

Current and Emerging Therapies to Prevent Hereditary Angioedema Attacks

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Prior to 2008, treatment options for hereditary angioedema (HAE) in the United States were severely lacking or associated with significant adverse effects (AEs)¹; however, 6 effective medications have now been FDA approved, with additional agents currently undergoing clinical trials. These therapies act on different targets within the contact/kinin system (CKS) to reduce bradykinin production or its effects, decrease angioedema, and improve outcomes in patients with HAE.²

Current Treatment Options for HAE

Bradykinin, the primary mediator of swelling in HAE, is produced by cleavage of high-molecular weight (HMW) kininogen by plasma kallikrein. Kallikrein is formed through activation of prekallikrein by factor XIIa.³ Once bradykinin is generated, it binds to bradykinin receptors on vascular endothelial cells; this binding leads to vasodilation and increase in vascular permeability, resulting in localized swelling known as angioedema.^{3,4} Control of this process relies on inhibition of key steps by complement component 1 esterase inhibitor (C1-INH), but in patients with HAE, adequate functional C1-INH is lacking.^{3,5} Without a correctly functioning inhibitory mechanism, the CKS produces excess bradykinin, resulting in angioedema.³ In addition to working within the CKS, C1-INH inhibits C1 esterase in the classic complement pathway, plasmin in the fibrinolytic system, and factor XIa in the intrinsic coagulation system.⁶ Four agents/classes (shown in green in [Figure 1](#)^{2,6,7}) target steps in the CKS to block key components of the CKS, decreasing the amount of bradykinin or its effect on the vasculature and thereby reducing vascular leak that causes the swelling.²

Recommendations for Treatment and Prevention of Swelling Attacks

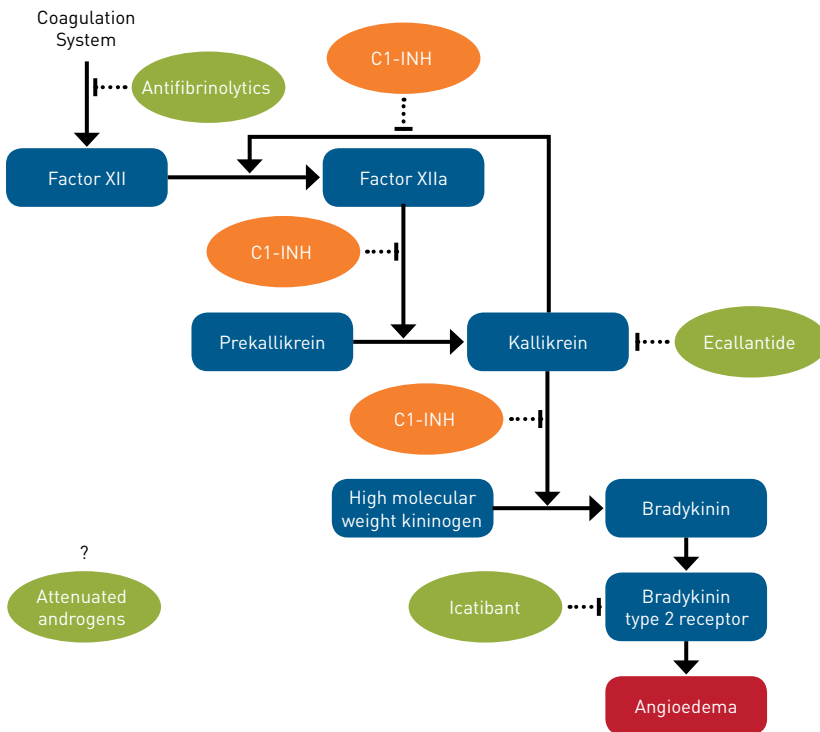
Therapy for HAE can be generally divided into 2 approaches, acute (or “on-demand”) treatment of attacks and prevention of attacks, which is broken down into short-term prophylaxis (STP) and long-term prophylaxis (LTP).⁷ While every patient with HAE should have access to on-demand therapy for acute attacks, not all patients require prophylaxis.⁷ The 2017 revision and update to the international

ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disease defined by recurrent attacks of edema, causing a substantial burden for patients, with morbidity, mortality, and reduced quality of life. This burden is increased by delayed diagnosis, inappropriate treatment, and suboptimal follow-up and patient education. Several novel therapeutics have recently been approved or are currently under evaluation for prevention of HAE attacks.

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For author information and disclosures, see end of text.

