Hereditary angioedema (HAE) is a rare genetic condition that manifests as pain-ful and potentially life-threatening episodic attacks of cutaneous and submuco-sal swelling. It results from functional deficiency of C1 inhibitor (C1 INH), which is a regulator of the complement, fibrinolytic, kinin (contact), and coagulation systems. In patients with HAE, the low plasma concentration of functional C1 INH leads to overactivation of the kinin cascade and local release of bradykinin. Bradykinin is responsible for the pain, vascular permeability changes, and edema associated with HAE. Until recently, therapeutic options for HAE have been very limited. Many new therapies have emerged, however, such as C1 INH replacement drugs and medications aimed at components of the contact system (eg, plasma kallikrein inhibitor and bradykinin B2 receptor antagonist).

The authors review current and novel treatments for patients with HAE.

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H
ereditary angioedema (HAE) is a rare autosomal dominant disorder resulting from
deficiency of C1 inhibitor (C1 INH) protein or function. Individuals with HAE
undergo “attacks,” or episodic swelling, which most often affect the skin of the
extremities or the mucosal tissues of the upper respiratory and gastrointestinal tracts.

The disease is caused by a mutation in the gene-encoding C1 INH protein located on
chromosome 11. C1 INH, a serine protease inhibitor (serpin), is a primary regulator of the
complement and kinin systems. Deficiency of C1 INH leads to unregulated activation of
bradykinin. Data from various studies1-3 indicate that bradykinin plays an important role in
mediating HAE symptoms such as pain and vascular permeability changes that lead to
edema.

Two main types of HAE, type I and type II, account for the majority of HAE cases. Type
I HAE (found in approximately 80%-85% of patients with HAE) is characterized by low
levels of C1 INH. Type II HAE (found in 15%-20% of patients with HAE) is characterized by
normal or elevated levels of dysfunctional C1 INH.4,5 A newer subtype of HAE, type III,
has been described within the past decade. In some patients, type III HAE is characterized by
X-linked dominant inheritance.6 It is more common in female individuals, but it has also been
identified in male individuals. Both estrogen-dependent and estrogen-independent forms of
type III HAE have been described. Type III HAE is not associated with C1 INH deficiency,
but it manifests with symptoms similar to those of types I and II. Some cases of type III HAE
are associated with genetic defects involving factor XII (Hageman factor).6 Type I and type
II HAE could perhaps more correctly be described as “C1 INH deficiency disease” and are clinically indistinguishable. Once angioedema is clinically suspected, laboratory findings for C4 and C1 INH levels, as well as C1 INH function, can support a specific diagnosis (Table 1). In the present review, we will focus on types I and II HAE.

Prevalence
Hereditary angioedema is estimated to affect approximately 1 in 50,000 persons, with no ethnic group differences.7 Attacks of HAE follow an unpredictable pattern. Anatomical site, frequency, and severity vary among individual patients. Subcutaneous attacks commonly affect the extremities but can affect any part of the body. In the United States, HAE attacks have been associated with 15,000 to 30,000 emergency room visits annually.8 Mortality, secondary to laryngeal edema and asphyxiation, has been reported in up to 30% of patients who were previously undiagnosed.8 Abdominal attacks can lead to hospitalizations and unnecessary surgical procedures. Some patients develop narcotic dependence because of the chronic severe abdominal pain associated with HAE attacks, whereas other patients may require psychiatric care to manage the stress and anxiety associated with their disease preventing them from leading a productive life.7,8

Standard Treatment Options
Because of the morbidity, mortality, and greatly reduced quality of life associated with HAE, treatment strategies for patients with this disease have been aimed at attack prevention (prophylaxis) and management (on demand) (Table 2).

Until recently, prevention and management options for acute HAE attacks were limited in the United States. Prophylactic therapy was limited to attenuated androgens and antifibrinolytics, both of which have substantial contraindications and adverse effects.7 Management of HAE attacks was restricted to supportive measures such as intravenous fluids administration and pain management. Corticosteroids, epinephrine, and antihistamines have also been used to manage HAE attacks but are not efficacious.7 Fresh frozen plasma (FFP) has been used to abort attacks because it contains C1 INH, but there is a theoretic concern that FFP can worsen acute edema by supplying substrates involved in the generation of edema.7 In addition, the risk of blood-borne pathogens is greater with FFP than with human plasma–derived C1 INH,7 a treatment option that has until recently been unavailable in the United States but that has been used in European countries for many decades.

