2, a significant difference was reported between icatibant and tranexamic acid (2 vs 12 h, respectively; $p < 0.001$). In FAST-3, the primary end point was patient-assessed time to onset of symptom relief for the first attack, defined as 50% reduction in the three-symptom composite visual analog scale. Icatibant significantly reduced the median time to onset of symptom relief versus placebo (2.0 vs 19.8 h; $p < 0.001$) in the FAST-3 trial. The most commonly reported adverse events were injection-site reactions, which occurred in 97% of patients. Other common adverse reactions reported with icatibant use include dizziness, rash, headache, pruritus and erythema. During the open-label extension of FAST-1 and FAST-2, 597 HAE attacks were treated with icatibant. In 59 attacks (9.9%), symptoms recurred and in 60.9% of the recurrences, a second injection was required. Four patients needed a third injection [103]. During the same trials, in 50 laryngeal-eligible attacks, a second icatibant injection was administered in

10% of the recurrences [46,103]. One subsequent study reported a similar frequency of rebound symptoms (12.7% of attacks) [47]. Rebounds of attacks following icatibant injection are probably due to its short half-life.

Icatibant should be administered with caution in patients with acute ischemic heart disease or unstable angina pectoris, since the blockade of bradykinin B2 receptor can decrease coronary blood flow with worsening of cardiac function. Although there is evidence supporting a positive effect of bradykinin antagonism immediately following a stroke, icatibant should also be administered carefully in patients after ischemic cerebral events, since it may attenuate the beneficial late phase of the neuroprotective effects of bradykinin [43].

Ecallantide

Ecallantide (marketed as Kalbitor® in the USA by Dyax Corp., MA, USA) is a recombinant 60-amino acid protein that consists of segments of human tissue factor pathway inhibitor. This protein is produced in the yeast *Pichia pastoris* and is a potent inhibitor of plasma kallikrein. Kalbitor is approved in the USA for the acute treatment of HAE in patients ≥ 16 years of age, but is not approved in Europe [48]. An integrated analysis of two double-blind, placebo-controlled Phase III studies demonstrated that 30 mg of ecallantide given as three separate 10-mg (1 ml) subcutaneous injections was effective and well tolerated when administered within 8 h of onset of a moderate to severe HAE attack in patients ≥ 10 years of age. The primary efficacy end point in these two trials was changed from baseline in mean symptom complex severity (MSCS) score 4-h postdose (MSCS: 0 = normal, 1 = mild, 2 = moderate, 3 = severe). The secondary end point was treatment outcome score 4 h after dosing (100 = significant improvement, 50 = improvement, 0 = same, -50 = worsening, -100 = significant worsening). In the integrated efficacy analysis, which included 70 ecallantide-treated patients and 73 placebo-treated patients, the change in MSCS score at 4 h was significantly greater among ecallantide-treated patients than in the placebo group (-0.97 ± 0.78 vs -0.47 ± 0.71 , respectively; $p < 0.001$). Similarly, the treatment outcome score was significantly greater in the ecallantide-treated patients at 4 h (55.5 ± 46.5 vs 20.0 ± 58.9 , respectively; $p < 0.001$). In the integrated safety analysis of these two trials, the most common adverse events in patients treated with ecallantide were headache, nausea, diarrhea, pyrexia and nasopharyngitis. Hypersensitivity reactions, including anaphylaxis, occurred in 2.7% of the patients receiving subcutaneous ecallantide in the overall clinical trial program [49]. Because of this risk, ecallantide must be administered by a healthcare professional and cannot be self-administered.

Long-term prophylaxis of HAE recurrences

This treatment approach is aimed to reduce the frequency and severity of angioedema recurrences and thereby reduce the burden of the disease on HAE patients. It is given to patients when they are symptom free and therefore is administered continuously and potentially lifelong. The 2010 International Consensus Algorithm for the diagnosis, therapy and management of hereditary angioedema suggests considering a long-term prophylaxis approach for

patients with frequent and/or severe attacks and/or those whose attacks cannot be managed adequately with on-demand therapies [24]. Crucial to the decision of starting a patient on long-term prophylaxis is an expectation that benefits will outweigh expected side effects. Assessment of disease severity, treatment efficacy and safety profile are essential elements to consider. Craig *et al.* have developed HAE therapy consideration criteria that can assist in decisions about which patients are eligible for routine prophylaxis [50]. They suggest that the physician should evaluate the nature and frequency of attacks, the burden of illness, the progression of attacks, risk for morbidity and mortality, access to emergency care and history of healthcare resource utilization. However, these criteria were developed for the USA at a time when treatment for acute attacks was not available and therefore they must be reconsidered based on the present availability of therapies. Given the variability in the severity and burden of HAE, decisions to initiate prophylaxis should be made on a case-by-case basis, with careful consideration of the patient's and family/caregiver needs. A useful practical criteria for starting long-term prophylaxis is extensive use of on-demand treatments without adequate disease control.