FIGURE 1. The Kallikrein-Kinin System and Current Treatment Options for HAE^{2,6,7}

C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guideline for the management of HAE provides evidence-based recommendations for both of these approaches.⁷ The medications' FDA-approved indications (acute treatment or prophylaxis of HAE), availability as home therapy, pediatric age groups, and routes of administration (these may differ in other countries) are provided in [Table 1](#),^{8,9} followed by summaries of the new guideline recommendations.

C1-INH: Plasma-derived and Recombinant Formulations

Supplementation for the lacking or dysfunctional C1-INH protein is accomplished with human plasma-derived protein (Berinert, Cinryze, Haegarda) or recombinant purified protein (Ruconest). C1-INH replacement can be used for either treatment or prevention of attacks.⁷ Human plasma-derived C1-INH (pdC1-INH) is purified from human plasma through processes of cryoprecipitation, adsorption, precipitation, purification, pasteurization, and nanofiltration. Recombinant C1-INH (rhC1-INH) is extracted from the milk of transgenic rabbits using a 3-step chromatography purification process.⁷ Both types of C1-INH are effective and safe for treatment of HAE swelling attacks.⁷ Although derived from human

plasma, pdC1-INH has not been associated with the transmission of hepatitis B or C, or human immunodeficiency virus.¹⁰⁻¹² Because rhC1-INH is derived from rabbit milk, transmission of human viruses is not a concern; however, rhC1-INH is contraindicated in any patient with known or suspected allergies to rabbits or rabbit-derived products.¹³ Both agents have identical mechanisms of action but distinct serum half-lives; pdC1-INH has a half-life of over 30 hours, whereas the half-life of rhC1-INH is approximately 3 hours.⁷ Despite the shorter half-life, a recent study found that treatment with rhC1-INH demonstrated a sustained response of at least 72 hours in 93% of patients with HAE who were treated for an acute attack.¹⁴ C1-INH is given intravenously (IV) using weight-based dosing for on-demand treatment of swelling attacks at either a fixed-dose IV or weight-based dose subcutaneously (SC) for prevention of attacks.

Dosing and administration of pdC1-INH, based on the results of their corresponding clinical trials, is as follows: For adults and adolescents: 20 international units (IU)/kg IV for Berinert¹⁵; 2500 units (maximum: 100 IU/kg) IV every 3 days for Cinryze¹⁶; 60 IU/kg SC every 3 days for Haegarda.¹⁷ For children: 12 years: 20 IU/kg IV for Berinert¹⁵; 2500 units (maximum: 100 units/kg) IV every 3 days for Cinryze¹⁶; safety and efficacy of Haegarda has not been established. Six to 11 years: 20 IU/kg IV for Berinert¹⁵; 1000 IU IV every 3 days for Cinryze¹⁶; safety and efficacy of Haegarda have not been established. One to 5 years: 20 IU/kg IV for Berinert; safety and efficacy of Cinryze and Haegarda have not been established. Recommended dose of rhC1-INH (Ruconest) for acute attack in both adults and adolescents is 50 IU/kg with a maximum of 4200 IU is to be administered as a slow IV injection over approximately 5 minutes.¹³

PdC1-INH

In 2017, the pdC1-INH agent (Haegarda) was approved by the FDA for prophylaxis of HAE in adolescent and adult patients. This is the second agent approved for HAE prophylaxis and the first C1-INH for SC administration.¹⁸ This agent is a concentrated form of pdC1-INH (Berinert). This agent was evaluated in the COMPACT phase 3 trial involving 90 patients (12 years of age or older) who had presented with 4 or more attacks in a consecutive 2-month period within 3 months before screening. In this international, multicenter, double-blind, randomized, placebo-controlled, crossover trial, patients were randomized to 1 of 4 treatment groups that self-administered

TABLE 1. HAE Treatment Options^{8,9}

Drug	Indication			Home Therapy Available?	Pediatric Age Groups		Route
	Acute Treatment	Prophylaxis			Children Aged <12 years	Adolescents Aged 12-17 years	
		Short Term	Long Term				
C1-INH							
pdC1-INH (Berinert)	✓	^a		✓	✓	✓	IV
pdC1-INH (Cinryze)		✓ ^a	✓	✓	✓	✓	IV
pdC1-INH (Haegarda)		✓	✓	✓		✓	SC
rhC1-INH (Ruconest)	✓			✓		✓	IV
Icatibant (Firazyr)	✓			✓			SC
Ecallantide (Kalbitor)	✓			✓ ^b		✓	SC
Attenuated androgens		✓ ^a	✓	✓			Oral
Antifibrinolytics							
Tranexamic acid (Lysteda)			✓	✓			Oral
Epsilon-aminocaproic acid (Amicar)			✓	✓			Oral

