

Acute Management of Hereditary Angioedema Attacks



Constance H. Katelaris, MD, PhD, FRACP

KEYWORDS

- Hereditary angioedema • HAE acute attacks • Treatment of HAE
- C1-inhibitor concentrate • Icatibant • Ecallantide • rh C1-INH

KEY POINTS

- Management of acute hereditary angioedema (HAE) attacks has changed dramatically over the last decade with 4 clinically proven, options available in some countries.
- Acute treatment options include 2 plasma-derived C1 inhibitor concentrates, a recombinant C1 esterase inhibitor, a kallikrein inhibitor, and a bradykinin 2 receptor antagonist.
- Better education for patients with HAE and adoption of the principles of self-management with “on-demand” treatment have improved quality of life and outcomes for patients.

INTRODUCTION

Modern management of hereditary angioedema (HAE) includes managing the acute attack, short-term prophylaxis for procedures that place the patient at risk of an attack, and long-term management for those where the attack rate is high or impacts adversely on ability to work and conduct daily life.

Acute HAE attack management has changed dramatically over the last 10 years. For more than 2 decades, plasma-derived C1 inhibitor concentrate (pdC1-INH) was the only specific treatment available; now there are 4 clinically proven effective options available, although not all are available in every country as yet. Preferred contemporary use of the treatment options discussed herein is as “on-demand treatment,” where treatment is in the hands of the patient to be used once an attack is evident. In this way, delays in treatment access are avoided. Several excellent reviews have explored this topic previously; this article summarizes, in a practical fashion, the

Disclosure Statement: The author has conducted clinical trials with CSL Behring (Berinert) and Shire (icatibant) for which the author have received no personal payments. The author has chaired advisory boards on HAE for Shire Australia and CSL Behring the author has received honoraria for participation in meetings and lectures from Shire Australia and CSL Behring. Immunology and Allergy Unit, Department of Medicine, Campbelltown Hospital, Therry Road, Campbelltown, Sydney, New South Wales 2560, Australia
E-mail address: Connie.Katelaris@sswhs.nsw.gov.au

Immunol Allergy Clin N Am 37 (2017) 541–556

<http://dx.doi.org/10.1016/j.iac.2017.04.002>

0889-8561/17/© 2017 Elsevier Inc. All rights reserved.

immunology.theclinics.com

attributes of each of these treatment options, listing their indications, risks and benefits, and hopefully will serve as a useful guide to those prescribing acute treatment for HAE patients.

MEDICATIONS FOR TREATING ACUTE ATTACKS

Several treatment modalities have become available for management of acute HAE attacks in the last 10 to 15 years. Most are now available to patients in North America, Europe, United Kingdom, and Australia, but few of these options exist for many patients living in developing countries.

PLASMA-DERIVED C1 INHIBITOR THERAPY

Berinert

HAE is caused by a deficiency or abnormality in C1-INH, a factor that has numerous inhibitory functions within the contact, fibrinolytic, and complement pathways. Replacement therapy with plasma-derived C1-INH has been used since 1973, with Berinert P first licensed in Germany in 1979. Berinert is nanofiltered and currently licensed for the treatment of acute HAE attacks in Europe, the United States, Australia, and numerous other countries.

Studies of efficacy

A pivotal phase III prospective, multinational, randomized, parallel-group, placebo-controlled, dose-finding, 3-arm, double-blind clinical study (I.M.P.A.C.T. 1 [International Multi-center Prospective Angioedema C1-Inhibitor]) assessed the efficacy and safety of Berinert in 124 adult and pediatric patients (6–72 years) who were experiencing an acute, moderate to severe attack of abdominal or facial HAE.¹ Two doses (10 and 20 U/kg) were compared with placebo, given by intravenous infusion (4 mL/min) within 5 hours of the onset of an attack.

Subjects treated with a 20 U/kg dose experienced a significant reduction ($P = .0025$) in the median time to onset of relief from symptoms of an HAE attack (30 minutes) as compared with placebo (90 minutes). The median time to complete resolution of HAE symptoms was significantly shorter ($P = .0237$) in the Berinert 20 U/kg group (4.9 hours) than in the placebo group (7.8 hours). The study demonstrated that a 20 U/kg dose of Berinert was significantly more efficacious than 10 U/kg or placebo.

In a subsequent study, Wasserman and colleagues² demonstrated that Berinert at 20U/kg dose provided rapid and effective relief for successive abdominal and facial attacks. They treated 663 abdominal attacks in 50 patients and 43 facial attacks in 16 patients. The median time to onset of relief for all attacks was 19.8 minutes, with a median time to complete resolution of 11 hours.

Cinryze

Another pd C1-INH product, Cinryze, is distributed internationally and like Berinert, is purified from human plasma. It was introduced in Europe in 1972 and was approved in 2008 by the Food and Drug Administration in the United States for prophylaxis of HAE.

Zuraw and colleagues³ reported a randomized trial of nanofiltered C1-INH (Cinryze) for the acute treatment of HAE attacks. Sixty-eight HAE subjects were randomized to receive Cinryze or placebo within 4 hours of the onset of an episode of moderate to severe nonlaryngeal edema (laryngeal episodes were treated with open-label Cinryze). Unlike the Berinert I.M.P.A.C.T. 1 trial, a fixed dose of 1000 U of C1-INH was used in all subjects. There was a significant reduction in time to onset of relief in the treatment

group (2 hours) compared with placebo group (>4 hours; $P = .02$); the proportion of subjects achieving unequivocal relief within 4 hours was 60% (42% in the placebo group; $P = .06$). Two-thirds of subjects treated with Cinryze required a second dose of the drug at 60 minutes because of inadequate improvement compared with 80% of those treated with placebo. Interestingly, in the open-label extension phase of the trial the rate of response to treatment within 4 hours was 93%; the authors commented on psychological factors affecting perception of pain in abdominal attacks.

