

Management and Treatment of Hereditary Angioedema in the United States: Current Perspectives

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ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by recurrent self-limiting episodes of soft tissue swelling, which affect different parts of the body. Acute HAE attacks range from benign but disfiguring skin edema to painful abdominal edema or even life-threatening laryngeal attacks. The disease is caused by an aberrant or deficient C1 esterase inhibitor (C1-INH), which regulates complement, fibrinolytic, and contact pathways. An elevated serum level of bradykinin is thought to be the major mediator of pain and edema formation in HAE because of contact pathway activation. Current therapy of acute HAE attacks in the United States was limited, but new therapies have recently been approved. Fresh frozen plasma provides some reconstitution of C1-INH, but the efficacy and safety of this treatment is controversial. In some European countries, 2 human-derived C1-INH concentrates have been used successfully to treat acute attacks. Prophylactic therapy for patients with frequent HAE attacks until recently has been confined primarily to attenuated androgens, although in some countries, antifibrinolytics have been used. Recent approval of C1-INH concentrate for prophylaxis and acute treatment has been a significant step forward for patients with HAE. Despite this advance, there are unmet needs for patients with HAE, and this manuscript will discuss some of the research that may change how we care for patients with HAE in the future. (*Angioedema*. 2010;1[2]:xx–xx) © 2010 Excerpta Medica Inc.

INTRODUCTION

Hereditary angioedema (HAE) is an autosomal-dominant disease (Mendelian Inheritance in Man #106100)¹ characterized by sporadic self-limiting soft tissue swelling. The prevalence of HAE is not well defined, but is estimated between 1:10,000 and 1:150,000 worldwide. Recent epidemiological data from 2 different countries reported prevalence in the general population ranging from 1.09:100,000 to 1.51:100,000.^{2,3} In the United States, the number of patients with HAE is commonly referenced as 6000 to 10,000 people; however, many feel this is an underestimated figure. Most data show no deviation correlated to either sex or race. There is, however, a significant age-related difference in presentation and frequency of clinical HAE attacks, with a possible reduction in severity with age.⁴

The underlying cause of HAE is attributed to mutations in the C1 esterase inhibitor (C1-INH) gene (SERPING1 gene), which was mapped to chromosome 11 (p11.2-q13). More than 150 mutations of this gene have been linked to clinical HAE manifestations.⁴ The majority of HAE cases show familial pattern of inheritance, while about 25% are related to spontaneous genetic mutations.

Two types of HAE account for the majority of cases and are most extensively studied. An estimated 85% of all patients have type I HAE, characterized by low production of functionally active C1-INH. The majority of non-type I patients have type II HAE, characterized by a normal volume of C1-INH production, but with a functional impairment of the protein itself. Besides the 2 dominant types of HAE, type III HAE (Mendelian Inheri-

tance in Man #610618)¹ was initially diagnosed in women and was therefore thought to be estrogen dependent. While clinically indistinct from the first 2 types of HAE, type III differs in that no abnormality in C1-INH level or function was initially found. Today, a mutation in coagulation factor XII protease (Hageman factor) with dominant inheritance is suspected to cause type III HAE in a subset of patients, though many patients who fit the clinical description of type III HAE appear not to have this specific mutation.^{5,6} Furthermore, type III HAE has also been diagnosed in some men.^{7,8}

Nearly half of all HAE patients manifest the disease before puberty. The earliest onset occurs within the first year of life and, in 35% of sufferers, HAE presents before the age of 20 years.^{9,10} Another 15% develop their first episode later in young-adult life, with only ~4% of patients experiencing their first HAE attack after age 40 years.^{10,11}

The number of HAE attacks also varies among individuals. Evidence indicates that patients with an onset of symptoms before age 5 years experience attacks more frequently than those who develop angioedema after age 15 years.¹⁰ In a study of 226 patients with HAE,⁹ the number of yearly attacks varied, with 50% experiencing 5 or less, while 30% had more than 12 attacks per year. HAE diagnosis is commonly delayed, with the average time from the beginning of symptoms to diagnosis ranging between 13 and 21 years.^{2,12} This delay results in significant morbidity and even mortality in affected patients. Knowledge of affected family members expedites recognition of the disease.