HAE indicates hereditary angioedema; IV, intravenous; SC, subcutaneous. ^aNot FDA approved. ^bSelf-administration not allowed.

twice-weekly SC C1-INH 40 or 60 IU/kg followed by placebo for 16 weeks each, or vice versa.¹⁹ The primary efficacy end point of the study was reduction of the time-normalized number of HAE attacks. The secondary end points included the responder rate and the number of rescue medication uses. Both doses compared with placebo reduced the rate of attacks of HAE. The treatment response (50% reduction in attacks) occurred in 90% of patients receiving the 60-IU/kg dose and in 76% receiving the 40-IU/kg dose. The need for rescue medication was decreased with treatment compared with placebo. The median reduction in the attack rate relative to placebo was 89% with 40 IU and 95% with 60 IU in patients being treated during the two 16-week clinical trial periods.¹⁹ Although mild, AEs did not differ from placebo. The most common AEs experienced by patients included injection-site reaction, hypersensitivity reaction (pruritus, rash, urticaria), nasopharyngitis, and dizziness.^{17,19}

FDA approval of pdC1-INH (Berinert) in 2009 was based on the IMPACT 1 study, a placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group, dose-finding, 3-arm clinical study.^{15,20} The 124 adult and pediatric participants enrolled were experiencing acute, moderate to severe attacks of laryngeal, abdominal, or facial HAE. Patients were randomized to receive a single 10 unit/kg body weight dose of pdC1-INH (Berinert), a single 20 unit/kg dose of pdC1-INH (Berinert), or a single dose of placebo by slow IV infusion (recommended to be given at a rate of approximately 4 mL per minute) within 5 hours of an attack.²⁰ If the attack did not improve, the participants were given an extra 10 IU/kg body weight, placebo, or 20 IU/kg body weight, respectively, at 4 hours. pdC1-INH (Berinert) relieved symptoms from an established attack significantly sooner than placebo. Participants treated

with 20 units/kg of pdC1-INH (Berinert) experienced a significant reduction in time to onset of relief from symptoms of an attack as compared with placebo (median of 50 minutes for pdC1-INH [Berinert] 20 units/kg body weight, as compared with >4 hours for placebo). The time to onset of relief from symptoms of an HAE attack for participants in the 10 unit/kg dose of pdC1-INH (Berinert) was statistically insignificant compared with participants in the placebo group.²⁰ The efficacy of pdC1-INH (Berinert) 20 units/kg was confirmed by observing the reduction in intensity of HAE symptoms at an earlier time compared with placebo,²⁰ rendering pdC1-INH (Berinert) as an on-demand treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric patients. Potential AEs associated with the use of pdC1-INH (Berinert) include nausea, risk of anaphylaxis (rare), thrombotic events, and viral transmission (theoretical).¹⁵

Approval of pdC1-INH (Cinryze) as a therapy for preventing HAE attacks was evaluated in the CHANGE trial, a 24-week, multi-center, double-blind, placebo-controlled, crossover study. The FDA approved this medication in 2008 for routine prophylaxis of HAE in adult and adolescent patients.¹⁶ The primary efficacy outcome was the total number of angioedema episodes in each treatment period in adults and adolescents. An attack of HAE was defined as swelling in any location on the patient's body following a report of no swelling on the previous day.²¹ Patients received blinded pdC1-INH (Cinryze) 1000 units IV twice weekly for 12 weeks at the study site and then crossed over to receive twice-weekly IV infusions of placebo for 12 weeks at the study site, or vice versa. The primary end point was the number of attacks of angioedema per period. The number of attacks was reduced significantly with the treatment group, and both the severity and duration of attacks were

also reduced.²¹ Estimated median time to the onset of symptom relief was 2 hours in the treatment group, as compared with more than 4 hours in the placebo group. There is a concern for clotting and infection with the use of pdC1-INH (Cinryze) for prophylaxis via indwelling venous ports.²¹ Patients can be taught to self-administer the pdC1-INH (Cinryze) IV dose by their healthcare provider. Common AEs presenting in clinical trials were headache, nausea, rash, hypersensitivity, and vomiting.¹⁶

