

Hereditary angioedema: Management of laryngeal attacks

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ABSTRACT

Background: Hereditary angioedema (HAE) patients suffering from laryngeal attacks in the United States faced severely limited treatment options until 2008. These potentially life-threatening episodes occur in over one-half of the patients affected by HAE during their lifetimes. Acute therapy had been relegated to supportive care, intubation, and consideration of fresh frozen plasma (FFP)—the latter with the potential for actually accelerating the speed and severity of the swelling.

Methods: In this article we will review the recently approved and emerging HAE treatments that have evolved from the recognition that bradykinin generation is the fundamental abnormality leading to attacks of angioedema.

Results: Acute therapy for laryngeal attacks will be discussed including purified plasma-derived C1 inhibitor (C1INH), recombinant C1INH, an inhibitor of plasma kallikrein (ecallantide), and a B2 receptor antagonist (icatibant). Prophylactic care has also been transformed from a reliance on attenuated androgens with their attendant side effects to C1INH replacement.

Conclusion: The arrival of these novel therapies promises to transform the future management of HAE.

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Hereditary angioedema (HAE) is clinically characterized by attacks of abdominal, cutaneous, and laryngeal edema. All episodes of swelling potentially have a high attendant morbidity.^{1,2} Although the least common, laryngeal attacks will occur in >50% of affected individuals during their lifetime.³ These unpredictable events can end fatally in up to one-third of cases if unrecognized and untreated. Until 2008 the management of HAE in the United States was largely driven by efforts to prevent attacks of swelling, relying on prophylactic therapy with either 17 α -alkylated androgens or antifibrinolytic agents. Although these drugs decrease the number and severity of angioedema attacks, they are associated with dose-related significant adverse health effects.⁴ The acute treatment of laryngeal attacks was limited to supportive care, protecting the airway, and fresh frozen plasma (FFP). The use of FFP has been complicated, however, by questions regarding its infectious safety as well as the concern that it can lead to rapid worsening of angioedema attacks. Taken together, the treatment of laryngeal attacks before 2008 could be summed up in a single sentence, “Please call the Head and Neck Surgeon.”

Fortunately, there are now available options for both the prevention and the acute treatment of laryngeal swelling. As discussed in the accompanying article presented during this symposium, scientific insights regarding the mechanism of swelling in HAE have led to the development of targeted therapies. It is now accepted that bradykinin is the primary biological mediator of swelling in attacks of HAE. Pharmacologic strategies have capitalized on this knowledge to prevent the production of bradykinin as well as inhibit engagement of the bradykinin B₂-receptor (B2R). In this article we will review the

approved and emerging treatments for acute and prophylactic care of laryngeal attacks. It is anticipated that these novel therapies will transform the management of HAE.

CLINICAL PRESENTATION OF LARYNGEAL ATTACKS

Laryngeal attacks of angioedema can occur in isolation or in association with facial or tongue swelling. Symptoms include voice changes with deepening, hoarseness, and aphonia. Patients can experience dysphagia, stridor, globus sensation, tachypnea, and dyspnea. Individuals will report an appropriate sense of foreboding with a fear of asphyxiation. Generally, the swelling will progress slowly over hours allowing time to seek medical assistance.⁵ Disturbingly, there have been fulminant cases reported with progression to death by asphyxiation over 20 minutes.^{6,7} Unrecognized and untreated, attacks of laryngeal swelling have a high rate of mortality estimated between 15 and 33%.⁸

PHARMACOLOGIC MANAGEMENT OF LARYNGEAL ATTACKS

Replacement of C1 Inhibitor

Plasma-Derived C1 Inhibitor. The success achieved by treatment of attacks of HAE with FFP was a harbinger of the potential efficacy of C1 inhibitor (C1INH) replacement therapy.⁹ The effectiveness of plasma C1INH administration for acute attacks of HAE was confirmed >25 years ago.^{10–12} Multiple studies have led to C1INH concentrates becoming the preferred modality of treatment for acute attacks of HAE in countries where it has been available.^{13–16} C1INH infusion results in an immediate increase in C1INH plasma levels, rapid improvement in symptoms (typically within 30–60 minutes), and a delayed increase in C4 levels.^{5,17,18} The efficacy of C1INH concentrates appears to be equal for all types of HAE attacks, including laryngeal attacks where it can be lifesaving.^{14,19}

