

Update on treatment of hereditary angioedema

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Summary

Background: Hereditary Angioedema (HAE) is a rare disease characterized by recurrent, self-limiting episodes of swelling. New therapies have recently emerged and are now available; however, many physicians are not aware of the new medications, and their indications and contraindications.

Objective: To update allergists and primary care physicians on new advances in HAE therapies.

Data sources: A PubMed literature search was used to develop this manuscript.

Study Selections: English language peer-reviewed angioedema articles were selected. High quality Phase II and III placebo-controlled clinical trials were reviewed and summarized.

Results: Until 2008, therapy for HAE consisted of symptom relief with narcotics, hydration and fresh frozen plasma (FFP). Androgens and FFP are frequently used despite multiple, significant side effects. Newer therapies include C1-inhibitor - both human plasma derived and recombinant - as well as contact system modulators such as ecallantide and icatibant. All of these products can be used for treatment of acute attacks of HAE, and C1-inhibitors can also be used for prophylaxis.

Conclusion: New, disease-specific therapies have recently emerged which are more efficacious, are proven to work by placebo-controlled studies, have minimal adverse effects, and can be utilized for the treatment of HAE. (*Asian Pac J Allergy Immunol 2012;30:89-98*)

Key words: hereditary angioedema - treatment, prophylaxis, C1-esterase inhibitor, bradykinin, recombinant C1-inhibitor, c1-inhibitor, ecallantide, icatibant

Abbreviations

BK2R	=	bradykinin 2 receptor
C1-INH	=	C1-inhibitor
FFP	=	fresh frozen plasma
HAE	=	Hereditary Angioedema
IV	=	intravenous
nfC1-INH	=	nano-filtered C1-inhibitor
pdC1-INH	=	plasma derived C1-inhibitor
rhC1-INH	=	recombinant C1-inhibitor
SDP	=	solvent detergent treated plasma
TA	=	tranexamic acid

Introduction

Hereditary angioedema (HAE) is a rare disease characterized by self-limiting tissue swelling. Data regarding the epidemiology of angioedema is limited. The incidence of HAE is one in 10,000-50,000 people in the United States.¹ Mortality rates are estimated at 15-33%, resulting primarily from laryngeal edema and asphyxiation. HAE leads to 15,000-30,000 emergency department visits per year.¹

The underlying cause of HAE is attributed to autosomal-dominant inheritance of mutations in C1-INH gene (SERPING1 gene), which is mapped to chromosome 11 (11q12-q13.1). More than 200 mutations of this gene have been linked to the clinical HAE manifestations.²⁻⁴ The majority of HAE patients have a family history; however, 25% are the result of new mutations.

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Two types of HAE account for the majority of cases. An estimated 85% of patients have Type-1 HAE, characterized by low production of functionally active C1-INH. Type-2 HAE is characterized by normal or elevated levels of C1-INH, but with functional impairment of the protein. Type-3 HAE has similar clinical manifestations to the first two types, but differs in that there are no abnormalities in C1-INH level or function.⁵ A mutation in coagulation factor XII protease (Hageman factor) is suspected to occur in some cases of Type-3 HAE, but causation has not been documented.^{6,7} Type-3 HAE typically affects women, but case reports involving men have also been identified.⁸ This manuscript will focus on type 1 and 2 HAE.

There is a significant age-related difference in frequency of HAE attacks, with an increase at the time of puberty.^{9,10} The earliest onsets of HAE occur within the first year of life but the majority of cases present before 20 years of age. Another 15% develop their first episode later in young-adult life, with only approximately 4% of patients experiencing the first attack after age 40¹¹. Some patients experience early signs of an evolving attack, but the severity and location of the attack can be unpredictable.¹² The number of attacks also varies among individuals. Evidence indicates that patients with onset of symptoms before age five have attacks more frequently than those who develop angioedema after 15 years of age.¹¹ The diagnosis of HAE is commonly delayed, with the average time from the beginning of symptoms to diagnosis ranging between 13 and 21 years.¹³ This delay results in significant morbidity and mortality in affected patients.