Onset of Action of Plasma-Derived C1 Inhibitors

The median times to onset of patient-reported symptom relief were 30 minutes with Berinert 20 U/kg versus 90 minutes with placebo ($P = .0025$)¹ and 120 minutes with Cinryze 1000 U versus 240 minutes with placebo ($P = .02$).^{4,5}

Rebound and Relapse

In patients with abdominal or facial attacks treated with pd C1-INH 20 U/kg, no new attacks occurred before the complete resolution of the previous attack, indicating an absence of rebound angioedema. Pd C1-INH was generally found to be equally effective and well-tolerated in patients receiving repeated doses.⁶

SPECIFIC CIRCUMSTANCES

Laryngeal Attacks

Approximately 1% of all HAE attacks are laryngeal⁷; 50% of HAE patients will experience a laryngeal attack at some stage. These account for the life-threatening nature of the condition, with death caused by asphyxiation if urgent treatment or airway support is not available. Before effective treatment, 25% to 30% of patients died from a laryngeal attack,⁸ with higher numbers (50%) quoted for those with undiagnosed HAE.⁹ Studies of patients with untreated laryngeal attacks have demonstrated that an attack may progress over 8 to 24 hours to its peak, persist for 24 to 48 hours and have a mean total duration of 103 hours.¹⁰

Until recently, data on the efficacy of C1-INH administration in acute laryngeal attacks were limited and empirical,¹¹ but there trial data are now available to support efficacy.

In an extension of the randomized controlled trial of Berinert, I.M.P.A.C.T 2 enrolled patients in a prospective, open-label study for administration of a single weight-based dose of 20 U/kg of Berinert for treatment of attacks at any location. This study demonstrated the efficacy and safety of the treatment in 16 patients experiencing 39 laryngeal attacks. The median time to onset of relief was 0.25 hours (range, 0.1–1.3) and the median time to complete resolution was 8.25 hours (range, 0.6–48.9). Onset of symptom relief was reported within 1 hour in 95% of patients.⁸ There was no evidence of rebound swelling or of diminution in efficacy after repeated administration for other attacks. No emergency procedures such as intubation were required after Berinert treatment. This was also the case in a retrospective case series of 61 patients treated with Berinert for laryngeal attacks reported by Bork and associates.¹² In this, the study mean duration of laryngeal edema in treated patients was 15 hours (208 attacks).

Treatment in Pediatric Patients

There is a lack of systematic studies of acute treatment for HAE attacks in pediatric patients; however, most of the treatments for acute attacks have been used in children and seem to be safe. The use of pdC1-INH for acute attacks of HAE in pediatric patients has been reported in a variety of trials including retrospective cohort studies, prospective open-label studies and randomized placebo-controlled trials.^{9,13–15}

Dosing used has varied by product, with fixed dosing for Cinryze and weight-based dosing for Berinert after 2008.

Consensus guidelines recommend use of pdC1-INH in children.¹⁶ In the EU, the United States, and Australia, Berinert is approved for pediatric use. In Europe, Berinert has been used safely in pediatric practice for more than 20 years.^{17,18} Cinryze, at a fixed dose of 1000 U, has been used also in pediatric populations.

Craig and colleagues¹⁵ recently reviewed pediatric treatment with pdC1-INH in a systematic review, reporting data on nearly 3000 infusions including many in children less than 12 years of age. Children were included in both the Berinert and Cinryze studies, and the results were comparable with those from adult subjects with no adverse effects.

Further evaluation of pediatric data was performed by Lumry and colleagues.¹³ Data from 2 randomized, placebo-controlled studies and open-label extensions were analyzed.^{3,19,20} Forty-six children and adolescents ranging in age from 2 to 17 years received a total of 2237 Cinryze infusions in the 4 studies. Overall, those receiving active treatment had superior responses. In the open-label extension, 22 children experiencing 121 attacks were evaluated. There were 113 attacks (97%) that had clinical relief within 4 hours after the initial dose of Cinryze. Only 4 attacks (2 gastrointestinal and 2 facial) did not achieve clinical relief within 4 hours.

Pregnancy and Breast Feeding

The safety of pd C1-INH products in pregnancy and lactation has not been proven in controlled clinical trials; however, experience with treatment of women during these periods has not revealed any concerns regarding impact on mother or child. The decision to use Berinert or Cinryze during pregnancy and lactation should be based on clinical need.

ADVERSE EVENTS WITH C1 INHIBITOR PRODUCTS

Berinert has been used for more than 30 years in more than 400,000 treatments and has an excellent safety record.²¹ In the pivotal phase III study, the most common adverse effects reported 4 hours after the 20 U/kg dose were nausea, dysgeusia, abdominal pain, and headache; however, no serious adverse events were noted.

Adverse reactions reported with Cinryze have been mild, including nonspecific rash, dizziness, and headaches.