The clinical presentation of HAE can involve any area of the skin, larynx, or abdomen. Almost all patients with HAE experience skin swelling in their lifetime. The disease commonly affects extremities but can target any body part, causing temporary debilitation and disfigurement that can last for up to a week. Skin edema is not life threatening and is self-limiting; it is thus frequently left untreated. It should not be underestimated, however, for the potential to limit productivity and school and employment absenteeism. Facial edema may occasionally progress to laryngeal swelling. While dangerous laryngeal attacks are rare, especially compared with the frequency of skin or abdominal HAE, laryngeal

edema can cause prolonged intensive respiratory care or even death from asphyxia.¹³ Laryngeal edema is most common in patients between the ages of 11 and 45 years.¹⁴ Untreated laryngeal edema usually progresses for up to 8 to 12 hours and can last for up to 4 days.¹⁴ Patients with laryngeal edema may require urgent ventilator support and therefore should be observed in well-equipped facilities such as emergency departments or intensive care units.

Abdominal HAE represents a different scope of medical and social problems for patients. Abdominal attacks can last for 2 to 4 days, often keeping patients on bed rest with a loss of productive time, and most children who experience these attacks require hospitalization. These patients may suffer from significant pain that is often misdiagnosed as an acute surgical abdominal emergency.⁹ Accordingly, more than one third of patients with HAE have had their appendix removed or carry a history of exploratory laparoscopies,⁹ and the opioid analgesics frequently used for pain control of such procedures can lead to abuse, dependence, and further complications.

CARE OF PATIENTS WITH HAE

Dealing with HAE varies by patient and occasion, as different methods of treatment include that for acute attacks, chronic therapy for patients with frequent attacks or history of laryngeal swelling, and short-term prophylactic treatment prior to known exposure to triggers such as surgery, dental work, and trauma. According to the current guidelines,⁴ supportive therapy remains the focus of treatment for acute HAE in the United States. There are currently no up-to-date protocols in the United States that predictably and effectively guide the treatment of acute HAE attacks.

Due to this lack of guidance, multiple clinical approaches are used to attempt to improve HAE outcomes. Although used frequently, common modes of treatment for anaphylaxis and histamine-induced angioedema and urticaria, including epinephrine, antihistamines, and corticosteroids, are not effective in HAE. The infusion of fresh frozen plasma (FFP), however, is effectively used by some physicians in severe cases of laryngeal or abdominal attacks.¹⁵ Active C1-INH is one of the ingredients in FFP, which replenishes this protein. Despite successes, reserva-

tions regarding the use of FFP persist due to the risks of blood-borne pathogens that are present in any human-derived products. Some physicians have even reported a worsening of angioedema after FFP infusion, which can be explained by simultaneous infusion of additional plasma proteases and kinin substrates. Nonetheless, data show that FFP infusion is effective and well tolerated in most cases.¹⁶

For patients with frequent episodes of angioedema or a history of airway compromise, preventive measures with attenuated androgens, antifibrinolytics, or C1-INH are suggested. Danazol is the most common androgen used worldwide. While not commercially available in the United States, stanozolol, another commonly used attenuated androgen, can often be compounded by pharmacies. Two other androgens, methyltestosterone and oxandrolone, are used as alternatives in many countries.^{17,18} Oxandrolone is the preferred androgen for the pediatric population.^{19,20} While the exact mechanism that allows androgens to be effective is not well defined, the clinical effect of protection from edema is thought to result from increased blood levels of C1-INH with chronic use of androgens. However, because of a wide range of serious adverse effects (weight gain, hypertension, dislipidemia, acne, virilization, menstrual irregularities, decreased libido, hepatic necrosis, and hepatic neoplasms), patients treated with attenuated androgens must be closely monitored.^{21,22} These drugs are contraindicated for women during pregnancy and lactation, as well as for men with prostate cancer and most children.

