

New and evolving therapies for hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare, autosomal dominant, genetic disorder associated with a deficiency in C1 inhibitor protein. HAE is characterized by recurrent and unpredictable episodes of swelling of the extremities, abdomen, face, and upper airway. There are several newly approved drugs as well as investigational products that are currently under study for the management of patients with HAE, with the potential to optimize care and improve quality of life for patients with HAE. We reviewed the evolution of HAE treatment options in the United States and discussed mechanisms of action, routes of administration, and efficacy of these therapies.

(Allergy Asthma Proc 40:7–13, 2019; doi: 10.2500/aap.2019.40.4195)

Hereditary angioedema (HAE) is a rare, autosomal dominant genetic disorder associated with a deficiency in C1 inhibitor protein. The reported prevalence of HAE in the literature ranges from 1:50,000 to 1:100,000.^{1–4} Patients with HAE have recurrent and unpredictable episodes of swelling of the extremities, abdomen, face, and upper airway. Angioedema that involves the gastrointestinal tract can lead to intestinal wall edema, which results in abdominal pain, nausea, and vomiting. Laryngeal swelling is life-threatening and may lead to asphyxia. Patients with HAE face a significant burden of illness, including an average of 20 missed days from school or work per year,⁵ poorer health quality of life compared with population norms,⁶ and increased rates of depression.⁷

Symptoms of swelling in patients with HAE are caused by dysregulation of the bradykinin pathway, with increased bradykinin levels that lead to vasodilation and vascular permeability. Activation of the kallikrein-kinin system generates bradykinin, which binds to the bradykinin B2 receptor on endothelial cells. C1 inhibitor is a serine protease inhibitor that normally inhibits proteases, *e.g.*, kallikrein, involved in the bradykinin pathway (as well as several other plasma enzyme cascades, including complement, coagulation, and fibrinolytic pathways).⁸ Therefore, when C1 inhibitor is either deficient or dysfunctional, the generation of bradykinin is uninhibited, which leads to increased

vascular permeability and the clinical symptoms of swelling seen in patients with HAE.⁹

Reducing morbidity and mortality in HAE must begin with an early and accurate diagnosis. HAE is classically categorized into three subtypes. HAE with C1 inhibitor deficiency type I is characterized by low antigenic and functional C1 inhibitor levels, whereas type II is characterized by normal or elevated antigenic levels, but low functional C1 inhibitor levels. HAE with normal C1 inhibitor (previously known as type III HAE) is characterized by normal complement studies, although some patients have been identified as having specific genetic mutations, including factor XII, angiotensin-converting enzyme 1, or plasminogen gene mutations.^{10–12}

To provide optimal care and improve quality of life, treatment of patients with HAE needs to be individualized based on patient-specific factors, including patient preference, intravenous (IV) access, access to emergency department care, comorbidities, and adverse effects. There are several newly approved drugs and investigational products currently under study for the management of patients with HAE, with the potential to optimize care. We reviewed the evolution of HAE treatment options in the United States and discussed mechanisms of action, routes of administration, and efficacy of these therapies.

MANAGEMENT OF HAE

The therapeutic strategies for HAE management are threefold. The first is treating HAE attacks to resolve symptoms as quickly as possible after onset of swelling. The second is long-term prophylaxis to decrease the overall number and severity of angioedema attacks. The third is short-term prophylaxis to reduce the likelihood of swelling in response to anticipated events that are likely to precipitate an attack (*e.g.*, medical or dental procedures).^{13,14} Historically, in the United States, treatments for patients with HAE were lacking, in that the treatment options had limited efficacy in acute attacks^{15,16}; were associated with significant ad-

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S. Barmettler and A. Banerji received a stipend from EAC

Presented at the Eastern Allergy Conference, June 2, 2018, Palm Beach, Florida

A. Banerji has received grants or honorariums from Shire, Biocryst and CSL Behring.

S. Barmettler has received grants from Shire and Biocryst. Y. Li has nothing to disclose pertaining to this article

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verse effects, such as virilization and liver abnormalities with androgen use^{15,16}; or were associated with a risk of bloodborne infections or theoretical risk of worsening or precipitating an acute attack of HAE, such as with fresh frozen plasma.¹⁷ However, the medical management of HAE has improved significantly in recent years, with the availability of several new safe and effective therapies.