RhC1-INH

The approval of rhC1-INH by the FDA in 2014 was based on the results of a randomized, double-blind, placebo-controlled, phase 3 trial (RCT) including an open-label extension (OLE). The pivotal RCT and OLE studies analyzed the results from 44 participants who experienced 170 HAE attacks.²² RhC1-INH is the only recombinant C1-INH treatment option approved for treatment of acute angioedema attacks in both adult and adolescent patients with HAE. This was a 2-part phase 3 clinical trial of rhC1-INH that evaluated the safety and efficacy in treatment of acute attacks of HAE. Studies enrolled 75 patients with HAE, with results demonstrating rhC1-INH to be a safe and effective option to treat patients experiencing acute HAE attacks. The study evaluated the safety and efficacy of rhC1-INH in 2 treatment arms. Participants in the double-blind phase 1 study were randomized to receive 100 IU/kg of rhC1-INH or saline solution in a 1:1 ratio once.¹³ Results from this study showed significant reduction in median time to beginning of symptom relief. Common AEs presenting in participants included headache, nausea, diarrhea, and risk of anaphylaxis.¹³

Ecallantide: Kallikrein Inhibitor

Ecallantide is an SC administered fixed-dose potent and selective inhibitor of plasma kallikrein that is FDA approved for the treatment of attacks of HAE in patients 12 years or older.²³ As shown in Figure 1, ecallantide's action on plasma kallikrein prevents cleavage of HMW kininogen, which produces bradykinin and blocks the positive feedback loop that activates factor XII, leading to less kallikrein production.²³ During a multicenter, randomized, double-blind, placebo-controlled trial and phase 3 trials, EDEMA-3 and EDEMA-4, ecallantide was found to be effective in treating HAE attack, showing clinically and statistically significant improvements at 4 hours compared with placebo in scores of mean-symptom complex severity and treatment outcome score.²⁴ Dosing may be repeated once within 24 hours if this initial dose is not effective. The most common AEs associated with ecallantide were headache, nausea, diarrhea, pyrexia, injection-site reactions, and nasopharyngitis.²³ Hypersensitivity reactions, including anaphylaxis, occurred in 3% to 4% of ecallantide-treated patients in the clinical trials. Therefore, administration of the drug must be performed by a healthcare professional at home or in a healthcare setting with appropriate support to manage an anaphylactic reaction should one occur.²³

Icatibant: Bradykinin 2-Receptor Antagonist

Icatibant is an SC administered fixed-dose synthetic peptide that prevents binding of bradykinin to the bradykinin type 2 (B2) receptor through specific and selective competitive antagonism (see Figure 1^{2,6,7}).²⁵ This effectively prevents bradykinin from binding to these receptors and initiating the vascular leak resulting in angioedema. Icatibant received FDA approval in 2011 for the treatment of swelling attacks of HAE in adults 18 years and older.²⁵ The phase 3 FAST-3 trial evaluated the efficacy and safety of a single SC injection of 30 mg icatibant administered to adults with type I or II HAE within 6 hours of an attack.²⁶ Compared with those receiving placebo, patients receiving icatibant for cutaneous or abdominal attacks had significantly reduced median times to 50% or more reduction in symptom severity (2.0 vs 19.8 hours; $P < .001$), onset of primary symptom relief (1.5 vs 18.5 hours; $P < .001$), or almost complete symptom relief (8.0 vs 36.0 hours; $P = .012$), and time to initial symptom relief (0.8 vs 3.5 hours; $P < .001$).²⁶ During clinical trials, 97% of patients reported transient injection-site reactions, including localized swelling, itching, burning, and redness when using icatibant. Less frequent AEs included pyrexia, transaminase increase, dizziness, and rash.²⁵ In contrast to ecallantide, icatibant may be self-administered SC by patients upon recognition of an attack.²⁵ If the first injection is not sufficient, additional injections may be administered at intervals of no less than 6 hours, with no more than 3 injections within a 24-hour period.²⁵

Attenuated Androgens

Attenuated androgens, such as danazol, have been used since 1976 to prevent HAE attacks.^{6,7} Androgens cannot be administered as-needed for an attack because they require several days to become effective.⁸ Androgens are believed to increase the level of C1-INH in a dose-dependent fashion, probably by inducing production in hepatocytes; however, the exact mechanism of action is unknown. These agents are effective in patients with HAE; however, numerous dose-dependent AEs occur in nearly all patients, including virilization, weight gain, diminished libido, hirsutism, headache, myalgia, depression, hepatotoxicity, hypercholesterolemia, and acne.^{6,7} Androgens are contraindicated during pregnancy, in prepubertal children or adolescents, and patients with hepatic disease, breast cancer, and prostate cancer.^{7,26} Furthermore, androgens interact with many other drugs, such as statins, and long-term use requires semiannual blood and urine tests, along with an annual ultrasound of the liver.⁷