Viral Transmission

Because pd C1-INH is a plasma product, there is the risk of blood-borne viral transmission (**Table 1**). The manufacturing process for Berinert includes pasteurization (at 60°C for 10 hours), hydrophobic interaction chromatography and virus filtration (also called nanofiltration by 2 filters, 20 nm and 15 nm, in series) to reduce the potential for pathogen transmission. In 30 years of postmarketing surveillance, there have been no reports of viral transmission with Berinert.²²

The manufacturing process used to extract Cinryze from screened human plasma incorporates 3 virus inactivation/removal steps: polyethylene glycol precipitation (20% polyethylene glycol 4000, pH 5.8), pasteurization (10 hours at 60.5 ± 1.0°C) and 15 nm filtration to remove the smallest known viral particles.

Thromboembolic Events

There have been concerns about thromboembolic events with C1-INH products (see **Table 1**).²³ In postmarketing surveillance of those receiving Berinert for on-demand

Table 1
Specific safety concerns

Treatment	Risks
C1-INH Berinert	Risks associated with blood products, for example, viral transmission (nil recorded in any clinical trial). Very rare reports of thromboembolism.
C1-INH Cinryze	Risks associated with blood products, for example, viral transmission (nil recorded in any clinical trial). Very rare reports of thromboembolism.
RC1-INH Ruconest	Anaphylaxis hypersensitivity to rabbit proteins.
Ecallantide	Hypersensitivity reactions (anaphylaxis).
Icatibant	Injection site reactions.

Abbreviations: C1-INH, C1 inhibitor; RC1-INH, recombinant C1 inhibitor concentrate.

treatment, very few events have been recorded and the majority have been with high-dose off-label use.²⁴ In the Cinryze studies, the risk of thromboembolic events seemed to be related to prophylactic use, specifically in those with indwelling catheters.

Immunogenicity

Anti-pd C1-INH antibodies were demonstrated in 19% of 57 treated patients but there was no correlation with efficacy or adverse events.²⁵ Anaphylaxis, although reported, is rare with pdC1-INH.^{26,27}

INDICATION AND ADMINISTRATION

Berinert (CSL Behring) is a highly purified, freeze-dried C1-INH derived from human plasma. It contains 500 U of C1-INH per vial (50 U/mL). One unit is equal to the amount of C1-INH in 1 mL of human plasma, which is equivalent to approximately 240 mg/L of plasma. The product is administered intravenously and is immediately available in the plasma, with a plasma concentration corresponding to the administered dose.

Berinert is indicated for the treatment of acute attacks in patients with HAE (Berinert product information; available at: www.cslbehring.com.au).

Cinryze (Shire Pty. Ltd.) is indicated for treatment, preprocedure prophylaxis, and long-term prophylaxis of angioedema in adult and pediatric HAE patients. Recommended treatment dose for an acute episode is 1000 U (2 vials) for adults or children, with provision for a second 1000-U dose after 60 minutes if response is inadequate. Cinryze is supplied as a freeze-dried powder with solvent for reconstitution and can be stored for up to 2 years at room temperature (<25°C). After reconstitution, a single dose is 1000 U/10 mL with a concentration of 100 U/mL. Regulatory labeling in Europe and the United States allows self-administration of both plasma C1INH products with appropriate patient education and training (Table 2).

RECOMBINANT C1 INHIBITOR CONESTAT ALFA

A brief review of the data on recombinant C1-INH (rh C1-INH) is given. More detailed information has been provided in a recent review.²⁸

Introduction

Conestat alfa is a human recombinant C1 esterase inhibitor (rh C1-INH), developed as an alternative to pd C1-INH, to address the potential risks of bloodborne pathogen transmission that exists with plasma-derived products. It has a sequence identical

Table 2 Dosing		
Treatment	Dosing to Treat HAE Attack	Product Details
Pd C1-INH (Berinert)	20 U/kg, slow IV administration, 4 mL/min; with appropriate training, suitable for home/self-administration.	Highly purified, freeze-dried C1-INH derived from human plasma. It contains 500 U of C1-INH per vial (50 U/mL). Supplied as 1 carton containing the single-use vial of Berinert and one 10-mL vial of water for injection, and a second carton containing 1 Mix2Vial filter transfer set, a disposable 10-mL syringe, an infusion set, 2 alcohol swabs, and a plaster (adhesive bandage). Store below 25°C.
Pd C1-INH (Cinryze)	1000 U (2 vials) for adults or children, with provision for a second 1000-U dose after 60 minutes if response is inadequate. IV administration; with appropriate training suitable for home/self-administration.	Single-use vial of glass containing 500 U of C1 esterase inhibitor as a nanofiltered, freeze-dried powder. The vial is sealed with a rubber type I stopper, and an aluminum seal with a plastic flip-off cap. <i>Solvent:</i> 5 mL of water for injections in a vial of colorless glass, which is closed with a rubber stopper and an aluminum seal with a plastic flip off cap.
Rh C1-INH (Ruconest)	50 IU/kg for patients weighing <84 kg; up to 4200 IU for patients weighing ≥84 kg; administered as a slow IV injection over 5 min. An additional dose of the same recommended amount can be administered if symptoms persist, but do not exceed 2 doses in 24 h; with appropriate training suitable for home/self-administration.	Lyophilized powder for reconstitution for injection in a single-use 25-mL glass vial containing 2100 IU of rhC1INH per vial
Ecallantide	30 mg (3 vials per dose) subcutaneously; given by a health care provider.	Clear solution, three 10 mg/mL single-use vials packaged in a carton. Each vial contains 10 mg of ecallantide. Keep refrigerated (2°C–8°C/36°F–46°F). Vials removed from refrigeration should be stored below 86°F/30°C and used within 14 d or returned to refrigeration until use.
Icatibant	30 mg injected subcutaneously in the abdominal area. If response is inadequate or symptoms recur, additional injections of 30 mg may be administered at intervals of ≥6 h. Do not administer >3 injections in 24 h. Patients may self-administer upon recognition of an HAE attack.	Pre-filled syringe, 30 mg/3 mL.
FFP	Two units of FFP are given, repeating 2–4 hourly until there is benefit. Administered in health care facility.	