Clinical presentation of HAE can involve any area of skin, upper airway, or abdomen. The disease commonly affects extremities and can cause temporary debilitation and disfigurement that can last for up to a week. Facial edema may occasionally progress to laryngeal swelling, which can be life threatening, causing prolonged intensive respiratory care or even death from asphyxia. Laryngeal edema is most common in patients between 11 and 45 years of age, and untreated laryngeal edema can lead to urgent ventilator support and monitoring in intensive care units.¹⁴

Abdominal HAE represents a different scope of medical and social problems for patients. During abdominal attacks, patients may experience significant pain, which may be misdiagnosed as a

surgical abdominal emergency. There are reports that HAE can mimic acute appendicitis and it is not unusual that patients have multiple abdominal surgeries before the realization that the pain is HAE.¹⁵ Abdominal attacks can last for 1 to 8 days, causing significant morbidity. HAE can also be a cause of acute genital swelling.¹⁶

Therapy for HAE consists of treatment of acute attacks, as well as short-term and long-term prophylaxis.¹⁷ Until recently, except in Western Europe, therapeutic options for HAE were limited, and consisted of androgens, narcotics, hydration and fresh frozen plasma (FFP).¹⁸ Androgens are used for both short and long term prophylaxis and are effective, but the long term use may have significant adverse events especially when the dose exceeds 200 mg a day of danazol. The risk of blood-borne disease transmission with FFP exceeds the risk of transmission from C1-inhibitors, and unlike C1-inhibitors, controlled data demonstrating efficacy of FFP is absent. Also, worsening HAE attacks have been reported, however, not in the literature.

New therapies have dramatically changed the management of HAE. However, many physicians are not aware of the indications, contraindications, dosing, and adverse events of the medications that have recently been introduced.¹⁹ The goal of this manuscript is to review the newly approved HAE therapies.

Diagnosis confirmation

According to the 2010 International Consensus algorithm for the diagnosis, therapy and management of HAE, diagnosis should be confirmed by measuring serum complement factor 4 (C4) and serum C1-inhibitor protein and functional levels.²⁰ Low levels of C4 and C1-INH in a young patient with family history of HAE confirm the diagnosis of HAE Type-1. Low levels of C4 and normal or high levels of C1-INH suggest type 2 and a functional assay that is low would confirm the suspicion. In patients without family history, especially if symptoms develop later in life, a C1q level should be obtained. Low levels of C1q would suggest acquired angioedema, which will not be discussed in this manuscript. Normal levels of C4 and C1-INH in a person that has typical symptoms should be reconfirmed during the acute attack. Normal results rule out HAE Type-1 and Type-2 and require consideration of angioedema types other than HAE Type-1 and Type-2 (such as angioedema

secondary to ACE inhibitors, HAE Type-3 or histamine induced angioedema).

Therapeutic Interventions

Supportive therapy combined with specific therapies discussed below is the preferred therapy for attacks of HAE Type-1 and Type-2.²⁰

Treatment of Acute Attacks

The current consensus is to treat acute attacks as early as possible.¹⁷ Treatment involves supportive measures (hydration, pain relief) and prompt use of the disease-specific treatment (plasma derived C1-inhibitor or contact system modulators) (Table 1). If these first line drugs are not available, solvent detergent treated plasma (SDP) or fresh frozen plasma (FFP) may be used as second line agents.²⁰ Treatment with epinephrine, corticosteroids and antihistamines are not recommended but still frequently used despite the lack of effectiveness. Intubation may be required during an acute attack for the purposes of airway protection and a focus on maintaining the airway should take priority. C1-INH replacement drugs include:

Berinert, CSL Behring - approved in Europe, Argentina, Australia and North America at 20 units/kg IV for acute attacks.

Cetor, Sanquin- approved in the Netherlands, Belgium and Turkey at 1000 units IV for acute attacks.

Cinryze, Viropharma – approved in the U.S. and EU at 1000 units IV for acute attacks, short term prophylaxis and 1000 units IV twice a week for prophylaxis.