Antifibrinolytic agents may be used when androgens are contraindicated, treatment efforts have failed, or when patients develop adverse effects. However, these options are generally less effective than androgens. Despite this, some recommend antifibrinolytics as a drug of choice in children.²⁰ Their therapeutic effect is thought to be due to the deactivation of plasminogen and subsequent decreased consumption of C1-INH. Epsilon-aminocaproic acid, while commonly used for the treatment of HAE in the past, is now often replaced by tranexamic acid because of its fewer side effects and better tolerability.²⁰ Because tranexamic acid is not available in the United States, the use of fibrinolytics is un-

common here.²⁰ Nanofiltered C1-INH (nfC1-INH; Cinryze™, ViroPharma, Exton, Pennsylvania) has recently been approved for prophylaxis and is now an important option for those with severe HAE requiring prophylaxis.²³

To prevent HAE attacks from surgery, injury, or dental work, short-term replacement therapy or prophylaxis is effective. Danazol is currently recommended in the United States at a 600-mg maximal daily dose for 5 to 7 days prior to and 2 days after the planned procedure. FFP infusion is another recommended option, at a rate of 2 units infused 1 hour prior to the procedure and possibly repeated during prolonged surgeries.^{16,17} With the approval of C1-INH for acute HAE attacks and prophylaxis, it is likely that both products will be used interchangeably and in place of danazol and FFP.^{24,25}

Several new drugs have recently completed Phase III clinical trials. Two of these drugs, pasteurized C1-INH (pC1-INH; Berinert P®, CSL Behring, Germany) and nfC1-INH (Cinryze) are now approved by the US Food and Drug Administration (FDA). Recombinant human C1-INH (rhC1-INH; Rhucin®, Pharming Group NV, Leiden, The Netherlands) has been studied as an acute treatment for HAE. Two other drugs, ecallantide (Dyax, Cambridge, Massachusetts) and icatibant (Shire, formerly Jerini AG, Berlin, Germany), improve edema by regulating the bradykinin pathway. A summary of general information about these drugs can be found in the [table](#).

REPLACEMENT THERAPY WITH C1-INH

Replacement therapy with C1-INH concentrate derived from human plasma has been used effectively in the treatment of acute HAE for the past 35 years in Europe.^{24,25} Sanquin (Amsterdam, The Netherlands) produces the C1-INH concentrate (Cetor®) in Europe, which is now available in the United States as a nanofiltered product for the prevention of HAE attacks. A second C1-INH concentrate (Berinert, CSL Behring, Marburg Germany) was just approved in the United States for the treatment of acute HAE attacks.²⁶⁻³⁰

Internationally, no standard of dosing for pC1-INH has been agreed upon. A wide range of

TABLE. COMPARING MEDICATIONS APPROVED OR SOON TO BE APPROVED IN THE UNITED STATES FOR HAE.

Product	Effective for Acute Treatment	Effective for Short-term Prophylaxis	Effective for Chronic Prophylaxis	Benefits	Disadvantages
Fresh frozen plasma	X	X		Replaces C1-INH	Viral potential, anaphylaxis, may worsen attack
Androgens		X	X	Effective, easy to take, oral, inexpensive	Liver toxicity, vascular disease, other toxicities
Tranexamic acid	x		x	Oral	Multiple toxicities
Epsilon-aminocaproic acid			x	Oral	Requires multiple dosing, multiple toxicities
Ecallantide	X			Subcutaneous	Short half-life, ? anaphylaxis, no home administration
Icatibant	X			Subcutaneous, room temperature stable, self administration	Local pain and burning at injection site, short half-life
Recombinant C1-INH	X	x		No viral risk	Short half-life, potential for allergic reaction
Plasma-derived C1-INH	X	X	X	Very effective, replaces deficient protein, long half-life	Viral transmission possible, IV only, expensive

HAE = hereditary angioedema; X = very effective; C1-INH = C1 esterase inhibitor; x = less effective; IV = intravenous.