Abbreviations: C1-INH, C1 inhibitor; FFP, fresh frozen plasma; HAE, hereditary angioedema; Pd C1-INH, plasma-derived C1 inhibitor concentrate; RC1-INH, recombinant C1 inhibitor concentrate.

to the natural protein so it has an identical mode of action to human C1-INH. There are differences in the glycosylation of rh C1-INH and pdC1-INH that do not affect rh C1-INH specificity, but result in a shorter half-life compared with pd C1-INH.²⁹

Recombinant human C1-INH is purified from the milk of genetically modified rabbits.³⁰ The benefit of recombinant technology is that it enables a reliable supply of a product with uniform quality. One international unit of rh C1INH activity is defined as the equivalent of C1 esterase inhibiting activity present in 1 mL of pooled normal plasma. Population pharmacokinetic modeling supports a dosing scheme of 50 IU/kg, which achieves C1INH levels above the lower level of the normal range (0.7 U/mL) in at least 94% of patients.³¹

Trial Data

The efficacy of rh C1-INH in the treatment of acute attacks in HAE patients has been evaluated in 3 randomized, double-blind, placebo-controlled studies^{32–34} and 3 open-label extension studies^{35–38} using patient-reported outcomes with a validated visual analog scale instrument. The North American study used rh C1-INH at 50 and 100 IU/kg, demonstrating effectiveness and safety of both doses, while the European study used a dose of 100 IU/kg showing similar superiority over placebo.³² The treatment was effective for HAE attacks at various sites.

Open-label extension studies^{35,36} demonstrated that efficacy was maintained for subsequent acute HAE attacks. In these 2 studies, 362 attacks in 119 patients were treated with 80% of repeat attacks responding within 4 hours and most requiring only a single dose of rh C1-INH.

Li and colleagues³⁷ conducted an open-label extension study evaluating the efficacy and safety of the treatment of multiple HAE attacks in North American and European patients. For 44 patients experiencing 224 HAE attacks, a single 50 IU/kg dose of rh C1-INH was effective for improving symptoms of an HAE attack and the incidence of symptom relapse was low for initial and subsequent attacks. Almost all attacks were treated with only a single dose of rh C1-INH. A total of 215 of 224 attacks (96%) were treated with a single 50-IU/kg dose of rh C1-INH, and no increase in dose was needed for treatments of repeat attacks.

Onset of Action

In the pivotal trials, patients were treated within 5 hours of onset of HAE attack symptoms. The primary efficacy endpoint was the median time to onset of symptom relief. A pooled analysis indicated a significantly faster onset of symptom relief for both doses of rh C1-INH, 50 U/kg (122 minutes; 95% confidence interval, 72–136; $P = .013$) and 100 U/kg (66 minutes; 95% confidence interval, 61–122; $P = .001$), versus placebo (495 minutes; 95% confidence interval, 245–520).^{28,32}

Rebound and Relapse

In the study by Li and colleagues,³⁷ the vast majority (96%) of patients required only 1 dose of rh C1-INH. Relapse within 24 hours of treatment for patients responding to a single dose of rh C1-INH has been low in all clinical trials to date.^{32,36}

Response by Anatomic Location

In the North American open-label study,³⁶ the median time to onset of relief at different anatomic locations (most attacks were peripheral or abdominal) with both doses of rh C1-INH (range, 50–124 minutes) was faster than with placebo (range, 243–560 minutes). Few attacks (10%) required treatment with a second dose, and of these, most were orofacial or pharyngeal–laryngeal attacks.

In the European open-label study, the fastest median time to symptomatic relief occurred with abdominal attacks (33 minutes), followed by peripheral attacks (61 minutes), orofacial and pharyngeal–laryngeal attacks (120 minutes), and genitourinary attacks (480 minutes).³⁵

SPECIAL POPULATIONS

Pediatric Use

The safety and efficacy of rh C1-INH was evaluated in 17 adolescent patients (13–17 years of age) treated for 52 HAE attacks. No serious adverse reactions were reported in these patients, with the most common reactions being abdominal pain, headache, and oropharyngeal pain.

Pregnancy and Breast Feeding

Rh C1-INH is pregnancy category B. There are, however, no adequate and well-controlled studies in pregnant women. It should only be used during pregnancy if clearly needed. It is not known if rh C1-INH is excreted in human milk.³⁰

Adverse Events

Rh C1-INH is contraindicated in patients with a history of allergy to rabbits or rabbit-derived products and in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations (see [Table 1](#)).²⁹ Anaphylaxis was the most serious adverse reaction during the clinical studies of rh C1-INH; headache, nausea, and diarrhea were the most common adverse reactions ($\geq 2\%$) with a similar incidence to that reported with placebo.

Immunogenicity

Preexposure and postexposure testing of patients in all the trials demonstrated a very low potential for induction of anti-drug-related or anti-host-related antibodies.²⁸

Thrombogenicity

To date, there have been no signals from the various trials that there is a risk of thromboembolic complications.³⁹

Administration

Ruconest is supplied in 25-mL vials containing 2100 IU rh C1INH for reconstitution with sterile water for injection. It is administered using weight-based dosing of 50 IU/kg as a slow IV injection over 5 minutes and may be self-administered by the patient after appropriate training (see [Table 2](#)).