Antifibrinolytics

Although it is not well understood how the coagulation system plays a role in bradykinin elevation, C1-INH acts on plasmin, which is capable of activating factor XII in the CKS.²⁷ Therefore, antifibrinolytics, such as epsilon aminocaproic acid and tranexamic acid, have

been historically used as preventive treatment of HAE. However, these agents are not FDA approved and not recommended for long-term prophylaxis in HAE-C1-INH deficiency due to inferior efficacy compared with other options.⁷ These agents are usually reserved for patients for whom other treatments are contraindicated or if other therapies are not available.⁷

Treatment Strategies

Treatment typically focuses on 3 objectives when treating a patient with HAE experiencing an attack: pharmacotherapy, airway management (if required), and supportive therapy (if required).¹ Early treatment of an attack has been associated with better outcomes, including shorter time to resolution of symptoms and shorter duration of attack, regardless of location or severity.^{7,28} Laryngeal angioedema with resulting asphyxiation is responsible for substantial mortality in HAE.^{7,20} A study by Bork et al evaluated mortality in patients with HAE and found that 33% of patient deaths were due to laryngeal angioedema.²⁷ Patients who are experiencing an attack involving their airway should use their on-demand therapy if readily available and then proceed to the closest emergency medical facility.

Because self-administration improves time to treatment, all patients should be considered for home therapy and self-administration training with on-demand therapy.⁷ When an attack occurs, WAO/EAACI clinical guidelines recommend IV C1-INH, SC ecallantide, or icatibant for acute treatment.⁷ As noted above, self-administration with ecallantide is not recommended.²³

STP should be provided to patients if circumstances such as a medical or dental procedure is likely to trigger an attack. Patients who anticipate facing particularly stressful situations may be considered for STP. Procedures associated with mechanical interventions to the upper aerodigestive tract, such as endotracheal intubation, bronchoscopy, or esophagogastroduodenoscopy, may lead to swelling near the site of intervention.⁷ The WAO/EAACI guideline recommends that all patients undergoing any medical, surgical, or dental procedure involving any mechanical impact to the upper aerodigestive tract receive C1-INH as preprocedural prophylaxis as close as possible to the start of the procedure. Dosage has yet to be fully established.⁷ Androgens (eg, danazol 200 mg thrice daily) given 5 days before and 2 days after the procedure are recommended as an alternative to C1-INH, and although the guideline acknowledges the use of tranexamic acid in the past for STP, most panel experts recommended against this use.⁷

LTP should be considered in patients when HAE is particularly burdensome.⁷ Successful treatment requires a high degree of compliance, so LTP therapy must be individualized based on disease activity, frequency of attacks, patient's quality of life, availability of healthcare resources, failure to achieve adequate control through use of on-demand treatments, and patient preference.⁷ The WAO/EAACI guideline recommends C1-INH currently available in both

IV and SC formulations as first-line therapy for LTP if available. Patients may experience breakthrough attacks while receiving LTP, so on-demand therapy should be provided for all patients regardless of using preventive therapy. Patients should be evaluated annually for changes in response to therapy and/or treatment modifications required.⁷

A key factor that should be considered when prescribing therapy for HAE is route of administration. Whether acute or prophylactic treatment, route of administration can affect patient satisfaction with treatment, which ultimately impacts compliance. A survey by Riedl et al sought to evaluate satisfaction with IV C1-INH products among patients with HAE.²⁹ Of 47 patients, 34 (72%) reported administering C1-INH through peripheral veins, and 19 (40%) were currently or had previously used a central venous port for administration. Of patients administering C1-INH through a peripheral vein, 62% reported having difficulty finding a usable vein or getting the infusion to work properly, and 47% of patients with ports reported problems, such as occlusion, thrombosis, and infection associated with their port.²⁹ Although the WAO/EAACI guideline does not recommend any particular route of administration, it acknowledges the improved convenience with SC administration,⁷ which may play a role in compliance. To this point, a recent study by Jose et al found that 50% of patients with HAE prefer a noninvasive route of administration, including oral (24%), SC (18%), or non-IV route (8%).³⁰ **Table 2** provides a summary of guideline recommendations for acute treatment and prophylaxis with available HAE medications.⁷

New and Emerging Treatments

Pediatric Developments

RhC1-INH is currently undergoing a phase 2, multicenter, open-label study (NCT01359969) to evaluate the agent's safety, immunogenicity, and pharmacology in patients aged 2 to 13 years experiencing an acute attack. Preliminary results from this trial were announced in October 2017.³¹ After 20 children were treated for 73 attacks, the median time to onset of relief was 60 minutes (95% CI, 60-63 minutes) and to minimal symptoms was 122 minutes (95% CI, 120-126 minutes).³¹ In addition to demonstrating efficacy at resolving attacks, rhC1-INH was safe and well tolerated. No patients withdrew from the study for AEs, and no serious AEs, hypersensitivity reactions, or neutralizing antibodies were reported.³¹