On-Demand Treatment in HAE

A decade ago, in the United States, several agents were approved by the U.S. Food and Drug Administration (FDA) for on-demand treatment of HAE attacks, including a plasma-derived C1 inhibitor concentrate (Berinert, CSL Behring, King of Prussia, PA), a kallikrein inhibitor (Kalbitor, Dyax Corp, Burlington, MA), a bradykinin B2 receptor antagonist (icatibant), and a recombinant C1 inhibitor (Ruconest, Pharming, the Netherlands).

Berinert is a plasma-derived C1 inhibitor concentrate that was FDA approved in 2009 for treatment of HAE attacks and, in 2017, was approved for use in all ages. In a randomized, double-blind, placebo controlled study, C1 inhibitor concentrate at a dose of 20 U/kg showed a significant reduction in the time to onset of relief of symptoms (0.5 versus 1.5 hours; $p = 0.003$) as well as a reduction in the time to resolution compared with placebo (4.9 versus 7.8 hours; $p = 0.02$).¹⁸ The dosing for plasma-derived C1 inhibitor concentrate for treatment of an HAE attack is 20 U/kg IV at 4 mL/min. Analysis of data supports the safety of plasma-derived C1 inhibitor concentrates,¹⁹ with no reported episodes of viral transmission (given the theoretical risk of bloodborne viral transmission associated with plasma products).

Ecallantide (Kalbitor) is a potent kallikrein inhibitor approved for treatment of HAE attacks in patients ages ≥ 12 years. A randomized, double-blind, placebo controlled study of 30 mg of subcutaneous ecallantide showed a significantly greater decrease in mean symptoms complexity severity score 4 hours after dosing compared with placebo (-0.8 versus -0.4 ; $p = 0.01$), with the benefit of ecallantide becoming apparent within 2 hours after dosing.²⁰ Due to the risk of anaphylaxis and/or anaphylactoid reactions (reported at 3.5% in one study),²¹ ecallantide is only approved for administration by a health care professional with appropriate support and supervision. Ecallantide is given as a 30-mg subcutaneous dose (three injections of 1 mL each).

Icatibant (Firazyr, Shire, Lexington, MA) is a B2 receptor antagonist, approved for treatment of HAE attacks in patients ages >18 years.²²⁻²⁴ In a double-blind, randomized, multicenter trial, the effect of icatibant was compared with oral tranexamic acid (FAST [For

Angioedema Subcutaneous Treatment] 2) trial and found to have a significantly reduced median time to clinically significant relief of symptoms (2 versus 12 hours; $p < 0.001$).²² In the FAST-3 trial, a phase III, randomized, double-blind, placebo controlled study, icatibant significantly reduced the median time to a $\geq 50\%$ reduction in symptom severity compared with placebo (2.0 versus 19.8 hours; $p < 0.001$) (primary end point) as well as the onset of primary symptom relief (1.5 versus 18.5 hours; $p < 0.001$) (key secondary end point).²⁴ Icatibant is given as a subcutaneous injection of 30 mg (in 3 mL), and, if symptoms recur, additional injections of 30 mg may be administered after 6 hours (with no more than three injections in 24 hours).²⁵ No serious drug-related adverse events were reported in the phase III study, and no patient discontinued the medication due to adverse events.²² Common adverse effects are mild swelling and erythema at the injection site,²⁴ and it is approved for patient self-administration.

Recombinant C1 inhibitor (Ruconest) was approved in 2014 for on-demand treatment of HAE attacks in adolescents and adults (>12 years old). Recombinant human C1 inhibitor (rhC1INH) was developed as an alternative to plasma-derived C1 inhibitor given the theoretical risk of bloodborne pathogen transmission and is purified from the milk of genetically modified rabbits, which results in a uniform and reliable supply.²⁶ The amino acid sequence of recombinant human C1 inhibitor is identical to endogenous human C1 inhibitor, with slight differences in the glycosylation pattern, which leads to a shorter half-life.²⁷ Two randomized, double-blind, placebo controlled studies showed a reduction in the time to beginning of relief of symptoms compared with placebo (median, 66 minutes for rhC1INH at 100 U/kg; 122 minutes for rhC1INH at 50 U/kg; 495 minutes for saline solution placebo; $p < 0.001$ and $p = 0.01$, respectively refer to each dose compared with placebo) as well as the time to minimal symptoms with recombinant C1 inhibitor concentrate (median, 266 minutes for rhC1INH at 100 U/kg; 247 minutes for rhC1INH at 50 U/kg; 1210 minutes for saline solution placebo; $p < 0.001$ and $p = 0.001$, respectively).²⁸ No patient discontinued the study because of an adverse reaction.²⁸ Reported adverse effects included headache, nausea, diarrhea, and nasopharyngitis; however, there were no systemic allergic reactions and/or anaphylaxis, thrombotic events, or other serious complications reported.²⁸⁻³⁰ It is contraindicated in patients with a history of rabbit allergy²⁶ and classified as pregnancy category B.