ECALLANTIDE

Introduction

Ecallantide (Kalbitor Dyax Corp) is a 60-amino acid recombinant protein discovered through phage display technology. A potent kallikrein inhibitor, it blocks the plasma-binding site resulting in reduced bradykinin production. Kallikrein plays a role in the activation of factor XIIa and that function is also blocked by ecallantide.

The absolute bioavailability of ecallantide is approximately 90%; sex, age, and body weight do not significantly affect exposure. Its metabolism is not via cytochrome P-450 isoenzyme pathways, so drug interactions via these isoenzymes are not expected. It is eliminated by the kidneys.

Clinical Trial Data

The efficacy and dosage for ecallantide were studied in 3 phase II and 2 phase III trials known as the EDEMA trials (Evaluation of DX-88's Effect in Mitigating Angioedema). EDEMA 3 and EDEMA 4 had similar designs as randomized, double-blind, placebo-controlled studies enrolling adolescents and adults, using the treatment outcome score and the mean symptom complex severity score as endpoints. Both studies had open-label extension phases. A total of 168 patients were enrolled across the 2 studies. The results from these trials demonstrated that ecallantide is an effective treatment for acute attacks of HAE and acts by both preventing progression and reducing HAE symptoms. In addition to the individual results from EDEMA 3 and EDEMA 4, integrated analysis of the 2 trials further illustrated the effectiveness of ecallantide in relieving acute HAE attacks.^{40–42}

Onset of Action

MacGinnitie and colleagues,⁴³ analyzing results from EDEMA 3 and 4, demonstrated the onset of action of ecallantide to be within 4 hours with median time to improvement of 2 hours. These figures resemble those published for C1-INH (range, 2.0–2.9 hours) and icatibant (range, 2.0–2.5 hours).

Rebound

Bernstein and colleagues⁴⁴ performed a post hoc analysis of EDEMA3 and 4 to investigate the likelihood of relapse or rebound symptoms after ecallantide treatment. One of 42 patients treated with ecallantide included in analysis, demonstrated likely relapse (2.4%), with an additional 3 patients showing possible relapse or rebound (7.2%). Pooled clinical trial data revealed that 12% of ecallantide-treated patients received a second ecallantide dose and this need was associated with the occurrence of peripheral attacks. There was no increase in treatment-related adverse events with a second dose of ecallantide.⁴⁵

Laryngeal Attacks

Treatment response to ecallantide has been shown to be related to anatomic site of the attack, with abdominal and laryngeal attacks responding better than attacks involving peripheral sites.⁴⁶ The efficacy of ecallantide for treating laryngeal attacks has been studied specifically by Sheffer.⁴⁷ The investigator analyzed 4 clinical studies (EDEMA2, EDEMA3, EDEMA4, and DX-88/19) that included 98 patients treated with ecallantide 30 mg subcutaneously for 220 laryngeal attacks. Eighty percent of patients experienced sustained improvement after ecallantide treatment and 63% achieved complete or near-complete resolution of symptoms within 4 hours of dosing.

Special Populations

The Food and Drug Administration extended approval of ecallantide use to 12 years and older in 2014.

Ecallantide is a pregnancy category C as assigned by the Food and Drug Administration because animal studies demonstrated developmental toxicity. The use of ecallantide in breastfeeding women is cautioned against because it is not known whether ecallantide is excreted in breast milk and it is not known what effects it may have on a developing, growing infant (Kalbitor prescribing info revised March 2015; available at: <http://www.kalbitor.com/hcp/remis/pdf/KalbitorFullPrescribing-Information.pdf>).

Adverse Events

In the patients enrolled in EDEMA 3 and 4, treatment-related side effects were reported in 11.1% of patients receiving study drug compared with 13.9% in those receiving placebo. Headache, nausea, fatigue, diarrhea, upper respiratory tract infection, injection site reactions, nasopharyngitis, vomiting, pruritus, abdominal pain, and pyrexia were the most common complaints.

Anaphylaxis

Anaphylaxis occurred in 4% of HAE patients treated with ecallantide.^{48,49} For this reason, ecallantide is only approved for administration by a health care professional in a setting with appropriate medical support (see **Table 1**).

Immunogenicity

There is a risk of antibody formation to ecallantide and this was found in nearly 5% of patients; however, the significance of this is unknown. There seems to be no correlation between antibody formation and anaphylaxis in patients receiving ecallantide nor did antibody formation affect clinical efficacy.⁴⁸

Administration

The drug concentration of each vial of ecallantide is 10 mg/mL; the recommended dose of ecallantide is 30 mg given as three 10-mg subcutaneous injections. The formulation should be kept refrigerated and protected from light. Once removed from the refrigerator, the drug is stable for 14 days (see **Table 2**). Ecallantide is approved for administration by a health care professional in a setting with appropriate medical support. (Kalbitor prescribing info revised March 2015; available at: <http://www.kalbitor.com/hcp/remis/pdf/KalbitorFullPrescribing-Information.pdf>).