Three classes of drugs, attenuated androgens, antifibrinolytic agents and recently pdC1-INH concentrate, underwent controlled clinical trials against placebo and these trials proved their efficacy [50–55].

Attenuated androgens

The most effective and widely used long-term prophylaxis drugs are the synthetic 17- α -alkylated androgens danazol and stanozolol. Anabolic androgens are orally administered and the daily dose should not exceed 200 mg for danazol and 2 mg for stanozolol. Doses may be titrated gradually upward or, alternatively, titrated downward to the lowest effective dose [24]. While the anabolic androgens increase hepatic synthesis and plasma levels of C1-INH and C4, symptomatic benefit is generally achieved at lower doses than those required to significantly change the complements levels. Therefore, it is important to adjust the dosage on clinical effect and not on laboratory values. Androgen therapy has been shown to be highly effective in preventing acute attacks in patients with HAE [52,56,57]. Bork *et al.* retrospectively examined data from 118 HAE patients treated with danazol for anywhere from 2 months to 30 years. In this study, 94% of the patients responded to treatment and about 24% were symptom-free during danazol treatment [56]. Seventy eight percent of the patients experienced adverse effects such as weight gain, virilization, menstrual irregularities, headache, depression and/or liver adenomas, and approximately a third of the patients discontinued therapy because of these side effects. Adverse effects such as virilization and menstrual irregularities may be especially problematic for women. In the aforementioned study, 76% of female HAE patients taking danazol experienced menstrual irregularities (including amenorrhea) and virilization.

Safety of attenuated androgens

Given the risk of potentially serious side effects, such as hepatic adenoma or increased cholesterol, all HAE patients taking danazol need to be closely monitored. Serum lipid profile, liver

function tests (including aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, albumin), creatine kinase, lactic dehydrogenase, blood urea nitrogen, creatinine, complete blood count and urinalysis need be obtained prior to androgen administration and repeated every 6 months for patients taking androgens. In addition, a liver and spleen ultrasound needs to be performed prior to continuous androgen administration and repeated at least once every year [24]. Danazol is contraindicated in patients with abnormal genital bleeding of unknown cause, marked hepatic, renal or cardiac dysfunction, and women who are pregnant or breastfeeding [58].

Antifibrinolytic agents

The antifibrinolytic drugs ϵ -aminocaproic acid and tranexamic acid are frequently, but not always, effective in preventing angioedema attacks in HAE [51,53,59]. For this reason, antifibrinolytic drugs are reserved for patients who do not tolerate androgens. Tranexamic acid is mostly used for prophylaxis in children. Tranexamic acid dosage is not well established [6,17,59–64]; the usually recommended starting dose is 20–50 mg/kg/day (split two- to three-times daily), with a daily maximum of 4 g [6,17,59,60,63,64,104]. The dose may be able to be reduced to 0.5 g once or twice daily [61].

A common adverse effect is dyspepsia, which can be reduced by taking the drug with food. Other reported side effects include myalgia, muscle weakness, elevated serum creatine phosphokinase or aldolase, rhabdomyolysis, hypotension, fatigue and retinal changes [63,64]. Antifibrinolytic agents have not been associated with excess thrombosis or myocardial infarction in controlled trials [65–68]. Few cases of thrombosis were reported in patients with hypercoagulable states treated with antifibrinolytic agents [69,70].

C1-INH concentrate

Cinryze is currently the only C1-INH formulation approved for both acute treatment and routine prophylaxis in adults and adolescents with HAE. In the prophylactic setting, Cinryze is administered as an intravenous infusion every 3–4 days at a dose of 1000 U. The efficacy of this product in preventing HAE attacks was evaluated in a double-blind crossover study in which 24 subjects with HAE were randomized to receive prophylaxis with Cinryze or placebo for 12 weeks and then crossed over to the opposite treatment for another 12 weeks [36]. The subjects were given blinded injections of Cinryze or placebo approximately two-times per week. Among the 22 evaluable subjects, the mean number of attacks per 12-week period was 6.26 during Cinryze treatment versus 12.73 during the placebo period ($p < 0.001$). Prophylactic treatment with Cinryze was also associated with significant decreases in the number of days of swelling (10.1 ± 10.73 vs 29.6 days; $p < 0.0001$), average duration of attacks (2.1 ± 1.13 vs 3.4 ± 1.39 days; $p = 0.002$) and the severity of attacks (1.3 ± 0.85 vs 1.9 ± 0.36 on a three-point scale; $p < 0.001$) compared with the placebo period. The most common adverse events possibly related to Cinryze administration were pruritus/rash, lightheadedness and fever, each occurring in one patient.

