

The New Era of C1-Esterase Inhibitor Deficiency Therapy

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Abstract Hereditary angioedema (HAE) is an autosomal dominant disorder clinically characterized by recurrent episodes of angioedema. Until late-2008, HAE therapy in the United States was largely limited to antifibrinolytic agents or attenuated androgens. Although these drugs decrease the number and severity of angioedema attacks, they are associated with significant dose-related adverse effects. Recent advances have dramatically changed the management of HAE. As a result, we are embarking on a new era of treatment for this condition that includes effective on-demand treatment of attacks as well as effective prophylactic treatment. Herein we discuss the various treatment options for C1-inhibitor deficiency, focusing on new developments and literature published over the past year, as well as the additional patient considerations that should be addressed when determining the most appropriate patient-specific treatment plan.

Keywords Hereditary angioedema · C1 inhibitor · Bradykinin · Plasma kallikrein · Home therapy · C1-esterase inhibitor deficiency therapy · Treatment · On-demand treatment · Review

Introduction

Hereditary angioedema (HAE) is a disorder characterized by recurrent angioedema that occurs on an inherited basis and has an estimated prevalence of approximately 1 in 50,000 in the general population. HAE can be broadly divided into two major categories, with either reduced C1 inhibitor (C1INH) activity or normal C1INH activity. HAE with reduced C1INH activity can then be subdivided into type I HAE (characterized by reduced C1INH functional and antigenic levels) and type II HAE (characterized by reduced C1INH functional levels but normal C1INH antigenic levels). Type I and type II HAE are caused by mutations in the *C1INH* gene [1, 2]. HAE with normal C1INH activity was first reported in 2000 [3, 4] and was initially thought to affect only women exposed to increased states of estrogen. It has subsequently become clear that men can suffer from type III HAE and that the role of estrogen in provoking attacks is not universal. Type III HAE may be associated with a mutation in factor XII (Hageman factor) in a minority of patients [5]; however, the underlying basis of type III HAE remains largely obscure.

Patients with HAE typically experience recurrent swelling episodes that involve the subcutaneous or submucosal tissue of the face, abdomen, genitourinary tract, extremities, and in some cases the oropharynx or larynx. Despite great advances in the treatment of HAE, laryngeal attacks can still be fatal [6]. Angioedema attacks usually begin in childhood, with increased symptoms appearing during puberty or adolescence. Attacks continue throughout life and are often brought on by stress or trauma but can be utterly unpredictable. A typical angioedema attack begins with progressive swelling over the first 24 h, followed by 3–5 days of additional swelling before the attack completely abates.

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Scientific insights concerning the mechanism of swelling in HAE have led to the development of mechanistically targeted therapies (Fig. 1) [1]. C1INH is a regulator of the plasma complement, contact, coagulation, and fibrinolytic systems. Substantial evidence has emerged to indicate that the swelling in HAE patients results from activation of the plasma contact system with generation of bradykinin, the primary mediator of swelling in attacks of HAE. Pharmacologic strategies to prevent the production of bradykinin as well as to inhibit engagement of the bradykinin B2 receptor have been validated in clinical studies.

This article reviews the current and future options for treating HAE patients in the United States while critically evaluating the literature published in the past year. First, the recent randomized clinical trials are reviewed, then the approach to treating HAE is summarized.

C1 Inhibitor Concentrates

Five different drugs have recently undergone randomized, placebo-controlled clinical trials for the treatment of HAE. Three of these drugs are C1INH concentrates. One is a pasteurized, plasma-derived C1INH; another is a nano-filtered, pasteurized, plasma-derived C1INH; and the third is a recombinant human C1INH (rhC1INH). The underlying basis for the use of C1INH replacement therapy dates back to 1963, when Donaldson and Evans [7] demonstrated that HAE was caused by a deficiency in C1INH. Beginning in the late-1970s, C1INH replacement therapy has been used to treat HAE in Europe and other parts of the world. Since that time, many uncontrolled studies have evaluated the safety and efficacy of C1INH replacement therapy [8, 9]. Further investigation has demonstrated that clinical improvement typically occurs within 30–60 min of receiving

C1INH replacement therapy. Due to concerns about the viral safety of a plasma-derived concentrate, however, C1INH was not licensed in the United States until recently. Two plasma-derived C1INH replacement therapies are currently US Food and Drug Administration approved for use in the United States.