ICATIBANT

Introduction

A major mediator of swelling in HAE is bradykinin, exerting its effects via the B2 receptor expressed on vascular endothelium. Binding leads to generation of numerous inflammatory mediators resulting in vasodilatation and edema. Icatibant, as a potent B2 receptor antagonist, has proven to be a specific and effective treatment for HAE attacks. Icatibant is a synthetic decapeptide with a similar structure to bradykinin. It has an excellent bioavailability profile when given subcutaneously, with rapid absorption from the injection site and peak concentrations reached within 30 minutes. It has a terminal half-life of 1 to 2 hours and undergoes hepatic metabolism before renal excretion. Cytochrome P450 enzymes are not involved in the metabolism of icatibant and dose adjustments are not needed in renal and hepatic impairment, although clearance is reduced in old age. It does cross the placenta and in rodent studies was shown to be excreted in breast milk. An open-label study in 15 patients established the dose of 30 mg as optimal.⁵⁰

Studies of Efficacy

The efficacy and safety of icatibant have been evaluated in 3 double-blind, randomized, controlled trials known as FAST (For Angioedema Subcutaneous Treatment) 1, 2, and 3.^{51,52} FAST 2 compared icatibant with tranexamic acid, whereas FAST 1 and 3 were placebo controlled. The inclusion criteria for all 3 FAST studies were individuals, greater than 18 years of age, diagnosed with HAE 1 or 2. Pregnant and lactating women were excluded from the studies.

The FAST-1 trial compared subcutaneous injection of icatibant with placebo in 57 subjects presenting acutely with superficial cutaneous or abdominal angioedema episodes. The primary outcome measure was the time to onset of a 30% symptom improvement, but unfortunately the results for the combined group did not attain statistical significance. This result was attributed to the placebo arm having a higher use of rescue medication including C1-INH increasing the overall perceived effectiveness of the placebo arm.

The FAST-2 trial compared subcutaneous icatibant with oral tranexamic acid using a double-blind, double-dummy design. In this trial, the median time to onset, 30% improvement, and almost complete symptom relief was significantly better in the icatibant group (0.8, 2.0, and 10.0 hours, respectively) than in the tranexamic acid group (7.9, 12.0, and 51.0 hours, respectively).

FAST 3 was a further placebo-controlled, randomized, double-blind trial in 88 subjects with HAE presenting with acute episodes affecting the abdomen, periphery, or airway. The primary endpoint of 50% reduction in symptom scores was significantly different between active treatment (2.0 hours) and placebo (19.8 hours). The time to initial symptom relief was 0.8 hours versus 3.5 hours.

Laryngeal Attacks

Eight patients in FAST 1 and 3 patients in FAST 2 received open-label icatibant for laryngeal attacks and the time to symptom improvement was 0.6 hours and 1.0 hour, respectively. At 4 hours after icatibant administration, 9 of the 11 patients were symptom free and the remaining 2 had mild symptoms.⁵¹ In the FAST 3 trial, a total of 21 subjects with 21 laryngeal attacks received icatibant. The median time to 50% or more reduction in symptom severity was 2.5 hours with icatibant versus 3.2 hours with placebo.⁵²

In a further analysis, Lumry and colleagues⁵³ reported trial data to evaluate the efficacy and safety of icatibant for the repeated treatment of multiple HAE attacks at any location including laryngeal attacks. In groups of patients with 1 to 5 icatibant-treated attacks at any location ($n = 88$), the median times to onset of symptom relief, onset of primary symptom relief and almost complete symptom relief were 1.9 to 2.1, 1.5 to 2.0, and 3.5 to 19.7 hours, respectively. The same outcomes for laryngeal attacks ($n = 25$) were 1.0 to 2.0, 1.0 to 2.0, and 1.5 to 8.1 hours, respectively. The analyses supported the sustained efficacy and safety profile of icatibant when used to treat multiple HAE attacks at any location, including laryngeal.

Adverse Events

Injection site reactions are the most common reported side effect after icatibant injection (see [Table 1](#)). Otherwise, its side effect profile across a number of studies was no different to that of placebo. Animal studies have demonstrated that blocking the B2 receptor can affect coronary blood flow adversely, so acute cardiac or cerebral ischemia and unstable angina are relative contraindications to its use.

Indications and Administration

Icatibant is supplied as a prefilled syringe, 30 mg/3 mL and has a shelf life of 2 years if stored at 4°C (see [Table 2](#)). Currently, it is indicated for the acute treatment of HAE attacks in those 18 years of age and older; however, trials in pediatric populations are underway.

Self-Administration

A large, prospective, open-label phase IIIb (EASSI [Evaluation of the Safety of Self-administration with Icatibant]) study has been conducted to evaluate the safety of

self-administration injections. Overall, self-administration of icatibant for an acute attack of HAE was shown to be safe and effective in the 56 patients evaluated⁵⁴ and icatibant is licensed for patient self-administration.

Other Considerations

Lack of efficacy of tranexamic acid for acute hereditary angioedema attacks

Any consideration that tranexamic acid may be used to treat acute HAE attacks has been removed by the demonstration of lack of efficacy in the FAST 3 trial where it was used as a comparator for icatibant.^{52,55}

FRESH FROZEN PLASMA

In many parts of the world, FFP is the only available treatment for acute HAE attacks. For years, FFP, which contains C1-INH, has been used in treatment of acute attacks of HAE, but there may be worsening of symptoms because of enhanced consumption of C1-INH by substrate proteins. No controlled studies have been conducted investigating its role or efficacy. It involves risks of transmissible infectious disease caused by nonpasteurized fresh frozen plasma products and transfusion reactions. When used, 2 U of FFP are given, repeating after 2 to 4 hours until there is benefit (see [Table 2](#)).⁵⁶