Long-Term Prophylaxis in HAE

Long-term prophylaxis is indicated in patients unable to achieve adequate benefit from on-demand

treatment of attacks, with individualized consideration of frequency and severity of attacks, access to emergency treatment, and patient quality of life and/or preference.^{13,31,32} Patients who used prophylaxis for HAE to reduce the frequency and/or severity of attacks must also have access to at least two doses of on-demand medications for breakthrough attacks.^{13,33} Newer options for HAE long-term prophylaxis include an IV formulation of plasma-derived C1 inhibitor concentrate (Cinryze, Shire, Lexington, MA) and a subcutaneous formulation (HAEGARDA, CSL Behring, King of Prussia, PA).

In 2008, plasma-derived C1 inhibitor concentrate (Cinryze) was approved for HAE prophylaxis for adolescents and adults, and is now FDA approved down to age 6 years. Cinryze is dosed at 1000 U IV every 3–4 days, administered at a rate of 1 mL/min at a concentration of 100 U/mL.³⁴ Doses up to 2500 U (not exceeding 100 U/kg) every 3–4 days may be considered based on individual patient response.³⁴ C1 inhibitor (C1-INH) concentrate was shown to significantly reduce the frequency of HAE attacks when used as prophylaxis in a randomized, double-blind, placebo controlled trial that compared twice weekly injections of 1000 U of nanofiltered C1 inhibitor concentrate with placebo (6.3 attacks per 12-week period in the C1 inhibitor concentrate group compared with 12.7 attacks in the placebo group; $p < 0.001$).³⁵ In the first 3 years of Cinryze prophylaxis, significant thrombotic events were documented.³⁶ These are suggested to be related to the use of indwelling catheters and not to the drug. Therefore, these devices are now contraindicated for IV C1-INH prophylaxis. Outside of the concern for catheter related thrombosis, no other thrombotic events have been related to the use of C1-INH in patients with HAE.^{37,38}

HAEGARDA was, in 2017, approved by the FDA as the first subcutaneous C1 inhibitor concentrate after a randomized, multicenter, double-blind, placebo controlled, phase III controlled clinical trial showed significantly reduced HAE attacks in patients who receive twice per week subcutaneous doses of HAEGARDA.³⁹ In this trial, 90 patients (ages, 12–72 years) were randomized to 40 or 60 IU/kg, or placebo subcutaneous injection twice per week, and the patients in both treatment groups experienced significantly reduced numbers of HAE attacks compared with placebo in the 16-week treatment period (mean difference with 40 IU, -2.42 attacks per month [95% confidence interval, -3.38 to -1.46]; and mean difference with 60 IU, -3.51 attacks per month [95% confidence interval, -4.21 to -2.81]; $p < 0.001$ for both comparisons). The FDA-approved dose for HAEGARDA is 60 IU/kg.⁴⁰ The most commonly reported adverse effects were injection-site reactions.

Short-Term Prophylaxis

Short-term prophylaxis should be used to prevent attacks of angioedema in situations in which the patient is at high risk of swelling (*e.g.*, surgical or dental procedures). There are limited data regarding short-term prophylaxis in HAE, with no controlled trials that compared the efficacy of different approaches to prophylaxis. A retrospective analysis of short-term prophylaxis in HAE showed that short-term prophylaxis reduced the number of postprocedural edematous episodes, and C1 inhibitor concentrate was the most effective treatment compared with oral medications.⁴¹ Another study found that short-term prophylaxis with C1 inhibitor concentrate significantly reduced symptoms after tooth extraction.⁴² The U.S. Hereditary Angioedema Association (HAEA) guidelines recommend consideration of short-term prophylaxis before medical, surgical, or dental procedures, and emphasize that it is critically important that effective on-demand treatment be available whether the patient is given short-term prophylaxis.³² C1 inhibitor concentrate is often used at a dose of 1000 U or 20 U/kg, as close as possible to the start of the procedure.¹³ Androgens, such as danazol 200 mg daily, for 5 days before and 2–3 days after an event or 2 U of fresh frozen plasma infused several hours before the procedure can also be considered as options for short-term prophylaxis.³²