Even if not currently approved for long-term prophylaxis, several observational studies reported that Berinert was effective in reducing angioedema attacks when administered two or three times per week [27,28,32,71–74]. This treatment was effective and safe also in pregnant women and children.

A recent paper described the use of Ruconest for long-term prophylaxis of HAE. In this study, a dose of 50 U/kg of Ruconest was administered once per week to a group of HAE patients with frequent recurrences and led to a reduction in frequency of attacks without main adverse events related to this therapy [75].

Short-term prophylaxis of HAE attacks

The goal of this approach is to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack. Dental and surgical procedures, particularly those that involve manipulation of the oral mucosa and larynx (e.g., tooth extraction, intubation) can trigger acute attacks in HAE patients. Laryngeal edema and death from asphyxiation after tooth extractions have been reported [76]. It is difficult to predict whether a given procedure will trigger an acute attack. In a retrospective review of patients with HAE who underwent tooth extractions, 21.5% of the procedures performed without prophylaxis were followed by facial swelling and/or potentially life-threatening laryngeal edema versus 12.5% of procedures performed with prophylaxis [77]. This suggests a substantial risk of laryngeal edema following dental procedures. In the per-patient analysis, 37.2% of those who did not receive prophylaxis experienced HAE symptoms following the procedure. The risk was reduced by 44.1% in those who received prophylaxis with C1-INH concentrate.

Cardiopulmonary bypass can activate the complement cascade as a result of contact between the blood and foreign substances such as air and artificial devices, increasing the risk of an HAE attack [78,79]. Moreover, hemodilution during cardiopulmonary bypass leads to further decreases in plasma C1-INH concentrations that can precipitate acute HAE attacks [80].

The recent 2010 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema suggests that preprocedural prophylaxis may not be necessary for minor manipulations if acute medications are immediately available in the event of an attack. However, for major manipulations or manipulations that are likely to trigger an attack (e.g., tooth extraction, intubation, heart surgery and cardiopulmonary bypass), prophylaxis with C1-INH should be considered [24]. The only C1-INH product that is approved in Europe specifically for pre-procedural prevention of HAE attacks is Cinryze. The recommended dose for adults and adolescents is 1000 U administered within 24 h of a medical, dental or surgical procedure. The efficacy of preprocedural administration of Cinryze was evaluated in an analysis of 41 subjects who received Cinryze for 91 procedures; 55% were dental procedures and 37% were surgical or interventional diagnostic procedures. A 1000-U dose of this product was administered within 24 h before each procedure – in four of the procedures, two doses were administered. HAE attacks reported within 72 h and adverse events occurring within 7 days of the preprocedural Cinryze dose were reviewed retrospectively. Two

HAE attacks were reported such as one genitourinary attack after dental work and one laryngeal attack after laparoscopy. Both events resolved after administration of a second Cinryze dose. Seven subjects reported adverse events within 7 days of the first dose, but none were deemed by the investigator to be drug related [81].

Attenuated androgens may also be used for short-term prophylaxis. Therapy is started 5 days before the procedure at a dose of 2.5–10 mg/kg/day up to a maximum of 600 mg/day and continued for 2–5 days after the procedure [24].

A recent paper on short-term prophylaxis in HAE patients before dental, diagnostic and surgical procedures reported that angioedema attacks recurred significantly less frequently after prophylaxis with Berinert than after prophylactic treatment with danazol or tranexamic acid [82]. The authors concluded that this C1-INH concentrate can be safely and effectively used for preprocedural prophylaxis.

Five-year view

Enormous progress has been made in the understanding of the pathophysiology of C1-INH deficiency [83] and new therapies have emerged in the management of HAE. Minimizing the morbidity and avoiding the mortality associated with HAE requires both effective treatments of acute attacks as well as strategies to prevent HAE attacks. Physicians should decide along with HAE patients the best therapeutic regimen to minimize the impact of the disease on their quality of life.