Better understanding of the pathophysiologic characteristics of HAE attacks has led to the development of novel treatment approaches for patients with HAE. In recent years, several new drugs have been approved for the prevention and management of HAE attacks. These agents are expected to substantially improve the quality of life for patients with HAE.

Novel Treatment Approaches

C1 INH Replacement Protein
C1 INH replacement protein is purified and concentrated from pooled human plasma and is administered intravenously for purposes of attack management and short- and long-term prophylaxis. Two products are available in the United States: Cinryze and Berinert.9,10 C1 INH by the manufacturer of Berinert (CSL Behring) has been available for decades throughout Europe.11,12 Sanquin, which produces Cinryze, also produces a C1 INH concentrate, called Cetor, that has been used in a limited number of European countries for decades.13 As of the time this review was written, all C1 INH is nanofiltered.

Human Plasma–Derived C1 INH
Human plasma–derived C1 INH (Cinryze) was approved by the US Food and Drug Administration (FDA) in October 2008 for the prevention of HAE attacks in
Table 1.
Distinguishing Disease Characteristics and Laboratory Findings in the Differential Diagnosis of Angioedema

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
<th>Laboratory Findings</th>
</tr>
</thead>
</table>
| Allergic (histamine induced)          | Most common form of angioedema
Urticaria usual
Angioedema most commonly occurs in the face and throat in response to an outside influence | C1 Normal, C4 Normal, C1 INH Normal, Function Normal |
| Idiopathic (histamine induced)        | Swelling or hives mainly from histamine
Many patients are autoimmune in etiology
Thyroid dysfunction should be considered | C1 Normal, C4 Normal, C1 INH Normal, Function Normal |
| Idiopathic Nonhistaminergic (bradykinin induced) | May account for up to 5% of cases of idiopathic angioedema
No urticaria | C1 Normal, C4 Normal, C1 INH Normal, Function Normal |
| Type I HAE                            | Accounts for 85% of HAE
Recurrent angioedema of skin and mucus membranes without urticaria
Recurrent episodes of abdominal pain and vomiting
Laryngeal edema
Positive family history of angioedema in most | C1 Normal, C4 Low, C1 INH Low, Function Low |
| Type II HAE                           | Accounts for 15% of HAE
Recurrent angioedema without urticaria
Recurrent episodes of abdominal pain, laryngeal edema, and skin swelling
Positive family history of angioedema in most | C1 Normal, C4 Low, C1 INH Normal to high, Function Low |
| Type III HAE                          | Rare
No urticaria
Presents like HAE I and II, but with normal C1 INH findings
Highly variable
X-linked dominant inheritance
Predominantly in women | C1 Normal, C4 Normal, C1 INH Normal, Function Normal |
| Acquired (types I and II)             | Rare
No urticaria
Symptoms similar to HAE
No family history
Later age of onset
Autoantibodies destroy C1 INH function | C1 Low, C4 Low, C1 INH Low, Function Low |
| ACE-inhibitor induced                 | Accounts for 4%-8% of angioedema
No urticaria
Presents hours to years after starting an ACE inhibitor | C1 Normal, C4 Normal, C1 INH Normal, Function Normal |

Abbreviations: ACE, angiotensin-converting enzyme; C1 INH, C1 inhibitor; HAE, hereditary angioedema.
A randomized, double-blind, placebo-controlled study (called the C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy, or CHANGE, trial)\(^1\) assessed the efficacy and safety of human plasma–derived C1-INH in the prevention and management of HAE attacks. In the first part of the study,\(^1\) the human plasma–derived C1 INH was assessed for the management of attacks of facial, abdominal, or genitourinary angioedema in patients with HAE. Participants were

adolescent and adult patients.\(^9\) Cinryze is a lyophilized intravenous preparation. This product is nanofiltered to remove viral and potentially prion-sized particles. In addition, it is screened using polymerase chain reaction and then subjected to multiple viral inactivation and removal steps, including pasteurization.\(^14\) The high level of safety of human plasma–derived C1 INH is a result of the multiple steps taken during collection and processing, which reduce the overall risk for blood-borne pathogens.