doses between 500 and 1500 units of pC1-INH per injection has been utilized. Some of the treatment strategies for acute HAE attacks have been based on weight (500 units for patients <50 kg, 1000 units for patients ≥50 kg but <100 kg, and 1500 units for patients ≥100 kg), while others have used a set dose.²⁸ Because of the historical lack of consistent

dosing, CSL Behring designed their International Multicenter Prospective Angioedema C1-INH Trial (IMPACT1) to determine the most effective dose for acute HAE attacks.²⁶ Twenty units/kg was statistically effective, while smaller doses did not show statistical differences from placebo. The 20-units/kg dose decreased the severity and duration of acute at-

tacks of the face and abdomen; time to first relief was ~30 minutes for both sites.²⁶ The use of pC1-INH before surgical or dental procedures and for long-term prophylaxis has also been shown to be successful.^{31–34}

Because of its well-established clinical efficacy and safety, pC1-INH is the drug of choice for the treatment of acute attacks of angioedema in Japan, Argentina, and select European countries. The Phase II/III IMPACT1 program, which confirmed the efficacy and safety of pC1-INH treatment during acute facial and abdominal HAE attacks,²⁶ was conducted in the United States, Canada, and multiple European countries. As noted above, it also was the first dose-finding study, which concluded that pC1-INH at 20 units/kg is effective and well tolerated. The safety of pC1-INH was also established in a report by Terpstra et al.³⁵ pC1-INH received FDA approval for the treatment of acute attacks of HAE in 2009 and has been commercially available for therapy since early 2010.

Another treatment option for HAE is nC1-INH, a C1-INH concentrate manufactured from US-licensed plasma, which undergoes nanofiltration as an additional purification step. Similar to earlier generations of nC1-INH such as Cetor, polyethylene glycol precipitation and pasteurization via heat treatment at 60°C in an aqueous solution minimize possible viral contamination. Additionally, the use of 2 serial 15-nm filters allows extra purification, with the total reduction of enveloped and nonenveloped viruses in the range of 8.7 to 19.1 log₁₀.^{35,36}

The randomized, double-blind, placebo-controlled, Phase III C1 Inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy (CHANGE) study recently evaluated the impact and safety of nC1-INH in the acute and prophylactic treatment of HAE. Although it was approved for the long-term prophylaxis of HAE, nC1-INH was not approved for use in acute attacks. In the prophylactic section of the study, 22 patients with a history of at least 2 acute episodes per month were randomized to receive 12 weeks of either nC1-INH or placebo in a traditional crossover design. Patients receiving chronic replacement therapy with nC1-INH showed a significant decrease in the number, severity, and duration of attacks.³⁷

A third C1-INH product, rhC1-INH, produced from the milk of transgenic rabbits,³⁸ is presently under review for approval by the FDA. A lactating rabbit may produce 10 L of milk per year, with the average levels of active C1-INH between 0.05 and 20 mg/mL. Collected milk undergoes several steps of purification, including skimming, multiple chromatography steps, viral inactivation via nf, and other processes.³³ The final product is 99.98% pure, containing <1 part(s) per million (ppm) of endogenous rabbit C1-INH and <20 ppm of rabbit milk proteins. Except for differences in glycosylation, which results in a shorter half-life and a possible risk of anaphylaxis, rhC1-INH is very similar to native human C1-INH.^{39–41} During Phase III studies, rhC1-INH has been well tolerated, with no significant adverse events reported. One healthy volunteer in a Phase I trial⁴² failed to disclose allergic sensitization to rabbits and developed hives and wheezing following injection of rhC1-INH. In contrast to human-derived C1-INH, rhC1-INH carries no risk of transmission of human blood-borne pathogens. Because of its short half-life, rhC1-INH is likely to be more effective for the treatment of acute HAE attacks than for prophylaxis.

TREATMENT THROUGH KININ PATHWAY MODULATORS

Other treatment options work as kinin pathway modulators, including ecallantide (DX-88), a 60-amino acid recombinant protein with a molecular weight of 7054 daltons, and a potent reversible inhibitor of plasma kallikrein produced by the yeast *Pichia pastoris*.^{43–48} Ecallantide has a rapid on-rate ($k_{\text{on}} = 2 \times 10^6 \text{ m}^{-1}\text{s}^{-1}$) and a slow off-rate ($k_{\text{off}} = 2 \times 10^{-5} \text{ s}^{-1}$), which result in a high affinity for inhibition. Once activity of kallikrein is suppressed, the cleavage of high-molecular-weight kininogen to bradykinin does not readily occur, enabling edema progression in acute HAE attacks to be aborted.