To provide evidence-based HAE treatment guidelines supported by the recent controlled studies with existing and new therapies a conference was held in Gargnano del Garda (Italy) on 26–29 September 2010 [84]. During this meeting, a consensus document about management approaches for HAE was approved by 58 HAE expert physicians. While recognizing that different areas of the world have unique patterns of care, based on different healthcare delivery systems, physicians caring for HAE patients now have the possibility of tailoring the treatment of HAE to specific patients' needs. Attack onset is unpredictable and the frequency, duration and severity of attacks can vary considerably between patients and even in the same individual from time to time. Any angioedema attack in an HAE patient can become disabling and/or life-threatening as a result of airway obstruction during laryngeal attacks. Therefore, all patients with HAE should have access to the disease-specific medicines such as pd and rhC1-INHs, icatibant and ecallantide. These drugs tested in controlled studies for angioedema attacks shorten the attacks' duration and therefore the attack-related disability and are an extraordinarily important development in the management of this disease. Patients should have the on-demand medicines at home to treat acute attacks and should be trained to self-administer these medicines. Ecallantide cannot be self-administered and must be administered by a healthcare professional because of risk of hypersensitivity reactions [49]. All attacks, irrespective of location, are eligible for on-demand treatment at home as soon as they are clearly recognized by the patient, before disabling symptoms develop. This recommendation is based on observational studies showing a higher efficacy of early on-demand

home treatment versus hospital treatment for angioedema attacks [85,86]. Furthermore, patients with HAE can experience delays in receiving the correct treatment because staff from emergency departments are unfamiliar with HAE and its treatment options. Patients should report to the hospital if laryngeal symptoms persist following an initial home treatment.

When on-demand treatment is insufficient to control angioedema symptoms in HAE patients, long-term prophylaxis must be considered to minimize the suffering related to the disease. Androgens, usually effective in preventing angioedema attacks, are contraindicated in children, or pregnant or lactating women and can expose patients to several adverse events. The efficacy of antifibrinolytics was not confirmed in general practice and appears to be limited to a restricted number of patients. Plasma-derived concentrates can be considered for long-term prophylaxis but intravenous administration of these products requires specific training and not all patients can easily self-administer pdC1-INH concentrates. Since cases of pdC1-INH-associated thrombotic events have been reported, continued surveillance and future epidemiologic study may be needed.

Due to individual pharmacokinetic variability of infused C1-INH and its relatively short half-life, long-term prophylaxis with intravenous C1-INH is not suitable for maintaining patients on constant replacement of their C1-INH deficiency. As a consequence, the efficacy of this approach is suboptimal. In order to improve the possibility of preventing angioedema attacks, subcutaneous formulations of pdC1-INH are being developed and clinical trials for subcutaneous administration of these products are currently ongoing that aim to provide a tool for real replacement of the genetic deficiency [105–107]. It is likely that such an approach will be available within the next 5 years. Other new prophylactic treatment options in development are a subcutaneous monoclonal antibody (DX-2930), long-acting inhibitor of plasma kallikrein activity and an oral plasma kallikrein inhibitor (BCX-4161) [87,88,108].

In the last 5 years, costs for HAE have markedly increased along with the improvement of patients' quality of life [89]. It is reasonable to expect a further increase due to the more widespread use of early on-demand treatments and prophylaxis approaches with pdC1-INH products. Sustainability of this increase in costs should be achieved by reducing hospital expenses by home therapy programs and by allowing HAE patients to improve their quality of life reaching normal working efficiency.

Financial & competing interests disclosure

A Zanichelli is a consultant/advisor for Shire Human Genetic Therapies (HGT) Inc., CSL Behring and ViroPharma, and has been an invited speaker for Sobi. M Cicardi has consultancy agreements with Dyax, Pharming Technologies BV and Shire Human Genetic Therapies Inc., is an advisor for Dyax, Shire Human Genetic Therapies Inc. and CSL Behring, and has been an invited speaker for Dyax, Shire Human Genetic Therapies Inc., CSL Behring, Pharming and ViroPharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Hereditary angioedema (HAE) is determined by a reduction in C1-inhibitor (C1-INH) activity that leads to different pathway activation and eventually to an increased vascular permeability due to bradykinin.
- HAE is characterized by recurrent self-limiting attacks of cutaneous edema, abdominal pain and even life-threatening airway obstruction. These manifestations have a great impact on patient health and quality of life.
- Different disease-specific drugs of proven efficacy and safety are now available both for acute management of HAE attack (C1-INH concentrates, icatibant, ecallantide) and long-term prophylaxis treatment (androgens, antifibrinolytic agents, plasma-derived C1-INH).
- The patient should be provided with these drugs and home treatment has been observed to improve clinical outcome and quality of life.
- Physicians caring for HAE patients should tailor the treatment of HAE to specific patients' needs.
- Subcutaneous preparation of C1-INH concentrate for prophylaxis is currently under evaluation in ongoing clinical trials and could improve the management of the disease in the future.

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