Recombinant C1-INH products (rcC1-INH) include:

Rhucin in the U.S. and Ruconest in Europe; Pharming - approved for use in the European Union at 50 units/kg and undergoing Phase III studies in North America.

C1-INH concentrate derived from human plasma has been utilized for the treatment of acute HAE for over three decades in Europe.^{21,22} There are now published Phase III clinical trials for all the C1-INH products providing Level I evidence for the efficacy of these drugs in adults.¹⁷ pdC1-INH is not yet approved for pediatric use, or during pregnancy or lactation.²³

pdC1-INH: Berinert (CSL Behring, King of Prussia, USA) has been approved in the U.S. since

2009 for acute attacks of HAE.²² In January 2012, IV Berinert was approved for self-administration therapy of acute HAE attacks. The largest randomized, double-blind, prospective, placebo controlled study, called International Multicenter Prospective Angioedema C1-inhibitor Trial (I.M.P.A.C.T), confirmed the efficacy and safety of Berinert in treatment of acute facial and abdominal HAE attacks. The I.M.P.A.C.T.1 trial demonstrated that 20 U/kg C1-INH is effective in treating acute abdominal and facial HAE attacks.²² I.M.P.A.C.T.2 was an open-label extension study of I.M.P.A.C.T.1 to evaluate the safety and efficacy of long-term treatment with C1-INH for successive HAE attacks at anybody location.²⁴ I.M.P.A.C.T.2 study concluded that a single dose of 20 U/kg C1-INH is safe and provides reliable efficacy in the long-term treatment of successive HAE attacks.²⁵ The study reported no treatment-related safety concerns or neutralizing antibodies. These Phase III trials provided Level I evidence for dosing at 20 units per kilogram intravenously. The most common adverse reactions, reported in over 4% of the subjects who received C1-INH, were headache, abdominal pain, nausea, muscle spasms, pain, diarrhea and vomiting.²² Most of these adverse events are thought to be secondary to symptoms related to the HAE attack and not the medication.²⁵

Sanquin (Leiden, The Netherlands) produces C1-INH concentrate in Europe (Cetor) and has been available in Netherlands since 1997. Sanquin also produces **Cinryze** (Viropharma, PA). Cinryze is a nano-filtered pasteurized C1-INH (nfC1-INH) concentrate for IV use. It was FDA approved in October, 2008 for adolescent and adult prophylaxis at a dose of 1000 units every three to four days. It has recently been approved in the EU for acute attacks and for prophylaxis.^{26,17}

CHANGE (C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy) Trial was a randomized double-blind, placebo-controlled study performed to assess the efficacy and safety of nf-C1-INH in treatment of acute attacks of HAE.²⁶ The time to beginning of unequivocal relief (primary endpoint) was measured, which was significantly shorter in the nf-C1-INH group (median time 2 hours) than in the placebo group (median time > 4 hours) ($p = 0.026$). However, the primary outcome was not robust enough and Cinryze was not approved in the U. S. for acute attacks.

Table 1. Comparison of HAE Medications.

Drug	Advantages	Disadvantages	Best use	Status
Plasma-derived C1-INH	Extensive clinical experience Corrects the fundamental defect Long half-life	Infectious risk Needs IV access Limited supply	Acute attacks Short-term Long-term prophylaxis Prodromes	Beriner: FDA approved for acute attacks Cinryze: FDA approved for prophylaxis Cetor in the EU
Recombinant C1-INH	Corrects the fundamental defect No human virus risk Scalable supply	Needs IV access Short half-life Potential for allergic reactions	Acute attacks Short prophylaxis Prodrome	Rhucin: awaiting FDA review
Ecallantide	More potent than No infectious risk Subcutaneous administration	Antibodies may cause allergic reaction or neutralization Short half-life	Acute attacks in office	Kalbitor: FDA approval for administration by health care provider
Icatibant	No infectious risk Stable at room temperature Subcutaneous	Short half-life Local pain or irritation	Home treatment of acute attacks	Firazyr: approved in Europe and recently in the USA
FFP	Inexpensive	Higher risk of viral transmission and may worsen HAE attacks	Short-term prophylaxis and for attacks	No controlled studies have demonstrated effectiveness and it is not FDA approved for HAE
Androgens	Inexpensive, oral and effective	Adverse effects are frequent	Short and long-term prophylaxis	Danazol: approved for HAE. Doses above 200 mg a day may be cause risk to outweigh benefit