In the United States pasteurized plasma-derived C1INH (pdC1INH-p) has been licensed for use in acute attacks since 2009. The product is produced by CSL Behring (King of Prussia, PA) and marketed under the name Berinert. It is identical to the most widely used C1INH product in Europe and has an excellent track record of safety with no

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evidence of transmission of infection agents. In the pivotal U.S. study the primary outcome, time to onset of symptom relief, was met with the 20 U/kg dose. Surprisingly, the 10-U/kg dose, which is commonly used in Europe, was not statistically superior to placebo.^{20,21} The randomized placebo-controlled study specifically excluded laryngeal attacks because of ethical concerns about giving these patients placebo. The results of an open-label extension trial showed that pdC1INH-p (20 U/kg) was highly effective in 39 laryngeal attacks affecting 16 patients, with a median time to onset of symptom relief of 15 minutes.²²

In addition to its use for acute attacks of HAE, C1INH concentrates have also been successfully used for both short-term and long-term prophylactic treatment of HAE. Long-term prophylaxis with C1INH may be particularly useful for patients with very severe disease and possibly during pregnancy in women who experience an increased frequency of attacks. Bork reported the successful use of C1INH concentrate for long-term prophylaxis in an HAE patient with frequent attacks that could not be well controlled with androgens or antifibrinolytic drugs.²³ Subsequently, other investigators have reported the successful use of long-term prophylactic C1INH (2–3 times/week) for severe HAE patients.²⁴ Long-term prophylaxis with C1INH has also been successfully used in pregnancy.²⁵ For short-term prophylaxis, purified C1INH should be at least as effective as FFP but with improved safety parameters. A number of reports have also established the efficacy of short-term prophylaxis with C1INH before dental work or surgery.^{26–30}

In the United States, a trial of regular scheduled C1INH for long-term prophylaxis of HAE was conducted using plasma derived, pasteurized and nanofiltered C1INH (C1INH-nf). The prophylactic C1INH-nf study was a 24-week crossover design involving 22 patients with relatively severe disease who were randomized for whether they received C1INH-nf or placebo prophylaxis first. Subjects received either 1000 U of C1INH-nf or placebo every 3–4 days, and all breakthrough attacks were eligible to be treated with open-label C1INH-nf for both groups. After 12 weeks, the subjects were crossed over and received the opposite treatment for the final 12 weeks. The primary end point was the number of attacks over the 12-week period. There was a highly significant reduction in the attack rate for subjects treated with prophylactic C1INH-nf ($p < 0.0001$), with almost one-half of the individuals attack free during the active treatment arm.³¹ Based on this study, C1INH-nf was approved by the Food and Drug Administration FDA for use as HAE prophylaxis and has been available in the United States since late 2008. The product is produced by ViroPharma (Exton, PA) and marketed under the name Cinryze.

Recombinant Human C1INH. A fully functional recombinant human C1INH (rhC1INH; Rhucin) was engineered by Pharming BV (Leiden, Netherlands) in transgenic rabbits, and two phase III studies of rhC1INH for the treatment of acute HAE attacks have been completed in the United States and Europe, respectively. The primary end point was patient-reported time to onset of relief. Statistically significant improvement was shown for both the 50- and 100-U/kg dose for the median time to beginning of relief as well as time to complete relief. The rhC1INH was equally effective irrespective of attack location. Fourteen subjects (4 rhC1INH and 10 placebo) had eligible orofacial/pharyngeal/laryngeal attacks in this study, with time to beginning of relief being 70 minutes in the 4 rhC1INH subjects and 306 minutes in the placebo subjects.³² The data have been submitted to the FDA for potential licensing in the United States.