A series of evaluations^{49,50} of the Effect in Mitigating Angioedema (EDEMA) Phase II/III trials assessed the efficacy of ecallantide. The results of the 2-stage, Phase III pivotal EDEMA 3 trial were reported at the American Academy of Allergy, Asthma & Immunology meeting in March 2008 in Philadelphia, Pennsylvania. Seventy-two patients

were randomized 1:1 to receive ecallantide 30 mg subcutaneously or placebo in a double-blind study,⁴⁹ which was followed by an open-label study.⁵⁰ Treatment outcome score (TOS, ranging from -100 to +100) showed faster improvement at 4 hours in patients who received ecallantide compared with those given placebo (53.8 vs 18.5; $P = 0.02$), sustained improvement at 24 hours (48.8 vs -0.5; $P = 0.03$), and a faster mean time to significant overall improvement (124.5 vs 196 minutes; $P = 0.04$).^{49,50}

In clinical trials,⁴⁷ the incidence of adverse events in patients treated with ecallantide was similar to that in placebo controls and generally well tolerated. Four patients had severe adverse events, of which 2 developed shortness of breath and wheezing within 5 minutes after the intravenous infusion of ecallantide and required respiratory treatment.⁵¹ One patient developed throat swelling within 25 minutes of injection and required treatment of steroids and epinephrine. A fourth patient developed coagulopathy, with thrombin time >120 seconds (normal is 1–18 seconds), that resolved without sequelae.⁵¹ In the Phase III trial,⁴⁹ when subcutaneous administration of ecallantide was used, only 4 patients (11.1%) in the treatment group and 5 (13.9%) in the placebo group experienced adverse events, and there were no cases of anaphylaxis. Generally, ecallantide was well tolerated when used subcutaneously.

Results from a second randomized, double-blind, placebo-controlled trial, EDEMA 4, were analyzed along with EDEMA 3, and the results were presented at the 2010 meeting of the American Academy of Allergy, Asthma & Immunology. Across all episodes, 4-hour TOS showed significant improvement ($P \leq 0.001$). The 4-hour change in mean symptom complex severity score from baseline also showed improvement ($P \leq 0.08$).⁵² The investigators concluded that ecallantide showed consistent efficacy and reported no new adverse events following repeated treatment of HAE.⁵²

Ecallantide was approved by the FDA on November 27, 2009, for the treatment of acute attacks of HAE.⁵³ Phase IV postmarketing surveillance studies will now be implemented to monitor the incidence of hypersensitivity reactions.⁵⁴

Another kinin modulator investigated for HAE is icatibant, a synthetic decapeptide, which is a specific and selective competitive antagonist of the bradykinin B2 receptor (BK2R). Structurally, icatibant is similar to bradykinin and binds to the BK2R with high affinity.^{55,56} The safety and tolerability of icatibant were studied in multiple Phase I trials^{55–57} evaluating both intravenous and subcutaneous preparations. Interestingly, the peak concentration time (0.5 hour) and half-life (1.2–1.5 hours) for icatibant were similar, regardless of the route of administration.⁵⁷ In a proof-of-concept Phase II pilot study,⁵⁸ 20 acute abdominal and peripheral HAE attacks in 15 patients were treated with icatibant. Rapid relief of symptoms was observed after drug administration, and results were similar in intravenously ($n = 12$) and subcutaneously ($n = 8$) treated groups. The time to onset of symptom relief in all treated patients was <4 hours, while symptoms of untreated attacks began to resolve in ~34 hours.⁵⁸

These data led to the Phase III For Angioedema Subcutaneous Treatment (FAST-1 and FAST-2) trials of the subcutaneous application of icatibant for the treatment of acute HAE attacks. In the double-blind, placebo-controlled FAST-1 trial, treatment with icatibant significantly shortened the time to onset of symptom relief versus placebo (0.8 vs 16.9 hours, respectively; $P < 0.001$).⁵⁹ However, no statistical difference in median time to significant symptom relief (2.5 vs 4.6 hours, respectively; $P = 0.142$) was observed.⁵⁹ These data resulted in the need for Shire to repeat their Phase III studies in the United States for resubmission to the FDA in the future.