Footnote: C1-INH= C1-inhibitor, FFP= fresh frozen plasma, IV= intravenous, FDA= Food and Drug Administration, EU= European Union, HAE= hereditary angioedema.

A cross-over study utilizing nf-C1-INH as long-term prophylaxis led to the approval of nf-C1-INH in the U.S. and more recently in the EU. The primary end point of the study was the number of attacks while taking the drug vs. placebo (6.1 vs. 12.7, $p < 0.0001$). The secondary end point was days of swelling, duration of symptoms, and severity of symptoms, and all three showed a significant benefit. Based on these data, nf-C1-INH received FDA approval for the prophylactic treatment of HAE.²⁶

Adverse events recorded during the study were sinusitis, rash (21.7%), headache, upper respiratory tract infection (17.4%), viral upper respiratory tract infection (13%), gastro-esophageal reflux disease, pruritus and vomiting (8.7%).²⁶ No events were reported to have led to death.

Recombinant C1-INH: In North America, rcC1-INH is **Rhucin** and in Europe, it is known as **Ruconest** (Pharming Technologies BV, Leiden, The Netherlands). It is a recombinant human C1-INH protein isolated from the milk of transgenic

rabbits.^{27,28} It has been approved by the European authorities for use in the European Union since 2008 at a dose of 50 U/kg. Pharming is currently repeating Phase III studies in the U.S. for treatment of acute attacks.

The half-life of Rhucin is dose dependent and the longest of approximately three hours was observed at the dose 100 U/kg. Because of the short half-life, Rhucin is expected to be more effective in treatment of acute HAE attacks than prophylaxis. In multiple studies, adverse effects were minimal and no immunogenic reactions against rhC1-INH or rabbit protein were observed.²⁷

In a Phase III randomized, double-blind, placebo controlled study of rhC1-INH for acute attacks of HAE, two different doses of rhC1-INH - 100 U/kg or 50U/kg - were used. This trial provided Level I evidence for use of this drug and concluded that 100 units per kg was no more effective than 50 units per kg.²⁸ The primary end point was time to onset of relief. Median time to onset was 68 minutes at the rhC1-INH dose of 100 U/kg, 122 minutes at dose 50 U/kg and 258 minutes for placebo. This study

demonstrated the effectiveness of this agent in all localizations of hereditary angioedema attacks.²⁹ Several studies demonstrated that a dose of 50 U/kg increases plasma C1-INH activity in almost all patients to values >0.7 U/ml (70% of normal), which is the lower limit of the normal range.^{28,30,31}

In conclusion, rcC1-INH appears to be safe and effective and only contraindicated in those with hypersensitivity to rcC1-INH or rabbits.²⁸ One subject who failed to disclose a history of rabbit allergy developed hives and wheezing. Except for differences in glycosylation, which results in a shorter half-life, rhC1-INH is very similar in action to native human C1-INH.³¹ The recombinant technology yields large amounts of fully functional C1-INH protein; however, due to unique carbohydrate additions (glycosylation) and residual rabbit proteins, there is a possibility that anaphylaxis may occur. Patients should be screened for rabbit allergy and the drug avoided if allergic. Thus far, allergic reactions to glycosylated protein have not been described. The benefits of rhC1-INH are that it carries no risk of transmission of human blood-borne pathogens, and production of the drug can be more easily controlled.

Contact System Modulators: Other treatment options work as kinin pathway modulators. Two representatives of this class are Ecallantide and Icatibant.

Contact system modulators:

Ecallantide, Dyax, DX-88, Kalbitor - approved in the U.S at 30 mg subcutaneous for attacks of HAE.