The pdC1-INH agent (Cinryze), approved for prophylaxis of HAE attacks in adolescents and adults, recently received FDA approval for prophylaxis in children aged 6 to 11 years.^{9,32} Interim results from a phase 3 trial published in mid-2017 reported a mean difference in the number of monthly angioedema attacks between the baseline and treatment period of -1.89 (SD, 1.31) with the 500-unit dose and -1.89 (SD, 1.11) with the 1000-unit dose, which were reductions of -84.8% and -88.1% , respectively.³³ No serious AEs or discontinuations occurred during the study.²⁶ In June 2018, the FDA approved

TABLE 2. Pharmacotherapy Treatment Recommendations From WAO/EAACI Guideline⁷

Recommendation	Evidence Grade	Strength of Recommendation	Percentage Agreement
Acute treatment			
All attacks are considered for on-demand treatment	D	Strong	100%
Attacks are treated as early as possible	B	Strong	100%
Attacks are treated with either C1-INH, ecallantide, or icatibant	A	Strong	90%
All patients have sufficient medication for on-demand treatment of 2 attacks and always carry on-demand medication	D	Strong	100%
C1-INH to be used for treatment of attacks in children younger than 12 years	C	Strong	>90%
C1-INH to be used for attacks during pregnancy and lactation	D	Strong	100%
Prophylaxis			
Short-term prophylaxis before procedures that can induce an attack	C	Strong	100%
Prophylaxis to be considered for patients who face life events that are associated with increased disease activity	D	Strong	>90%
Patients are evaluated for long-term prophylaxis at every visit; disease burden and patient preference should be taken into consideration	D	Strong	100%
C1-INH is recommended for first-line, long-term prophylaxis	A	Strong	50%-75%
Androgens are suggested as second-line, long-term prophylaxis	C	Weak	50%-75%
Suggest adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease	D	Weak	100%

Grade-of-evidence definitions

A: Randomized, double-blind clinical trial of high quality (for example, sample-size calculation, flow chart of patient inclusion, intent-to-treat analysis, sufficient sample size)

B: Randomized clinical trial of lesser quality (for example, only single-blind, limited sample size: at least 15 patients per study arm)

C: Comparative trial with severe methodological limitations (eg, not blinded, very small sample size, no randomization) or large retrospective observational studies

D: Adapted from existing consensus document or statement based on expert opinion voting during consensus conference

C1-INH indicates component 1 esterase inhibitor; EAACI, European Academy of Allergy and Clinical Immunology; WAO, World Allergy Organization.

the supplemental Biologics License Application (sBLA) to expand the indication for pdC1-INH (Cinryze) to include children 6 years and older.³² Currently, this is the only C1-INH prophylaxis option for children younger than 12 years.³⁴

In addition to expanded pediatric indications for C1-INH formulations, icatibant is undergoing evaluation for treatment of swelling attacks in children and adolescents.³⁵ In March 2018, a phase 3 trial of icatibant was completed, evaluating its use for HAE attacks in children and adolescents aged 2 through 17 years. Results published in late 2017 reported a median time to onset of symptom relief of 1.0 hour.³⁵ Additionally, more than 70% of patients experienced symptom relief by 1.1 hours and more than 90% by 2.0 hours.³⁶ Of 32 patients in the safety population, 9 (28.1%) experienced 32 treatment-emergent AEs, including gastrointestinal (GI) symptoms and injection-site reactions.³⁵ Most injection-site reactions resolved within 6 hours post-dose.³⁵ Although no announcement has been made regarding FDA approval of an expanded indication, the European Commission approved a label extension to use icatibant in adolescents and children 2 years and older in October 2017.³⁶

Other Developments*RhC1-INH for Prophylaxis*

RhC1-INH (Ruconest), the only FDA-approved rhC1-INH, is currently indicated for treatment of acute attacks in patients with HAE.¹³ A double-blind, placebo-controlled, international phase 2 trial (NCT02247739) was recently completed, evaluating the use of rhC1-INH for prophylaxis in patients with HAE.³⁷ Over 4 weeks, the mean number of attacks was reduced by 72.1% and 44.4% in patients who received the rhC1-INH twice and once weekly, respectively.³⁷ AEs were reported in 45% (13/29), 34% (10/29), and 29% (8/28) of patients in once-weekly, twice-weekly, and placebo groups, respectively, with headache (twice-weekly group) and nasopharyngitis (once-weekly group) being most common.³⁷ FDA acceptance to review the manufacturer's sBLA for rhC1-INH was announced in January 2018 with an action date of September 21, 2018.