The FAST-2 trial, however, was more successful than its predecessor. Seventy-four patients with acute HAE attacks⁵⁹ from 11 European countries and Israel were randomized to receive icatibant or tranexamic acid. Significant improvement was demonstrated in patients treated with icatibant, as the time to onset of symptom relief was 0.8 versus 7.9 hours ($P < 0.001$) with icatibant versus tranexamic acid, respectively,⁵⁹ and the median time to significant symptom improvement was 2 versus 12 hours.⁵⁹ Due to these data, the European Commission granted marketing authorization

for icatibant (Firazyr[®], Shire) for the treatment of acute HAE attacks within the European Union.

The safety of icatibant has been established in more than 580 patients with HAE attacks who were treated subcutaneously with the agent. No drug-related serious adverse events were reported. Lesser reactions did occur and were limited to localized mild erythema and edema at injection site and occasional minor burning sensations, itching, or pain, which resolved within a few hours.

DISCUSSION

HAE is a rare but serious disease that carries medical, social, and financial implications. The multiple possible clinical presentations of the disease range from self-limiting skin edema to debilitating abdominal and whole-extremity attacks to life-threatening laryngeal edema. HAE can manifest in all ages, but most commonly presents within the first decade of life. Patients and families live in constant fear of recurrences and the possible outcomes of the attacks. Some patients experience early signs of an evolving attack, but even then, severity and location of the attack are unpredictable.Ⓞ

Traditional treatment of histamine-induced edema (typically seen in allergic and idiopathic angioedema) with epinephrine, corticosteroids, and antihistamines is still frequently applied to the symptomatic treatment of HAE in the United States, despite a lack of data demonstrating the effectiveness of these agents for this indication.⁴⁸ FFP is frequently used for the treatment of HAE attacks and for short-term prophylaxis in the United States in spite of safety concerns; however, despite these concerns, it appears that FFP infusion is effective, with a low incidence of adverse events.¹⁶ With the recent approval of C1-INH, it is expected that the use of FFP will be in decline and limited to times when C1-INH is not available.

Oral tranexamic acid is used for the treatment of HAE in Europe, although it has a lower efficacy and more side effects than androgens. Because of a possible associated teratogenic effect in animals, tranexamic acid is not available in the United States.⁶⁰ The antifibrinolytic agent epsilon-aminocaproic acid has previously been studied and used for the treatment of HAE, but it has a poor side effect

profile and thus has been predominantly abandoned in the United States and Europe.

Prophylactic prevention of recurrent HAE attacks in the United States is predominantly achieved by the use of danazol and other attenuated androgens. Tolerability of androgens is poor at large to moderate doses, but at low doses, patients often have control of their HAE with few adverse events.²¹ The use of androgens is contraindicated in children, pregnant women, and patients with certain health conditions. When using androgens in appropriate patient populations, monitoring for side effects is necessary. The least effective dose should be used to suppress HAE attacks. Therapy should be adjusted based on clinical response, and not on the serial assessment of C4 or other laboratory tests. Most HAE experts recommend that blood pressure, liver function, and lipid levels should be monitored every 6 months and a liver ultrasound performed every 12 months.²¹

Of all the available treatment modalities for chronic prophylactic therapy, only C1-INH concentrate (nfC1-INH) currently represents specific, reliable, and pathophysiologically based treatment for the prevention of HAE attacks. The FDA-approved chronic use of C1-INH is based on limited data, and physicians will need to carefully monitor any post-marketing reports of adverse events. For now, however, it appears that the chronic use of C1-INH is safe and effective. The recommended dosage is twice a week based on the half-life of C1-INH. Rescue doses of C1-INH may be necessary, since breakthrough attacks occur in most patients despite replacement therapy. The main limiting factor for the use of C1-INH is cost. Therefore, C1-INH therapy should be considered carefully. Guidelines for the use of C1-INH in the United States are still pending, but a recent consensus document⁶¹ addresses some of the considerations for chronic C1-INH usage.