Pasteurized, Plasma-derived C1 Inhibitor Replacement Therapy

Beriner (CSL Behring, King of Prussia, PA) is a human pasteurized, plasma-derived C1INH product produced from pooled US donors. Pasteurized, plasma-derived C1INH has been approved and used safely and successfully in Europe to treat HAE attacks for more than two decades. Despite many reports of its efficacy and safety, there were few randomized, placebo-controlled studies, and the dose was determined empirically. In 2009, Craig et al. [10•] performed a randomized, double-blind, placebo-controlled study of 125 individuals with HAE given pasteurized, plasma-derived C1INH at two different doses or placebo for abdominal or facial attacks of HAE. Median time to onset of relief was significantly shorter with pasteurized, plasma-derived C1INH (dose of 20 U/kg) compared with placebo (0.5 vs 1.5 h; $P=0.0025$). Pasteurized, plasma-derived C1INH given at a dose of 10 U/kg did not show a statistically significant difference from placebo (1.2 vs 1.5 h; $P=0.2731$). As a result, pasteurized, plasma-derived C1INH replacement therapy was approved by the US Food and Drug Administration in 2009 for treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients at a dose of 20 U/kg. A subsequent prospective, open-label study showed that pasteurized, plasma-derived C1INH was also safe and effective for treatment of acute laryngeal attacks [11].

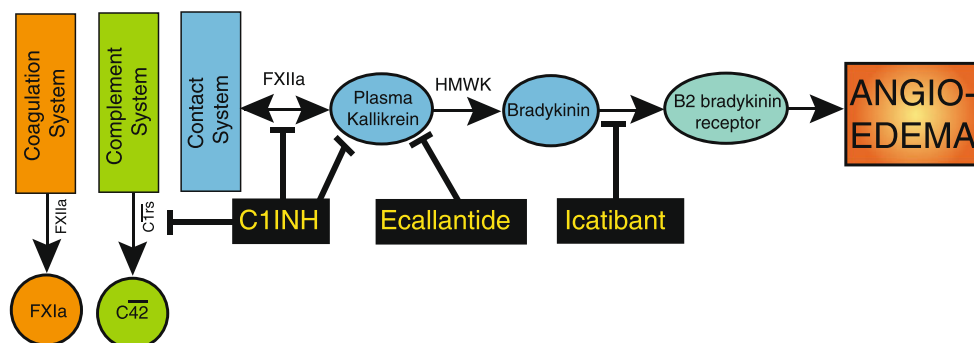


Fig. 1 Mechanistically targeted therapies for hereditary angioedema. Patients with a deficiency of C1 inhibitor (C1INH) demonstrate abnormalities in the regulation of the plasma coagulation, complement, and contact systems. The cause of angioedema is activation of the contact system with generation of bradykinin. C1INH concentrates inhibit two proteases in the contact system: factor XIIa (FXIIa) and

plasma kallikrein. C1INH also inhibits early complement proteases as well as factor XIa (FXIa) and plasmin in the coagulation and fibrinolytic systems. Ecallantide specifically targets plasma kallikrein. Icatibant prevents the binding of bradykinin to its receptor, the B2 bradykinin receptor. HMWK—high molecular weight kininogen