<table>
<thead>
<tr>
<th>Drug Classification</th>
<th>Acute Treatment</th>
<th>Short-Term Prophylaxis</th>
<th>Long-Term Prophylaxis</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh frozen plasma/ solvent detergent-treated plasma</td>
<td>Effective</td>
<td>Effective</td>
<td>NA</td>
<td>Inexpensive</td>
<td>Viral potential</td>
</tr>
<tr>
<td>Androgens</td>
<td>NA</td>
<td>Effective</td>
<td>Effective</td>
<td>Easy to administer (oral)</td>
<td>Toxic effect on liver</td>
</tr>
<tr>
<td>Ecallantide (kinin modulator)</td>
<td>Effective</td>
<td>NA</td>
<td>NA</td>
<td>Subcutaneous</td>
<td>Short half-life</td>
</tr>
<tr>
<td>Icatibant (kinin modulator)</td>
<td>Effective</td>
<td>NA</td>
<td>NA</td>
<td>Subcutaneous</td>
<td>Local pain and burning at injection site</td>
</tr>
<tr>
<td>Berinert or Cetor (nanofiltered C1 INH)</td>
<td>Effective</td>
<td>Effective(^a)</td>
<td>Effective(^a)</td>
<td>Replaces deficient protein</td>
<td>Viral transmission possible</td>
</tr>
<tr>
<td>Cinryze (nanofiltered C1 INH)</td>
<td>Effective(^a)</td>
<td>Effective(^a)</td>
<td>Effective</td>
<td>Replaces deficient protein</td>
<td>Viral transmission possible</td>
</tr>
<tr>
<td>Rhucin (recombinant C1 INH)</td>
<td>Effective(^b)</td>
<td>Effective(^b)</td>
<td>NA</td>
<td>No viral risk</td>
<td>Short half-life</td>
</tr>
</tbody>
</table>

\(^a\) Off-label use.

\(^b\) Not FDA approved.

**Abbreviations:** C1 INH, C1 inhibitor; FDA, US Food and Drug Administration; IV, intravenous; NA, not applicable.
randomly assigned to receive a 1000-IU dose of either C1 INH or placebo. Participants with no substantial relief within 60 minutes were then given a second dose of the same study drug that they had received initially. All participants were eligible to receive open-label C1 INH after 4 hours. The time to beginning of unequivocal relief (the primary endpoint) was measured, which was statistically significantly shorter in the C1 INH group (median time, 2 hours) than in the placebo group (median time, >4 hours).15 On the basis of these data, however, human plasma–derived C1 INH at 1000 U was not approved for the management of HAE attacks in the United States.

The second part of study15 involved the use of C1 INH as a long-term prophylaxis for preventing HAE attacks. In the 24-week, multicenter, double-blind, placebo-controlled, crossover trial, 22 patients with a history of frequent angioedema received C1 INH (1000 IU) or placebo 2 times per week for 12 weeks. The patients then crossed over and received the other intervention for an additional 12 weeks. The primary endpoint was the number of HAE attacks that occurred while patients were receiving C1 INH vs the number of attacks that occurred while patients were receiving placebo, with each participant acting as his or her own control. The number of attacks that occurred during the C1 INH treatment phase was statistically significantly less than the number of attacks that occurred during the placebo treatment phase (6.1 vs 12.7, \( P<.001 \)).15 Secondary endpoints, including days of swelling, also showed a statistically significant benefit for the active treatment phase (10.1 days vs 29.6 days, \( P<.001 \)).15 On the basis of these data, C1 INH received FDA approval for the prophylactic management of HAE.9

Adverse events recorded during the study were sinusitis, rash, headache, upper respiratory tract infection, viral upper respiratory tract infection, gastroesophageal reflux disease, pruritus, and vomiting.14,15 No events were reported to have led to death. Venous thrombosis has been reported, but it is not thought to be associated with C1 INH at the indicated dose.16