Plasma Kallikrein Inhibition. The first plasma kallikrein inhibitor, other than C1INH, to be used for the treatment of HAE was aprotinin (Trasylol, Bayer Pharmaceuticals), a broad-spectrum inhibitor with activity against trypsin, plasmin, and plasma kallikrein. Although aprotinin was effective for the treatment of acute attacks of HAE,^{12,33} it is a bovine protein and was associated with severe anaphylactic reactions.^{34,35}

More recently, Dyax, Inc. (Cambridge, MA), identified a highly potent and specific inhibitor of plasma kallikrein by screening a phage display library consisting of rationally designed variants of human lipoprotein-associated coagulation inhibitor.³⁶ The resulting molecule, ecallantide, is produced as a recombinant protein in the yeast, *Pichia pastoris*. Ecallantide is a reversible and highly potent plasma kallikrein inhibitor. It is administered by subcutaneous injection and has a half-life of ~2 hours.

Two separate phase III studies of ecallantide for the treatment of acute attacks of HAE have been performed in the United States.^{37,38} Both studies involved randomization of subjects to receive either ecallantide at 30 mg or placebo by subcutaneous injection. The first trial (EDEMA3®) primary end point used a treatment outcome score, a measure of the change in angioedema symptoms at all sites compared with prior to treatment. Statistically significant improvement in the ecallantide treated subjects was observed at both 4 and 24 hours ($p = 0.02$ and 0.03 , respectively). The second trial (EDEMA4®) primary end point used a mean symptom complex severity score, a measure of total angioedema symptom severity at a particular time point. A statistically significant benefit was again seen for the ecallantide-treated subjects at 4 hours ($p = 0.01$). A combined analysis of both studies showed that ecallantide was effective for laryngeal attacks.³⁹ Fifteen ecallantide-treated subjects and nine placebo-treated subjects had laryngeal attacks. Significant overall improvement within 4 hours after dosing was achieved in 60.0% of ecallantide-treated subjects and 11.1% of placebo-treated subjects. Ecallantide has been shown to be highly effective in the treatment of laryngeal attacks compared with placebo as measured by the treatment outcome score.^{40,41} Ecallantide has been licensed for use in the United States for the treatment of acute attacks of HAE since 2009 and is marketed under the name Kalbitor (Dyax Corp). Because of reports of anaphylactic-like reactions the drug does have a black box warning dictating that it be given in a medical facility.

Bradykinin Receptor Antagonist. Blocking the biological actions of bradykinin at the level of its receptor, B2R, on endothelial cells represents the final recently developed therapeutic strategy. Icatibant (Firazyr; Shire, Dublin, Ireland) is a synthetic decapeptide second-generation B2R antagonist that displays high affinity and an impressive resistance to peptidases.⁴² Icatibant has equivalent pharmacokinetics whether administered i.v. or subcutaneously, has a half-life of ~1.2 hours, and is stable at room temperature.

Three phase III studies for the treatment of acute HAE attacks using the subcutaneous formulation of icatibant have been completed. One study compared icatibant with placebo in 56 subjects in the United States, Argentina, Australia, and Canada (for angioedema subcutaneous treatment [FAST-1]). A separate study compared icatibant with tranexamic acid in 72 subjects in Europe and Israel (FAST-2). Primary end point for both was time to onset of relief measured by visual analog score.⁴³ In the FAST-2 study, time to onset of relief was significantly faster in the icatibant-treated subjects (2 hours versus 12 hours; $p < 0.0001$). Based on this, the drug was approved for use for acute attacks in the European Union. In contrast, the FAST-1 study failed to show a significant benefit for icatibant (2.5 hours versus 4.6 hours; $p = 0.13$). The FDA disapproved the application for licensure. The conclusion of a larger FAST-3 world study has now been released. Forty-four patients were enrolled with a composite visual analog score for time to onset of relief. Icatibant was shown to be superior to placebo ($p < 0.001$).⁴⁴ In the FAST-1 and FAST-2 trials, 11 subjects had laryngeal attacks and were treated with open-label icatibant. The median time to first improvement was less than an hour. Nine of the 11 subjects reported no symptoms at 4 hours and the other 2 subjects had mild symptoms at 4 hours. One subject required emergent intubation within 5 minutes of receiving icatibant. The current 30-mg subcutaneous dose of icatibant has been administered in >300 treatments with good tolerability although most subjects experience transient local pain and redness at the injection site. As is the case with C1INH replacement and plasma kallikrein inhibition,