Nanofiltered, Pasteurized, Plasma-derived C1 Inhibitor Replacement Therapy

Cinryze (ViroPharma, Exton, PA) is a human nanofiltered, pasteurized, plasma-derived C1INH product produced from pooled US donors. The nanofiltration step provides additional protection against viral and possibly prion infectious particles [12]. Two randomized, double-blind, placebo-controlled trials have been conducted in the United States with the nanofiltered, pasteurized, plasma-derived C1INH in the treatment of HAE [13•]. The first study evaluated the efficacy and safety of nanofiltered, pasteurized, plasma-derived C1INH for the treatment of acute facial, abdominal, and genitourinary attacks in 68 HAE patients. Treatment with nanofiltered, pasteurized, plasma-derived C1INH (1,000 U with the potential for a repeat treatment at 60 min if relief was not reported) resulted in a median time to onset of relief of 2 h, compared with a median time to onset of relief of greater than 4 h in the individuals receiving placebo ($P=0.02$). The second study was a crossover trial that investigated the use of nanofiltered, pasteurized, plasma-derived C1INH at a dose of 1,000 U twice weekly for prophylaxis versus placebo in 22 study participants with a history of having at least 2 attacks per month. The number of attacks was significantly reduced in the nanofiltered, pasteurized, plasma-derived C1INH treatment arm (6.26 attacks over the 12-week study period) compared with the placebo arm (12.72 attacks; $P<0.001$). Nanofiltered, pasteurized, plasma-derived C1INH was approved by the US Food and Drug Administration in 2008 for prophylactic HAE therapy in adolescent and adult patients, with an indication for self-administration. Although the acute attack study met the primary end point, nanofiltered, pasteurized, plasma-derived C1INH was not approved for treatment of acute HAE attacks.

Recombinant Human C1 Inhibitor Replacement Therapy

RhC1INH (Rhucin; Pharming Group NV [Leiden, The Netherlands] and Santarus [San Diego, CA]) is expressed in the milk of transgenic rabbits [14] and has been investigated for use in the treatment of acute HAE attacks. Initial open-label studies suggested that rhC1INH was safe and effective [15]. Two independent, double-blind, placebo-controlled studies were conducted to assess the efficacy and safety of rhC1INH [16•]. RhC1INH was investigated at doses of 100 and 50 U/kg compared with placebo. The time to the onset of relief of symptoms was statistically less in those individuals receiving rhC1INH (median of 66 min at dose of 100 U/kg, 122 min at a dose of 50 U/kg, and 495 min for placebo; $P<0.001$ and $P=0.13$, respectively). For the secondary end point of time to minimal symptoms, the median time for the higher treatment dose was 266 min,

compared with 247 min for the lower treatment dose and 1210 min in the placebo group ($P<0.001$ and $P=0.001$, respectively). No treatment-related side effects were reported. No postexposure antibodies against rhC1INH were detected. RhC1INH was recently licensed in Europe; however, the US Food and Drug Administration required additional data at the 50-U/kg dose from an ongoing phase 3b study before it would consider licensing rhC1INH in the United States.

Bradykinin Pathway–Specific Drugs

Early studies found that incubation of HAE patient plasma at 37°C generated a “vascular permeability factor” [17]. Overwhelming laboratory and clinical data have now demonstrated that the primary mediator of swelling in HAE is bradykinin [18]. Bradykinin is a biologically active nanopeptide that is generated when active plasma kallikrein cleaves high molecular weight kininogen [19]. Plasma kallikrein is activated from its inactive zymogen by the protease coagulation factor XII, and plasma kallikrein and factor XII are normally inhibited by C1INH. The released bradykinin moiety potentially increases vascular permeability by binding to its cognate receptor (the bradykinin B2 receptor) on vascular endothelial cells. Blocking the bradykinin B2 receptor in the C1INH knockout mouse was shown to inhibit increased vascular permeability [20]. Based on these observations, strategies to specifically inhibit plasma kallikrein or to block the B2 bradykinin pathway in HAE attacks were initiated.

Recombinant Plasma Kallikrein Inhibitor

Ecallantide (Kalbitor; Dyax Corp., Cambridge, MA) is a specific inhibitor of plasma kallikrein that is synthesized in the yeast *Pichia pastoris* [21]. Recently, a double-blind, placebo-controlled trial involving 71 HAE patients with acute attacks was reported [22]. Primary outcomes were based on patient-reported treatment outcome scores (+100 to −100 [significant improvement to significant worsening of symptoms]) and the change from baseline in the mean symptom complex severity score (+2 [representing a change from mild symptoms at baseline to severe symptoms after intervention] to −3 [representing a change from severe symptoms at baseline to no symptoms after intervention]) 4 h after administration. Ecallantide or placebo was given at a dose of 30 mg subcutaneously. The investigators found that 4 h after drug administration, the ecallantide group had a median treatment outcome score of 50.0, compared with 0.0 in the placebo group ($P=0.004$). Similarly, the median change in the mean symptom complex severity score was −1.0 in the ecallantide group, compared with −0.5 in the placebo group ($P=0.01$).