The FDA-approved dose for C1 INH is 1000 U administered intravenously twice weekly to prevent attacks.17 The FDA requested that postmarketing studies be performed to address (1) the optimal dose for prophylaxis in male and female patients, (2) immunogenicity, and (3) long-term safety (private communications with ViroPharma). C1 INH is not approved for pregnant women, but C1 INH is considered the safest prophylactic agent during pregnancy and lactation.18 It is also used off label for children with moderate to severe HAE.19

The 2010 international consensus algorithm20 for the diagnosis and management of HAE recommended that home C1 INH self-infusion programs be offered to patients. Training patients to perform self-infusion is important to reduce the burden of care. Quality assurance and reassessment of technique is important, however, to reduce the risk of adverse events. Indwelling ports used for infusion have been complicated with thrombosis and infections, and the use of C1 INH by this route is expected to have similar adverse events.20

Human Plasma–Derived C1 INH Concentrate
Human plasma–derived C1 INH concentrate (Berinert) is a pasteurized, nanofiltered, and lyophilized C1 INH concentrate derived from human plasma for intravenous injection. It was initially licensed in Germany in 1979 and has been available for decades throughout Europe, Canada, Japan, Australia, and Argentina.11,12 Berinert received approval from the FDA in 2009 for the management of angioedema attacks of the face and abdomen in adult and adolescent patients.10 In January 2012, Berinert received FDA approval to expand its label to include self-administration and acute laryngeal attacks of HAE.21-23

The largest randomized, double-blind, prospective, placebo-controlled, dose-finding study, called the International Multicentre Prospective Angioedema C1-inhibitor Trial (IMPACT), confirmed the efficacy and safety of Berinert in the management of acute facial and abdominal HAE attacks.24 The study included 125 patients with HAE who were randomly assigned to receive placebo or
negative plasma undergoes specific nucleic acid test and polymerase chain reaction assay for hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus type 1, and human parvovirus B19. Pasturization and nanofiltration complete the processing to ensure safety.

Recombinant Human C1 INH

Rhucin, a recombinant human (rh) C1 INH protein produced in the milk of transgenic rabbits, is under FDA review in the United States and recently received approval in Europe. The recombinant technology yields large amounts of fully functional rh C1 INH protein. Because of unique carbohydrate additions (glycosylation), however, the half-life of the protein is shorter than human-derived C1 INH, and although a possibility exists that anaphylaxis may occur, it has not yet been reported in phase II or III studies or postmarketing surveillance in Europe.

Pharming Healthcare, a Dutch biotechnology company, has recently completed phase I, II, and III studies to obtain approval to use rh C1 INH for acute attacks of HAE in the United States. In a phase I clinical trial, 12 asymptomatic patients with HAE received rh C1 INH. The drug was administered intravenously in doses ranging from 6.25 U/kg to 100 U/kg. There was an increase of plasma level of C4 and an inhibition of complement C4 cleavage. The half-life of rh C1 INH was dose dependent; the longest half-life, of approximately 3 hours, was observed at the dose of 100 U/kg. Because of the short half-life, rh C1 INH is expected to be more effective for the management of HAE attacks than for prophylaxis. Adverse effects were minimal; however, 1 patient with a rabbit allergy developed anaphylaxis secondary to residual rabbit proteins in rh C1 INH.

In an open-label, phase II clinical trial, 13 severe angioedema attacks in 9 patients were managed with Rhucin (100 U/kg). The mean time to onset of symptom relief was 1 hour (median time, 30 minutes). Time to minimum symptoms score (ie, almost complete resolution of symptoms) ranged from 6 to 12 hours. No adverse
reactions were reported, and no immunogenic reactions against rh C1 INH or rabbit protein were observed.