New SC Formulation

Currently, SHP616 is another pdC1-INH being evaluated for SC administration in HAE prophylaxis. In the phase 3 SAHARA trial,

which used a fixed dosage of C1-INH 2000 IU SC, SHP616 demonstrated a significant and clinically meaningful median HAE attack rate reduction of 79% from day 0, or 85% from day 15 (steady state achievement) in the active compared to the placebo treatment phase of the crossover study. Seventy-eight percent of patients experienced a 50% or greater reduction in their HAE attack rate, with 38% of patients remaining attack-free during treatment with SHP616. No treatment-related serious AEs or deaths were reported in this study. The most commonly noted AEs were injection-site reactions, viral upper respiratory tract infection, upper respiratory tract infection, and headache.⁹

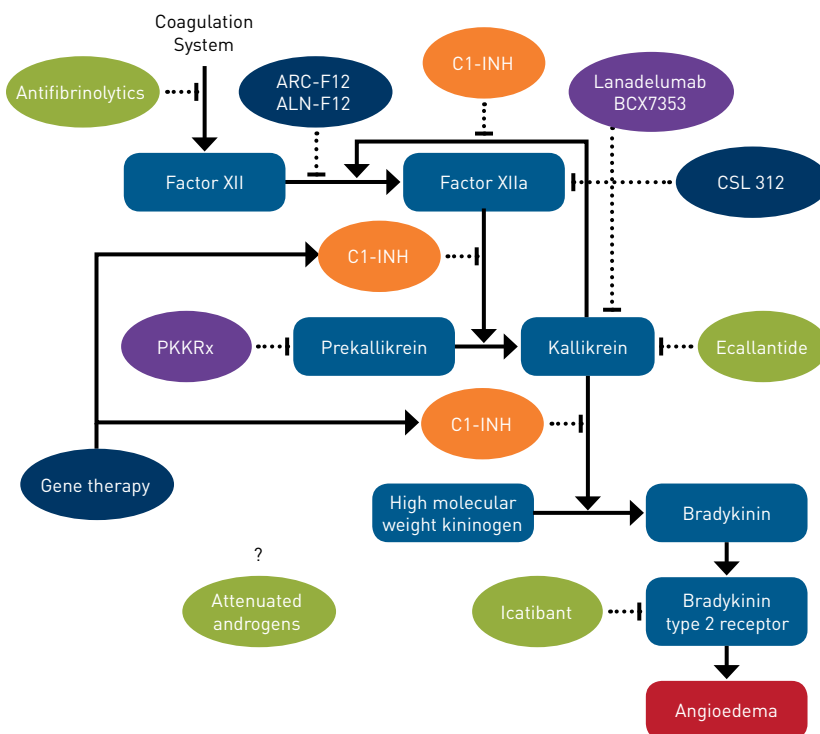
In addition to the expanded indications and improvements on known therapeutics reviewed above, several novel therapies are currently undergoing development for acute treatment or prophylaxis of HAE.² The mechanisms of action of these new agents are shown in purple in Figure 2,^{2,6,7} with agent information and recent clinical trial data summarized below.

Kallikrein Inhibitors

Lanadelumab, a fully human monoclonal antibody selective inhibitor of plasma kallikrein, which is administered SC, is undergoing development for HAE prophylaxis in patients 12 years and older.^{38,39} In February 2018, a press release announced the FDA accepted the BLA for lanadelumab, along with granting priority review.³³ During the pivotal phase 3 HELP trial, administration of lanadelumab every 2 weeks resulted in an 87% reduction in mean frequency of attacks, with no treatment-related serious AEs or deaths reported.³⁹ The most common AEs that emerged during treatment were attacks of angioedema, injection-site pain, and headache. An FDA decision date is set for August 2018.³⁹

Similar to lanadelumab, BCX7353 works by inhibiting plasma kallikrein; this agent is administered orally.⁴⁰ BCX7353 is currently undergoing development for on-demand treatment and prophylaxis of HAE attacks in patients 18 years and older with HAE.⁴¹ In the phase 2 APeX-1 prophylaxis trial, significant reductions in attacks were seen in 3 of 4 dose groups compared with placebo during weeks 2 to 4 of treatment (62.5 mg: -7%, $P = .715$; 125 mg: -73%, $P < .001$; 250 mg: -46%, $P = .006$; and 350 mg: -58%, $P < .001$).³⁵ After positive results from the APeX-1 trial, the phase 3 APeX-2 trial started in early 2018, with top-line results expected in the first half of 2019.⁴⁰ A phase 2 trial investigating oral use of a liquid formulation of BCX7353 for on-demand treatment of attacks (ZENITH) began in Europe in early 2018.