GUIDELINE-BASED CARE

Consensus guidelines have also been published by experts in the field to assist in the management of patients with HAE, with a focus on individualized care.^{13,14,32,43,44} These recommendations are focused on reducing morbidity and mortality in HAE, and emphasize the importance of an early and accurate diagnosis, specialist care for patients with HAE, and individualized treatments based on patient needs.^{14,32} Similar concepts exist across national and international guidelines, and many of these were emphasized in the 2017 revision and update for the International World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guideline¹³ for the management of HAE after reviewing existing evidence. All patients should have at least two doses of on-demand medication (Evidence grade: D; strength of recommendation: strong). All patients with HAE should have an HAE action plan (Evidence grade: D; strength of recommendation: strong) because HAE attacks can be unpredictable, painful, and life-threatening. All attacks, irrespective of location, should be considered for treatment (Evidence grade: D; strength of recommendation: strong) given that any angioedema attack in patients with HAE can become disabling and/or life-threatening. These attacks should be treated as soon as possible (Evidence grade: B; strength

of recommendation: strong) because HAE medications can shorten the duration of attacks and the attack-related interference on quality of life. Long-term prophylactic treatment is appropriate for patients who do not achieve adequate benefit from on-demand therapy (Evidence grade: D; strength of recommendation: strong).

CONSIDERATIONS IN PEDIATRIC PATIENTS

There are few prospective and randomized controlled trials that include pediatric patients, and recommendations for pediatric patients are largely based on expert opinion, descriptive studies, and expert committee reports.^{33,45} Additional considerations for the pediatric population include severity and frequency of attacks (prepubertal children often have less-severe disease and can often be managed by on-demand therapy), access to emergency medical facilities, and adverse effect profiles in a growing child. Currently, only IV medications are approved in the United States for on-demand treatment in pediatric patients, so the development of novel HAE medications and expansion of indications for currently available medications have significant potential to change the management of pediatric patients.

On-Demand Treatment in Pediatric Patients with HAE

The use of plasma-derived C1 inhibitor in pediatric patients has been well tolerated and effective in reducing symptoms of attacks.^{46,47} Berinert, a plasma-derived C1 inhibitor concentrate, was approved for children of all ages in 2017 and is recommended for the treatment of HAE attacks.^{13,48} Ruconest (recombinant C1 inhibitor) is approved for children ages ≥ 13 years and is currently under further study in pediatric patients (ages, 2–13 years).⁴⁹ Ecallantide, a plasma kallikrein inhibitor, is approved for patients ages ≥ 12 years. Ecallantide has been reported as being safe and effective in adolescents (ages, 9–17 years),⁵⁰ and a clinical trial is ongoing for pediatric patients ages < 12 years.⁵¹ A phase III clinical trial showed icatibant treatment effect and safety in pediatric patients between the ages of 2 and 18 years⁵²; however, icatibant is currently only FDA approved for ages ≥ 18 years in the United States. In Europe, icatibant is approved for use in pediatric patients ages ≥ 2 years.

Long-Term Prophylaxis in Pediatrics

Options for long-term prophylaxis of HAE in pediatric patients have been limited. In patients who need prophylactic therapy, plasma-derived C1 inhibitor is currently the recommended treatment of choice by expert opinion, with a recommended dose of 10–20 U/kg once or twice weekly, with an initial maximum

dose of 1000 U (level III evidence).³³ A plasma-derived C1 inhibitor concentrate (Cinryze) is approved for patients ages > 6 years.^{53,54} Long-term prophylaxis with antifibrinolytics, *e.g.*, tranexamic acid, can be considered in pediatric patients. However, these are contraindicated in patients with a history of thromboembolism or thrombophilia, and patients with a family history of thrombophilia defect should be screened. Attenuated androgens are usually not considered for pediatric patients before Tanner stage V, given the concern for adverse effects on bone maturation, sexual development, and growth.^{33,45}