Preparedness to Intubate

There are now a number of options for the acute treatment of upper airway edema in HAE. Patients need careful education about the early signs and symptoms of upper airway involvement and the need for prompt administration of their medical therapy. It is essential that, if upper airway swelling occurs, they present as soon as possible to a medical facility where intensive care management is available and they can be observed until complete resolution of symptoms. If alarming signs of airway obstruction (such as stridor, dyspnea, and signs of respiratory arrest) occur, airway patency should be reestablished and oxygen administered. If stridor, hoarseness, or hypoxemia are present, immediate intubation is essential. The severity of the edema may interfere with endotracheal intubation, requiring airway patency be restored by surgical intervention when intubation is not feasible.⁵⁷

Patient Self-Administration

Recent consensus guidelines emphasize the importance of patients having prompt access to therapies for management of acute attacks known as “on-demand therapy.”^{16,58–60} In this model of care, patients are trained to self-administer treatment either by subcutaneous injection for icatibant or by intravenous infusion for C1 inhibitor concentrate. This allows early treatment of attacks and limits the time of disability and discomfort caused by an attack as well as preventing complications resulting from progression to severe angioedema symptoms.

SUMMARY

Over the last decade, the development of new treatments and demonstration of their efficacy in placebo-controlled clinical trials have dramatically improved the outlook for patients with HAE. Recognition of the importance of comprehensive education and training in self-management have created the opportunity for autonomy and prompt treatment for many patients with HAE, thereby reducing greatly the impact of this distressing condition on daily life.⁵⁸

Unfortunately, effective and timely management of HAE attacks is not an option for those who live in developing countries, where these drugs are not available. All the agents discussed are high-cost drugs and their availability is limited in many parts of the world. Our challenge is to find mechanisms by which effective treatment may be made available to all who have a diagnosis of HAE. There is still much to learn about the best and most cost-effective management strategies for the individual patient with HAE. Ultimately, we look forward to a time when acute management of attacks is not necessary as new agents are developed with the capacity to restore homeostasis and completely prevent occurrence of angioedema attacks.

REFERENCES

1. Bernstein JA, Levy R, Wasserman RL, et al. Treatment of acute abdominal and facial attacks of hereditary angioedema (HAE) with human C1 esterase inhibitor (C1-INH): results of a global, multicenter, randomized, placebo-controlled, phase II/III study (I.M.P.A.C.T.1). *J Allergy Clin Immunol* 2008;121(3):795.
2. Wasserman RL, Levy RJ, Bewtra AK, et al. Prospective study of C1 esterase inhibitor in the treatment of successive acute abdominal and facial hereditary angioedema attacks. *Ann Allergy Asthma Immunol* 2011;106(1):62–8.
3. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;363(6):513–22.
4. Riedl MA. Update on the acute treatment of hereditary angioedema. *Allergy Asthma Proc* 2011;32(1):11–6.
5. Bhardwaj N, Craig TJ. Treatment of hereditary angioedema: a review (CME). *Transfusion* 2014;54(11):2989–96.
6. Bork K. Current management options for hereditary angioedema. *Curr Allergy Asthma Rep* 2012;12(4):273–80.
7. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012;109(6):395–402.
8. Craig TJ, Wasserman RL, Levy RJ, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J Clin Immunol* 2010;30(6):823–9.
9. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009;124(4):801–8.
10. Christiansen SC, Zuraw BL. Hereditary angioedema: management of laryngeal attacks. *Am J Rhinol Allergy* 2011;25(6):379–82.
11. Farkas H, Harmat G, Füst G, et al. Clinical management of hereditary angioedema in children. *Pediatr Allergy Immunol* 2002;13(3):153–61.
12. Bork K, Hardt J, Schicketanz K-H, et al. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch Intern Med* 2003;163(10):1229–35.
13. Lumry W, Manning ME, Hurewitz DS, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. *J Pediatr* 2013;162(5):1017–22.e1–2.
14. Schneider L, Hurewitz D, Wasserman R, et al. C1-INH concentrate for treatment of acute hereditary angioedema: a pediatric cohort from the I.M.P.A.C.T. studies. *Pediatr Allergy Immunol* 2013;24(1):54–60.
15. Craig TJ, Schneider LC, MacGinnitie AJ. Plasma-derived C1-INH for managing hereditary angioedema in pediatric patients: a systematic review. *Pediatr Allergy Immunol* 2015;26(6):537–44.