A second phase 3, double-blind, placebo-controlled study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema (EDEMA4) was performed by Levy and colleagues [23•] to evaluate the safety and efficacy of ecallantide. Ninety-six patients were enrolled, and the investigators noted the improvement in mean symptom complex severity score 4 h after dosing with 30 mg of subcutaneous ecallantide to be significantly greater than placebo (-0.8 ± 0.6 and -0.4 ± 0.8 , respectively; $P=0.01$). Patients receiving ecallantide also reported a significantly larger mean treatment outcome score 4 h after dosing with study drug compared with placebo (53.4 ± 49.7 and 8.1 ± 63.2 , respectively; $P=0.003$).

Based on these two phase 3 studies, ecallantide was approved for treatment of acute HAE attacks in the United States in 2009 in individuals 16 years of age and older. Patients have been shown to develop anti-ecallantide antibodies with repeated exposures to the drug. Because of a low incidence of allergic and possibly anaphylactic reactions to ecallantide, the US Food and Drug Administration requires that it only be administered by a health care professional with appropriate medical support to manage anaphylaxis. The long-term safety and antigenicity of ecallantide will require additional study.

Selective Bradykinin Type 2 Receptor Antagonist

Icatibant (Firazyr; Shire, Dublin, Ireland) is a 10-amino acid peptide-selective bradykinin B2 receptor inhibitor that inhibits bradykinin-induced vasodilation in humans [24]. Icatibant is administered subcutaneously in a single injection of 30 mg and has a half-life of approximately 1–2 h [25]. Cicardi et al. [26•] reported the safety and efficacy of icatibant from two phase 3 studies.

The first study, FAST-1 (For the Angioedema Subcutaneous Treatment), compared icatibant and placebo. In this randomized, double-blind, placebo-controlled trial, the investigators did not find a statistically significant change in median time to clinically significant relief of symptoms (2.5 h with icatibant vs 4.6 h with placebo; $P=0.14$). Sixteen patients in the FAST-1 study required treatment with rescue medication. The second study, FAST-2, compared individuals receiving icatibant (30 mg subcutaneously in one administration) with those receiving oral tranexamic acid (3 g/d for 2 days). The median time to clinically significant relief was 2 h in the icatibant group, compared with 12 h in the tranexamic acid group ($P<0.001$). It was speculated that the study design and the early use of rescue medication might have obscured the benefit of icatibant in the FAST-1 trial. As a result of these findings, icatibant was approved for use in Europe but has not been approved for use in the United States.

Early results from the FAST-3 trial, however, presented by Lumry and colleagues [27] at the American Academy of Allergy Asthma and Immunology Meeting in March 2011, may change the US Food and Drug Administration approval status for this medication. In the FAST-3 study, 98 patients with moderate to severe HAE attacks were randomly assigned in a double-blind, placebo-controlled trial [27]. They found that icatibant given at a dose of 30 mg subcutaneously resulted in a statistically significant median time to onset of clinically significant relief (2.0 vs 19.8 h; $P<0.001$). Icatibant was also superior to placebo for time to onset of initial symptom relief (0.8 vs 3.5 h; $P<0.001$), time to onset of primary symptom relief (1.5 vs 18.5 h; $P<0.001$), and time to “almost complete” symptom relief (8.0 vs 36.0 h; $P=0.012$). No serious adverse effects were noted, and the therapy was well-tolerated overall.