In a randomized, double-blind, placebo-controlled phase III study29 of rh C1 INH for the management of acute attacks of HAE, 39 patients with HAE were randomly assigned to receive 1 of 2 different doses of rh C1 INH (100 U/kg or 50 U/kg) or placebo. Primary endpoint was time to onset of relief; median time to onset was 68 minutes for patients who received the rh C1 INH dose of 100 U/kg, 122 minutes for patients who received the dose of 50 U/kg, and 258 minutes for patients who received the placebo.29

Recombinant human C1 INH has undergone separate phase III clinical trials in Europe and North America to assess its efficacy and safety in the management of acute HAE attacks.30,31 The double-blind, randomized, placebo-controlled phase III study in Europe was stopped earlier than anticipated because of ethical reasons: there was a statistically significant difference in median time to onset of symptom relief in patients who were receiving rh C1 INH compared with those who were receiving placebo (62 minutes vs 508 minutes, P = .009).30,31 These trials have demonstrated that rh C1 INH is safe and effective. It is contraindicated only in those with hypersensitivity to rh C1 INH or rabbits.29 The benefits of rh C1 INH are that it carries no risk of transmission of human blood-borne pathogens, and production of the drug can be more easily controlled because it is not dependent on plasma center donors.

**Inhibition of Kinin Pathway**

**Plasma Kallikrein Inhibitor (Ecallantide)**

Ecallantide (Kalbitor) is a selective reversible inhibitor of plasma kallikrein. It is a recombinant protein containing 60 amino acids and is produced in the yeast *Pi-chia pastoris*. Ecallantide binds with high affinity to kallikrein, thereby preventing bradykinin generation and edema progression in acute HAE attacks. In the United States, the 2 Evaluations of DX-88’s Effect in Mitigating Angioedema (EDEMA) studies32-34 led to the December 2009 FDA approval of ecallantide for the management of acute HAE attacks in patients aged 16 years or older.35

The randomized, double-blind, placebo-controlled, phase III EDEMA trials32-34 were conducted to assess the efficacy of ecallantide for the treatment of patients with moderate to severe HAE attacks. Patients who presented within 8 hours of a moderate or worse attack at any body location were randomly assigned (1:1) to receive either ecallantide (30 mg) or placebo by subcutaneous injection. The first trial (EDEMA3)33 involved 72 patients. The primary endpoint was Treatment Outcome Score (TOS) at 4 hours. The TOS is a patient-reported measure that assesses symptom severity and measures overall response relative to baseline. The scale ranges from 100 (significant improvement) to −100 (significant worsening). Patients who received ecallantide showed statistically significant improvements in TOS at 4 hours (P = .037) and 24 hours (P = .044) compared with patients who received placebo.33

The EDEMA4 trial had a study design similar to that of EDEMA3 and involved 96 patients with acute HAE symptoms.34 The primary endpoint was Mean Symptom Complex Severity (MSCS) score measured at 4 hours. The MSCS score is a patient-reported measure that rates severity of symptoms at a specific time on a scale ranging from 0 (none) to 5 (severe). A lower MSCS score after treatment compared with baseline was considered improvement. Compared with patients who received placebo, patients who received ecallantide reported statistically significant decreases in mean MSCS scores at 4 hours (0.37 vs 0.81, P = .01) and 24 hours (P = .044) compared with patients who received placebo.33

Ecallantide was well tolerated; the most common reported adverse effects were headache, nausea, fatigue, and upper respiratory infections.33 Hypersensitivity, including anaphylaxis, was also reported. Throughout the study, 10 of 255 patients (3.9%) who received ecallantide developed hypersensitivity that was consistent with anaphylaxis, with all reactions occurring within 60 minutes.
In the FAST-2 trial, 74 patients from Europe and Israel with acute HAE attacks were randomly assigned to receive a 30-mg subcutaneous injection of either icatibant or tranexamic acid. Statistically significant improvement was found in patients who received icatibant. The median time to onset of symptom relief was 0.8 hour in the icatibant group vs 7.9 hours in the tranexamic acid group (\(P<.001\)), and the median time to clinically significant symptom improvement was 2.0 hours in the icatibant group vs 12.0 hours in the tranexamic acid group (\(P<.001\)).

After randomization, future attacks that occurred in study participants in both trials were managed in an open-label fashion. Most of the attacks in both extension trials required management with a single injection of icatibant (87.1% in FAST-1 and 91.0% in FAST-2). No drug-related serious adverse events were reported. The most common adverse effects reported in the studies were limited to localized, mild erythema and edema at the site of injection and occasional minor burning sensations, itching, or pain, all of which resolved within a few hours.