Icatibant, Firazyr – approved for use in the European Union and in the U.S. (2011) at 30 mg subcutaneous for attacks of HAE.

Ecallantide (DX-88, Kalbitor, Dyax Corp, Cambridge, Massachusetts) represents a novel treatment option for patients with HAE. The recommended dose is 30 mg subcutaneously. It has been approved for treatment of acute attacks in the U.S. since December 2009. It is not recommended for self-injection at home because of the risk of anaphylaxis.

Ecallantide is a 60-amino acid recombinant protein that acts as a potent reversible inhibitor of plasma kallikrein.³² It has a rapid on-rate and a slow off-rate that results in high affinity binding and inhibition of kallikrein. Maximum ecallantide levels are reached 2-3 hours following subcutaneous

injection, and the half-life is approximately 2 hours.³³

Two separate randomized, double-blind, placebo-controlled Phase III studies of ecallantide have been performed, and provided Level I one evidence for use of this drug. The first trial's (EDEMA3) primary endpoint was patient-reported Treatment Outcome Score (TOS) at four hours, which ranged from +100 (designated in the protocol as significant improvement in symptoms) to -100 (significant worsening of symptoms).³³ Ecallantide patients reported a mean TOS score of 49.5 ± 59.4 (improved) vs. 18.5 ± 67.8 for placebo. The improvement was maintained over 24 hours. The second trial's (EDEMA4) primary outcome was Mean Symptom Complex Severity (MSCS) at 4 hours - a patient evaluation of symptoms at a specific time measured by a score range of 0 (none) to 5 (severe). Lower MSCS from baseline was interpreted as improvement. Patients in this trial reported a mean decrease of symptom score at 4 hours of 0.81 on Ecallantide vs. 0.37 on placebo ($p=0.01$).³⁴ A post hoc integrated analysis of the EDEMA4 and EDEMA3 clinical trials showed that change from baseline in MSCS and TOS was significantly better with ecallantide versus placebo for patients treated $>2-4$ hours after symptom onset ($n = 46$; $p = 0.002$; $p = 0.003$) and $>4-6$ hours after onset of symptoms ($n = 47$; $p = 0.044$; $p = 0.043$).³⁵

The most common reported side effects of ecallantide were headache, nausea, fatigue and upper respiratory infections. Hypersensitivity within 60 minutes after a dose, including anaphylaxis, has been reported in approximately 3.0% of patients, thus prompting a black box warning. The FDA mandated that this drug be administered by health care providers experienced in treating anaphylaxis.^{36,37}

Icatibant (Firazyr, Shire, Ireland) is another kinin modulator. It is a synthetic decapeptide, which is a specific and selective competitive antagonist of bradykinin B2 receptor (BK2R). It has been approved for use in treatment of HAE attacks in the European Union, United States, Brazil, Australia and other countries as a 30 mg subcutaneous injection.³⁶

For approval, three Phase III studies were done and called "For Angioedema Subcutaneous Treatment" (FAST-1, 2 and 3). FAST-1 was a double-blinded, placebo-controlled study. The treatment with icatibant significantly shortened onset time of symptom relief (0.8 vs. 16.9 hours, p



<0.001); however, it failed to meet the primary outcome statistical difference in median time to significant symptom relief (2.5 vs. 4.6 hours, $p = 0.142$). The latter required Shire to repeat their Phase III study (FAST-3) in the U.S. (36). The FAST-2 trial was more successful. Patients received either 30 mg subcutaneous injection of icatibant or tranexamic acid. The time to onset of symptom relief was 0.8 vs. 7.9 hours ($p < 0.001$). Based on the results from these trials, the European Commission granted marketing authorization for icatibant for treatment of acute HAE attacks within the European Union.³⁶ Recent studies showed efficacy of icatibant was not impaired by repeated administrations and no drug-related serious adverse events were reported.³⁸ Most common side effects reported in clinical studies were limited to localized erythema and edema at the site of injection, with occasional minor burning sensations, which resolved within a few hours.