Management of Hereditary Angioedema

The successful clinical trials of five new drugs for the treatment of HAE present tremendous new opportunities to normalize the lives of patients affected by HAE but also require rethinking how HAE patients are managed. The basic strategies for managing HAE patients rely on the treatment of acute attacks as well as prophylaxis to prevent attacks, as required (short term or long term). Tailoring an effective management plan for a given HAE patient is likely to involve individual factors such as disease severity (number and severity of attacks), comorbid conditions, patient preferences, and possibly pharmacogenomic differences in the response to different drugs. Nevertheless, it is important to consider the broad strategies that can now be utilized in the management of HAE (Table 1).

Treatment of Hereditary Angioedema Attacks

All five of the new drugs have been shown to be effective in the treatment of HAE attacks. Two of them (pasteurized, plasma-derived C1INH and ecallantide) are currently licensed in the United States for the treatment of acute attacks. In addition, it is anticipated that rhC1INH and icatibant will be approved for the treatment of HAE attacks in the United States in the relatively near future.

The goal of acute treatment of HAE attacks is to abort an ongoing attack of angioedema so that it does not progress, thereby preventing the attack from disrupting daily activities. To prevent serious morbidity and mortality, all HAE patients should be considered at risk of having a severe episode of angioedema, irrespective of their typical disease severity. More than 50% of HAE patients experience a potentially life-threatening episode of laryngeal angioedema during their lifetime [28]. Therefore, all patients with

Table 1 Drugs used in the targeted treatment of hereditary angioedema

Therapy	Route	Acute use, <i>dose</i>	Prophylactic use, <i>dose</i>	Safe for home infusion?	FDA approved?
Cinryze	Intravenous	1,000 U	1,000 U injected every 3–4 d	Yes	Yes (prophylactic), no (acute)
Berinert	Intravenous	20 U/kg	Not established	Yes	Yes (acute), no (prophylactic)
Ecallantide (Kalbitor)	Subcutaneous	30 mg (given as 3 1-mL injections)	Not established	Black box warning prohibits home use	Yes
Icatibant (Firazyr)	Subcutaneous	30 mg	Not established	Possibly in the future	No
Rhucin	Intravenous	50–100 U/kg	Not established	Not established	No

FDA—US Food and Drug Administration

HAE need to have an action plan that identifies how and where acute episodes of angioedema will be treated.

In the past, patients typically have received acute attack therapy at a clinic or medical facility. Several recent studies, however, have suggested that early home infusion of C1INH provides a superior outcome compared with treatment at a medical facility [29–34], probably due to shortening the interval between onset of symptoms and institution of effective therapy. As a result, a recent HAE international home therapy consensus recommends that every patient with physician-diagnosed HAE be considered for physician-supervised, self-managed home C1INH replacement therapy, and that therapy be initiated as soon as the patient notices the first symptoms of an HAE attack [32].

Prophylactic Treatment of Hereditary Angioedema

The goal of HAE prophylactic treatment is to minimize the frequency and severity of recurrent attacks. Prophylactic treatment can be given short term (when the patient will experience a situation likely to trigger an attack) or long term. Historically, the drugs of choice for long-term prophylaxis consisted of 17 α -alkylated androgens, which were shown to be efficacious in reducing HAE attacks in a randomized trial [35]. Although anabolic androgens administered in high doses lead to an increase in C1INH levels, the mechanism of their benefit in HAE remains unclear [36]. The great concerns with 17 α -alkylated androgens are the side effects, which can be serious, including weight gain, hepatic tumors, virilization, mood changes, anxiety, hypertension, and many other undesirable side effects [37]. Side effects are dose related and often lead to complete cessation of therapy. Due to concerns regarding adverse effects, it is strongly recommended that the dose of anabolic androgens be titrated down to the lowest possible dose to control angioedema attacks. Attenuated androgens are not recommended in children and are absolutely contraindicated during pregnancy.

Antifibrinolytic medications such as aminocaproic acid and tranexamic acid have been used in HAE treatment but

are not always effective in preventing angioedema episodes [38], and the mechanism of action is unknown. In addition, fresh frozen plasma can be used for short-term prophylaxis at a dose of 2 U several hours preceding an intended procedure [39].