In the FAST-3 trial, 88 patients with acute HAE attacks who received icatibant had statistically significant improvement in symptom relief compared with patients who received placebo. For cutaneous and abdominal attacks, the time to onset of primary symptom relief was 1.5 hours vs 18.5 hours (\(P<.001\)) and the median time to 50% symptom relief was 2.0 hours vs 19.8 hours (\(P<.001\)) for the icatibant group and placebo group, respectively. For laryngeal attacks, the median time to 50% symptom relief was 2.5 hours for the icatibant group vs 3.2 hours for the placebo group. No clinically relevant changes in safety parameters or serious adverse advents were reported.

In summary, the FAST trials demonstrated that icatibant was effective and generally well tolerated in patients with acute HAE attacks. These trials led to FDA approval for subcutaneous self-administration in patients aged 18 years or older.

Bradykinin Receptor Antagonism (Icatibant)

Icatibant, a bradykinin receptor antagonist, is a potent selective competitive antagonist of the bradykinin B₂ receptor. It is a synthetic decapeptide and is structurally similar to bradykinin. Icatibant is FDA approved for subcutaneous self-administration for management of acute HAE attacks in patients aged 18 years or older.

The randomized, double-blind For Angioedema Subcutaneous Treatment trials (FAST-1, FAST-2, and FAST-3) were conducted for approval of icatibant in the United States and Europe. The primary endpoint was time to onset of symptom relief, as reported by the patient using a visual analog scale. In the FAST-1 trial—conducted in North America, Argentina, and Australia—56 patients with severe cutaneous and abdominal attacks were randomly assigned to receive subcutaneous icatibant or placebo. Patients who received icatibant had statistically significantly shorter times to onset of symptom relief compared with patients who received placebo (0.8 hours vs 16.9 hours, \(P<.001\)). A statistically significant difference was not found, however, in median time to clinically significant symptom relief (2.5 hours vs 4.6 hours, \(P=.142\)). After the FAST-1 trial, icatibant required a repeat phase III study for FDA approval.

The randomized, double-blind For Angioedema Subcutaneous Treatment trials (FAST-1, FAST-2, and FAST-3) were conducted for approval of icatibant in the United States and Europe. The primary endpoint was time to onset of symptom relief, as reported by the patient using a visual analog scale. In the FAST-1 trial—conducted in North America, Argentina, and Australia—56 patients with severe cutaneous and abdominal attacks were randomly assigned to receive subcutaneous icatibant or placebo. Patients who received icatibant had statistically significantly shorter times to onset of symptom relief compared with patients who received placebo (0.8 hours vs 16.9 hours, \(P<.001\)). A statistically significant difference was not found, however, in median time to clinically significant symptom relief (2.5 hours vs 4.6 hours, \(P=.142\)). After the FAST-1 trial, icatibant required a repeat phase III study for FDA approval.
Future Perspective

Use of current HAE medications and proper care of the HAE patient has recently been outlined in a 2012 consensus document, and it is essential reading material for physicians who treat patients with HAE. Physicians should also be aware of developments in HAE management. As previously noted, rh C1 INH is a novel medication and is pending FDA approval to manage attacks of HAE. The FDA is requiring repeat phase III studies for this drug before it is approved in the United States. The addition of rh C1 INH to HAE treatment options will particularly benefit those patients who do not wish to be treated with a human blood product for religious, moral, or other reasons.

Other investigational products, including an oral medication to block bradykinin and a kallakrien inhibitor, are in very early stages of development. In addition, drug manufacturers ViroPharma Biologics and CSL Behring are investigating the use of subcutaneous C1 INH for prophylaxis against attacks, and Dyax is investigating a monoclonal antibody against kallakrien (all personal communications).

Conclusion

In the past several years, many new therapies have emerged for the prevention and management of HAE attacks. Several additional therapies are likely to be approved in years to come. Introduction of these new therapeutic agents will allow physicians to manage and individualize HAE care appropriately.

References


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