FIGURE 2. Emerging Treatment Options for HAE^{2,6,7}



C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

Antisense Targeting Prekallikrein

As shown in Figure 2, PKKRx reduces bradykinin by reducing prekallikrein production through an antisense mechanism. With lower amounts of prekallikrein, less plasma kallikrein can be generated and less bradykinin liberated.³⁶ Although still in early development, a phase 1 trial of healthy volunteers showed a 95% reduction in prekallikrein levels, with a well-tolerated safety profile.²

Preclinical Agents

In addition to the agents already covered, several novel therapeutics are undergoing preclinical studies, as shown in dark blue in Figure 2, including 2 RNA interference drugs affecting factor XII production, ALN-F12 and ARC-F12; a monoclonal antibody anti-factor XIIa, CSL 312; and gene therapy.² While still very early in the clinical trial process, these agents may provide new approaches to reducing production of bradykinin and thereby preventing HAE attacks.

Individualizing Therapy and Patient Education

The clinical, economic, and quality-of-life burden to patients with HAE is substantial. The disease course of HAE is unpredictable, painful, and potentially life-threatening. Treatment plans must

be individualized in partnership among the patient, family, and physician in order to achieve optimal outcomes.^{7,37} According to the Hereditary Angioedema Association Medical Advisory Board and WAO/EAACI guidelines, individualized treatment plans should address preventive measures, home care, and self-administration. An emergency plan with clear instructions and medications to use should be included for, if, and when an acute attack occurs. An HAE identification card, with instructions for managing an attack, along with on-demand medication, should always be carried.^{7,37}

In addition to individualizing therapy, healthcare providers must recognize the importance of patient education to successful outcomes in HAE treatment. Proper education about avoiding potential attack triggers, recognition and early treatment of attacks, and self-administration of medications is critical to improving outcomes in these patients.

The Icatibant Outcome Survey is an observational study to evaluate the safety and efficacy of icatibant use in patients with HAE in real-world settings.^{21,38} An analysis of survey data compared outcomes of 652 attacks across 170 patients who either self-administered icatibant or received administration from a healthcare provider.²¹ As expected, the median time to administer icatibant was significantly shorter in patients who self-administered compared with those who received their care in a healthcare facility (1.5 vs 2.4 hours; $P = .016$). Earlier treatment time was significantly associated with a median shorter time to resolution of attack (2.5 vs 5.0 hours; $P = .032$) and attack duration (3.0 vs 14.0 hours; $P < .0001$); these data indicate the ability to self-administer at the earliest symptoms of an attack can significantly improve outcomes among patients with HAE.²¹ The WAO/EAACI guideline recommends that all patients be taught to self-administer the medication at home whenever possible.⁷ **Table 3** provides a list of teaching objectives for patients who will treat their HAE in a home environment.³⁹

TABLE 3. Teaching Objectives for Home Therapy in HAE³⁹

Patient should be able to demonstrate knowledge of:	
1.	Basic information regarding the cause, pathophysiology, symptoms, and clinical course of HAE
2.	Which HAE attacks require treatment
3.	When to initiate treatment
4.	How to administer an intravenous or subcutaneous agent
5.	An appropriate backup plan if the first treatment is not successful
6.	Management of treatment-associated adverse events
7.	When and how to seek help from a healthcare provider
8.	Appropriate documentation of the time, location, severity, and outcome of each attack

HAE indicates hereditary angioedema.

Conclusions

HAE is a rare but debilitating and potentially life-threatening disease. There are currently 7 agents approved by the FDA to treat and/or prevent swelling attacks. These options for on-demand treatment and LTP have substantially improved the burden of disease and health-related quality of life in patients with HAE. The burden of treatment has also been decreased with the development of agents administered SC and requiring less-frequent dosing. As more patients opt to use prophylaxis alongside on-demand therapy, morbidity, mortality, and quality of life should further improve. Healthcare providers must prioritize patient–physician discussion of treatment options and strategies based on individualized patient factors, along with regular follow-up to monitor and adjust the plan as needed. Patient education is important for the proper and timely use of these life-altering and potentially life-saving agents. ■

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