16. Craig T. WAO Guidelines for the management of hereditary angioedema. *WAO Journal* 2012;5:182–99.
17. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. *Allergy Asthma Clin Immunol* 2010;6(1):18–28.
18. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents—a consensus on therapeutic strategies. *Eur J Pediatr* 2012;171(9):1339–48.
19. Riedl MA, Hurewitz DS, Levy R, et al. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. *Ann Allergy Asthma Immunol* 2012;108(1):49–53.
20. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med* 2012;125(9):938.e1–7.
21. Bork K, Steffense I, Neme A, et al. A systematic review of the efficacy and safety of a purified, pasteurized C1 inhibitor concentrate for the treatment of patients with type I or II hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;6(Suppl 1):P32.
22. De Serres J, Gruter A, Linder J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. *Transfus Apher Sci* 2013;29(3):247–54.
23. Bork K. Pasteurized and nanofiltered, plasma-derived C1 esterase inhibitor concentrate for the treatment of hereditary angioedema. *Immunotherapy* 2014;6(5):533–51.
24. Zanichelli A, Wu MA, Andreoli A, et al. The safety of treatments for angioedema with hereditary C1 inhibitor deficiency. *Expert Opin Drug Saf* 2015;14(11):1725–36.
25. Craig TJ, Bewtra AK, Hurewitz D, et al. Treatment response after repeated administration of C1 esterase inhibitor for successive acute hereditary angioedema attacks. *Allergy Asthma Proc* 2012;33(4):354–61.
26. Cicardi M, Zingale LC, Zanichelli A. A patient with hereditary angioedema who experienced anaphylaxis in response to C1 esterase inhibitor is successfully treated with DX-88 (Ecallantide), a potent human kallikrein inhibitor: a case study. *Mol Immunol* 2007;44:160–1.
27. Riedl MA, Bygum A, Lumry W, et al, Berinert Registry Investigators. Safety and usage of C1-inhibitor in hereditary angioedema: berinert registry data. *J Allergy Clin Immunol Pract* 2016;4(5):963–71.
28. Riedl M. Recombinant human C1 esterase inhibitor in the management of hereditary angioedema. *Clin Drug Investig* 2015;35(7):407–17.
29. Ruconest prescribing information. Available at: <https://www.ruconest.com/hcp/>. Accessed January 10, 2016.
30. Cruz MP. Conestat Alfa (Ruconest). *Pharm Ther* 2015;40(2):109–14.
31. Farrell C, Hayes S, Relan A, et al. Population pharmacokinetics of recombinant human C1 inhibitor in patients with hereditary angioedema. *Br J Clin Pharmacol* 2013;76(6):897–907.
32. Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010;126(4):821–7.e14.
33. Riedl MA, Bernstein JA, Li H, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2014;112(2):163–9.e1.

34. Reshef A, Moldovan D, Obtulowicz K, et al. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study. *Allergy* 2012; 68(1):118–24.
35. Moldovan D, Reshef A, Fabiani J, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. *Clin Exp Allergy* 2012;42(6):929–35.
36. Riedl MA, Levy RJ, Suez D, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. *Ann Allergy Asthma Immunol* 2013;110(4):295–9.
37. Li HH, Moldovan D, Bernstein JA, et al. Recombinant human-C1 inhibitor is effective and safe for repeat hereditary angioedema attacks. *J Allergy Clin Immunol Pract* 2015;3(3):417–23.
38. Caliezi C, Wuillemin WA, Zeerleder S, et al. C1-Esterase inhibitor: an anti-inflammatory agent and its potential use in the treatment of diseases other than hereditary angioedema. *Pharmacol Rev* 2000;52(1):91–112.
39. Relan A, Bakhtiari K, van Amersfoort ES, et al. Recombinant C1-inhibitor: effects on coagulation and fibrinolysis in patients with hereditary angioedema. *BioDrugs* 2012;26(1):43–52.
40. Levy RJ, Lumry WR, McNeil DL, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol* 2010;104(6):523–9.
41. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 2010;363(6):523–31.
42. Sheffer AL, Campion M, Levy RJ, et al. Ecallantide (DX-88) for acute hereditary angioedema attacks: integrated analysis of 2 double-blind, phase 3 studies. *J Allergy Clin Immunol* 2011;128(1):153–4.
43. MacGinnitie AJ, Campion M, Stolz LE, et al. Ecallantide for treatment of acute hereditary angioedema attacks: analysis of efficacy by patient characteristics. *Allergy Asthma Proc* 2012;33(2):178–85.
44. Bernstein JA, Shea EP, Koester J, et al. Assessment of rebound and relapse following ecallantide treatment for acute attacks of hereditary angioedema. *Allergy* 2012;67(9):1173–80.
45. Li HH, Campion M, Craig TJ, et al. Analysis of hereditary angioedema attacks requiring a second dose of ecallantide. *Ann Allergy Asthma Immunol* 2013; 110(3):168–72.
46. Bernstein JA, Qazi M. Ecallantide: its pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Expert Rev Clin Immunol* 2010;6(1):29–39.
47. Sheffer AL. Hereditary angioedema: optimal therapy. *J Allergy Clin Immunol* 2007;120(4):756–7.
48. Garnock-Jones KP. Ecallantide in acute hereditary angioedema: profile report. *BioDrugs* 2011;25(1):51–3.
49. Craig TJ, Li HH, Riedl M, et al. Characterization of anaphylaxis after ecallantide treatment of hereditary angioedema attacks. *J Allergy Clin Immunol Pract* 2015;3(2):206–12.e4.
50. Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 2007;119(6):1497–503.
51. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010;363(6):532–41.
52. Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B₂ receptor antagonist icatibant for the treatment of acute attacks of

- hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 2011; 107(6):529–37.
53. Lumry WR, Farkas H, Moldovan D, et al. Icatibant for multiple hereditary angioedema attacks across the controlled and open-label extension phases of FAST-3. *Int Arch Allergy Immunol* 2015;168(1):44–55.
 54. Ghazi A, Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. *Biologics* 2013;7:103–11.
 55. Longhurst HJ. Management of acute attacks of hereditary angioedema: potential role of icatibant. *Vasc Health Risk Manag* 2010;6:795–802.
 56. Longhurst HJ. Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? *Int J Clin Pract* 2005; 59(5):594–9.
 57. Farkas H. Management of upper airway edema caused by hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;6(1):19–27.
 58. Zanichelli A, Mansi M, Azin GM, et al. Efficacy of on-demand treatment in reducing morbidity in patients with hereditary angioedema due to C1 inhibitor deficiency. *Allergy* 2015;70(12):1553–8.
 59. Zuraw BL, Bernstein JA, Lang DM. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol* 2013;131:1491–3.e25.
 60. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012;67(2): 147–57.