As shown in recent clinical trials, nanofiltered, pasteurized, plasma-derived C1INH replacement therapy provides effective and safe HAE prophylaxis. This randomized study, however, was relatively small and of short duration. In addition, all participants were treated with open-label C1INH for breakthrough attacks, resulting in the individuals receiving large amounts of C1INH during the placebo period. Open-label experience in 146 patients with the nanofiltered, pasteurized, plasma-derived C1INH product for up to 3 years shows that the response is highly effective, durable, and safe (Zuraw et al., unpublished data).

Long-term HAE prophylaxis using C1INH concentrate by subcutaneous administration has attracted significant interest because it may provide more constant steady-state C1INH levels and would allow for easy self-administration in the home setting. An initial feasibility study was performed using a swine model [40]. Two study groups were investigated: an intravenous group and a subcutaneous group. Both groups received 50 U/kg, as this was expected to double the level of C1INH in the animal's blood. In the intravenous group, blood levels of human C1INH peaked by 1 h and slowly declined over the following 3 days. In the subcutaneous group, blood levels of C1INH peaked at 6 h, with levels remaining relatively stable over the following 3 days. This study provided the initial impetus for the subcutaneous delivery of C1INH replacement therapy and made the prospect of subcutaneous C1INH concentrate a potentially viable option for patients with HAE.

CSL Behring recently performed a human, randomized, open-label, crossover, phase 3 study (PASSION [Berinert P Study of Subcutaneous Versus Intravenous Administration]) to evaluate the pharmacokinetics of subcutaneous versus intravenous administration of Berinert P in individuals with HAE [41]. They evaluated 24 individuals with HAE in a randomized, crossover study, with the primary end points

including pharmacokinetics of C1INH and safety of subcutaneous administration. Mean $C_{\max}$ (maximum plasma concentration) of C1INH plasma activity was achieved 15 min after intravenous administration of C1INH, compared with 48 h after subcutaneous administration. Bioavailability of C1INH was less than 50% if given subcutaneously as compared with intravenously. Overall, subcutaneous C1INH was well-tolerated, with no serious side effects reported. At this point, further studies are warranted before subcutaneous C1INH will be ready for clinical use.

Conclusions

The treatment of HAE in the United States has undergone a rapid change over the past 3 years. Currently, three specific drugs for HAE patients are safe, effective, and well-tolerated. Two additional drugs are likely to be approved in the future. Additional therapies may include targeting factor XII [42], which may prevent bradykinin from being produced. Another potential therapy may be oral bradykinin receptor B2 antagonists [42]. Some evidence also suggests that targeting the bradykinin B1 receptor along with the bradykinin B2 receptor may provide additional efficacy in some HAE patients [43].

We strongly recommend considering all possible therapies when determining the best therapy for any particular HAE patient. The goal of HAE treatment should now be to allow patients to achieve a normal life with minimal disruption from attacks and minimal side effects. To achieve this, we recommend early, effective, on-demand treatment for all HAE attacks. Consideration for home treatment should be given, as this is likely to be the most effective method to obtain early relief in most HAE patients. For patients in whom on-demand treatment is not adequate, long-term prophylaxis should be considered, ideally using a drug that is safe and well-tolerated. The changing strategies for managing HAE are reflected in a very recent guideline document based on an international consensus meeting held in the fall of 2010 (Cicardi et al., unpublished data).

Disclosure Dr. Zuraw has served as chair of a medical advisory board for the HAE Association; has served as a consultant for ViroPharma, Dyax Corp., Shire, CSL Behring, Santarus, and BioCryst Pharmaceuticals; has provided expert testimony for Lev Pharmaceuticals; has received grant support from Pharming Group NV, Lev Pharmaceuticals, and Shire; has received honoraria for speaking at meetings from the HAE Association; has received payment for development of educational presentations from Current Views Allergy and the Robert Michael Educational Institute; and has had expenses covered to attend advisory meetings by Shire, ViroPharma, and CSL Behring.

Dr. Tourangeau reported no potential conflicts of interest relevant to this article.

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