NOVEL THERAPIES IN DEVELOPMENT

Lanadelumab is a recombinant, fully human immunoglobulin, monoclonal antibody inhibitor of kallikrein. A phase Ib, multicenter, randomized, double-blind, placebo controlled, multiple-ascending dose trial of subcutaneous lanadelumab showed a reduction in HAE attacks, with 100% and 88% fewer attacks in the 300-mg group and 400-mg group, respectively, compared with placebo.⁵⁵ The HELP (Hereditary Angioedema Long-term Prophylaxis) study⁵⁶, a phase III, randomized, multicenter, double-blind, placebo controlled study that evaluated the efficacy and safety of subcutaneously administered lanadelumab versus placebo over the course of 26 weeks has been completed. The patients were randomized to placebo, lanadelumab 150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg every 2 weeks. Early reports indicate reduction in the baseline attack rate as well as improvement in health-related quality of life with all three lanadelumab dosing regimens, irrespective of the baseline attack rate,^{56–58} although the full trial results have not yet been published. The most-common treatment-related adverse events were injection-site pain, erythema, bruising, viral upper respiratory tract infection, headaches, and dizziness.⁵⁹

An oral medication is also currently in development for the management of HAE. Current oral options for HAE are restricted to antifibrinolytics and attenuated androgens, which are limited by decreased efficacy compared with newer agents as well as by adverse effects.^{15,22} BCX7353 is a second-generation oral kallikrein inhibitor that is being studied as a once-daily medication. In a recent phase II trial with a three-part dose-ranging study for 28 days, BCX7353 was shown to be safe and well tolerated, with a significant reduction in frequency of HAE attacks when used as a preventative treatment.⁶⁰ Treatment emergent adverse events were mild to moderate in severity, with similar rates between placebo and active groups; there were higher numbers of gastrointestinal treatment emergent adverse events and transient liver enzyme abnormalities without liver dysfunction in patients who receive

higher doses of the medication.⁶⁰ A phase III trial is ongoing for BCX7353.⁶¹

Recombinant C1 inhibitor is currently under FDA review for long-term prophylaxis.⁶² The use of recombinant C1 inhibitor in the pediatric population is under study, including a phase II, multicenter, randomized, double-blind, placebo controlled crossover trial of recombinant human C1 esterase inhibitor for the prophylaxis of HAE, showed a significant reduction in the mean number of attacks over 4 weeks in patients who received both twice weekly and once weekly dosing of 50 IU/kg compared with placebo.²⁹ A phase II study of recombinant C1 inhibitor in pediatric patients (ages, 2–13 years)⁴⁹ is ongoing.

Other Investigational Therapies for HAE

There are several novel developments in the management of HAE that are currently under investigation. These include gene therapy to correct C1 inhibitor deficiency by delivering an extrachromosomal copy of *SERPING1* (Serp Family G Member 1, the C1 inhibitor gene) into patient cells by using an adeno-associated virus vector, which is currently in preclinical studies.⁶³ This would allow for long-term treatment of HAE rather than using repeated dosing for prophylaxis and on-demand treatment. Other investigational therapies include inhibiting factor XII by using RNA interference to reduce its expression (ALN-F12, Alnylam, Cambridge, MA), which has just completed preclinical studies,^{64,65} a human monoclonal antibody against factor 12 (CSL312, CSL Behring, King of Prussia, PA) in phase I,^{66,67} and antisense oligonucleotide to reduce the production of prekallikrein (IONIS-PKK_{RX}, Ionis Pharmaceuticals, Inc, Carlsbad, CA), which has just completed phase I trials.⁶⁸ Another oral kallikrein inhibitor (ATN-249, Attune Pharmaceuticals, New York, NY) has been developed, and results of preclinical studies indicate that it is highly selective and potent.⁶⁹ These investigational therapies have the potential to alter the course of the disease, with the goal of improving the quality of life for patients with HAE.

CONCLUSION

This is an exciting time for both patients and clinicians in managing HAE, with the availability of several new therapies as well as several novel treatment options in the pipeline. Many of these new therapies offer the potential for ease of administration (subcutaneous or oral), home therapy, and decreased dosing frequency. In going forward, ongoing research is imperative to develop diagnostic modalities and biomarkers to improve our management of patients with HAE, including those with normal laboratory results. As advances in the treatment of HAE continue to evolve, individualized treatment plans will provide an opportunity

to reduce the burden of disease and improve quality of life for patients with HAE.

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