Table 1 Comparison of drugs for the treatment of acute attacks of hereditary angioedema

	pdC1INH	rhC1INH	Ecaltantide	Icatibant
Route	i.v.	i.v.	Subcutaneous	Subcutaneous
Primary safety issue	infectious (?)	allergic (?)	allergic	local pain
Acute use	++++	++++	++++	++++
Short-term prophylaxis	++++	?	?	?
Long-term prophylaxis	++++	—	—	—
Home use	++	++	--	++++

pdC1INH = plasma-derived C1 inhibitor; rhC1INH = recombinant human C1 inhibitor.

icatibant has been shown to be specifically effective in attacks of laryngeal swelling.⁴⁵ It is anticipated that this will be presented to the FDA for consideration in 2011.

CONCLUSION

Management Considerations for HAE

All HAE patients, irrespective of their usual disease severity, are at risk of having a severe episode of angioedema. Over one-half of all patients will have a life-threatening episode during their lifetime of laryngeal swelling. New and effective medications available for prophylactic and acute treatment offer the possibility of normalizing the lives of patients affected by HAE. Patients may require different therapeutic approaches based on a number of parameters, including differences in attack frequency or severity, response to individual therapeutic agents, and the ability of patients to tolerate acute attacks because of age, pregnancy, coexisting medical conditions, or access to medical care. Current and emerging therapies are summarized in Table 1.

There is compelling data suggesting that the time to complete resolution of angioedema attacks is strongly influenced by the interval between onset of symptoms and institution of effective therapy.⁴⁶ Based on this, self-administration of C1INH concentrate by i.v. infusion has been tried and reported to be safe and effective in patients with frequent or severe attacks of angioedema. Self-administration was reported to decrease the interval between onset of symptoms and initiation of therapy and markedly reduce the time to complete resolution of symptoms. Studies in Europe and recently completed in the United States have concluded that time to initiation and complete relief of symptoms is superior for self-infused patients compared with drug delivery in a medical facility.⁴⁷ Individuals instructed to infuse pC1INH at the first sign of swelling had their attack rate fall essentially to zero.⁴⁸

Based on the significant advances in understanding the pathogenesis, therapies for HAE now encompass specific and effective interventions. Replacement therapy with purified pdC1INH or recombinant C1INH, treatment with plasma kallikrein inhibitor, or a bradykinin B2R antagonist each provide reliable interventions for acute attacks of laryngeal angioedema. In addition, C1INH replacement therapy provides new possibilities for both short-term and long-term prophylaxis.

International consensus guidelines were established in 2010 to guide the future approach to treatment of HAE.⁴⁹ Given the universal potential for HAE patients to have an attack of laryngeal edema, it was emphasized that all patients should have on-demand treatment available (including those receiving prophylactic treatment). Incorporating the knowledge that early treatment is more effective, it was agreed that all patients should be trained for self-administration and that attacks should be treated as soon as they are recognized. With the goal of normalizing the lives of patients with HAE, attacks in all locations are deemed eligible for treatment. Long-term prophylaxis was felt appropriate to offer when optimized on-demand therapy fails. Caution was highlighted for laryngeal attacks where it was

emphasized that patients with progressive symptoms should be hospitalized for observation. The improved options for care will hopefully make such events a rare occurrence in the future.

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