pC1-INH, like nfC1-INH, has a long half-life and may be effective when used as an off-label medication for the prevention of HAE attacks. At this time, FDA approval is limited to the treatment of acute HAE attacks. The weight-based dose of 20 units/kg should be used for optimal results.²⁶

For short-term prophylaxis before dental, surgical, or other procedures that may cause trauma of tissue integrity, the off-label use of human-derived

C1-INH is likely to be recommended because of its longer half-life. Well-established short-term prophylaxis includes the use of high-dose danazol 200 mg 3 times daily for 5 days before and 2 days after a procedure or 2 units of FFP infused before the procedure; both methods are safe and effective. pC1-INH and nfC1-INH are good alternatives to androgens and FFP, especially when androgens are contraindicated or not well tolerated.

The route of administration will likely be one of the defining factors for future marketing of these HAE drugs. pC1-INH and nfC1-INH are currently recommended for intravenous use only, and hence will be predominantly used in the hospital setting or infused by health care services at home. Both have been used for the treatment of HAE via self-administration in homes.⁶² Attacks treated within the first 2 hours have better outcomes compared with treatment that is initiated later and, thus, home therapy has its advantages.²⁸

Icatibant is a subcutaneous formulation with a storage duration of 1 year at room temperature, and it may become a preferred drug for self-treatment of acute HAE attacks. It is anticipated that icatibant will be available as a prefilled syringe and self-administered by the patient. A decision on FDA approval is anticipated within a couple of years, pending results of the additional Phase III study.

Ecallantide, also a subcutaneous formulation, has recently been approved for the treatment of acute HAE attacks. Because of the rare but documented occurrence of anaphylaxis, therapy with ecallantide will be limited to within a medical environment suitable to treat anaphylaxis, and only after informed consent is obtained from the patient, as directed by the **Risk Evaluation and Mitigation Strategies (REMS) program**. Despite these limitations, uptake by allergists is likely, since allergists give many subcutaneous injections each day and routinely face the possibility of anaphylaxis.

Compared with human-derived C1-INH, rhC1-INH is unique in the absence of risk of human blood-borne pathogen transmission. It is not indicated for patients allergic to rabbits because of trace rabbit protein within the product. The adverse-effect profile of rhC1-INH is otherwise benign. Therapy with rhC1-INH will probably be limited to acute

treatment because of its short half-life. It may be effective for use in short-term prophylaxis as well, but this use will be considered off label. It is anticipated that rhC1-INH will be used as an alternative in those unable or unwilling to receive blood products.

An exciting new approach to therapy is being implemented at the time of prodromal symptoms.^{63,64} Most patients with HAE have symptoms that are often nonspecific and, in some cases, specific (eg, erythema marginatum), that proceed an HAE attack by hours. Instituting therapies at the time of prodromal symptoms may potentially reduce the morbidity associated with an attack, decrease the potential for mortality, reduce emergency care, and improve absenteeism. Though it is known that prodromal symptoms occur before 60% to 85% of HAE attacks, the specificity of prodromal symptoms remains unknown. As a result, overtreatment is a possible concern; however, this may be preferable to treating an attack retrospectively, after symptoms have presented.

CONCLUSIONS

In general, all the newly approved or soon to be approved medications are well tolerated. Because of favorable safety profiles, these new therapies will likely replace FFP and antifibrinolytics as treatments of choice for HAE. The authors expect a role for androgens in the future because of the cost associated with C1-INH, but with a significant reduction in overall androgen use.

It is hoped that broader use of these new drugs in the treatment of HAE will provide an improved quality of life for patients, a better knowledge of safety for each of these medications, and stricter definitions of specific applications for each of them. Because HAE is episodic and unpredictable, it is likely that patient-controlled modes of administration of HAE drugs will gain more attention.⁶¹ In time, it is speculated that pC1-INH and nfC1-INH will be available as subcutaneous preparations for long-term prophylaxis, facilitating self-administration. Future developments hopefully will lead to an oral form of bradykinin antagonist or receptor inhibitor that can be beneficial for the long-term treatment and prophylaxis of HAE. Only an international ap-

proach to investigational drug studies can satisfy the need for better therapeutic options in the treatment of HAE and other rare diseases.

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