Second-line drugs

If first line drugs described above are not available, solvent detergent treated plasma (SDP) or FFP may be used as second line agents.²⁰ Active C1-INH is one of the ingredients in FFP, which replenishes the protein. FFP has been shown to be effective, but without blinded, controlled studies.^{20,39} Reservations about the use of FFP are greater risk of blood-borne pathogens when compared to C1-INH concentrate and anecdotal reports of worsening of angioedema after administration of FFP or SDP secondary to the kinin substrate contained in the products. Nonetheless, data support that SDP/FFP is effective and tolerated in the majority of cases, but should be used only when C1-INH, icatibant or ecallantide are not available.³⁹

Prophylaxis

Prophylaxis of HAE attacks includes short and long-term prophylaxis. Short-term prophylaxis is therapy intended to protect against an angioedema attack for an important event or for a known trigger. Triggers include dental procedures, surgical procedures, and stressful life events (including illness in family members, exam times, employment seeking, marriage, etc.).¹⁷

Long-term prophylaxis is used to prevent attacks. It is indicated for patients with frequent (defined as more than 24 days per year with angioedema symptoms even if mild or more than 12 severe attacks per year) or severe attacks, past laryngeal attacks, excessive loss of work or school, significant

anxiety, and poor quality of life.¹ More recent guidelines by Bowen et al. suggest chronic prophylaxis is indicated for those who can not be well controlled by treatment of acute attacks.

Short-term prophylaxis

Data are needed to compare different therapies for short-term prophylaxis. C1-INH has been used as a 500 unit dose, a 1000 unit dose and dosed at 20 units/kg single dose. The best comparative data are from Bork, K et al from 2011 (submitted for publication). He compared placebo and different doses of C1-INH, and found 1000 units to be the most effective dose, with both 500 and 1000 units being superior to placebo. He did not give higher doses nor units per kg, but it appears that higher doses may be necessary to completely prevent angioedema after oral procedures since a small percentage had angioedema even with the 1000 unit dose.

An alternative for short-term prophylaxis is danazol 200 mg by mouth three times daily for 5-7 days prior to a procedure and 2 days after the procedure.⁴⁰ Effectiveness of androgens compared to C1-INH has not been studied. Adverse events when androgens are used for short term prophylaxis are minimal. It is still unknown whether rhC1-INH at 50 units per kg single dose or the Bradykinin B2 receptor inhibitor would be effective for short term prophylaxis because of their short half lives.

Long-Term prophylaxis

Therapies for chronic prophylaxis include attenuated androgens, C-1-esterase inhibitor and anti-fibrinolytics. Danazol is the most commonly used androgen and can be used at 200 TID; however, newer recommendations suggest that the maximal dose of danazol should be 200 mg a day to avoid adverse events such as hepatitis. Three other androgens (methyltestosterone, stanozolol and oxandrolone) can be used as alternatives. Stanozolol is no longer available unless it is specifically compounded. Oxandrolone is the preferred androgen for the pediatric population.²⁴ Because of the wide range of potential adverse effects (weight gain, hypertension, dyslipidemia, acne, virilization, menstrual irregularities, decreased libido, hepatic necrosis, premature closure of growth plates, and hepatic neoplasms) patients treated with attenuated androgens should be closely monitored. Because of premature closure of the epiphyseal plate and virilization, the use of androgens are often delayed until after puberty, with the exception of use in short

term prophylaxis for which these risks are minimized.^{24,41} Therapy should be adjusted based solely on clinical response and not on serial assessment of C4 or other laboratory tests. Most experts in HAE recommend blood pressure, liver function studies and lipid panels be monitored initially and every 6 months and a liver ultrasound every 12 months.^{24,20}

The Phase III study done for FDA approval of nfC1-INH (Cinryze) demonstrated that it is effective as a prophylactic agent to reduce the number of attacks. The approximate reduction in attacks was 50%. Adverse events recorded during this trial were minimal and there were no recorded episodes of anaphylaxis or sero-conversion to HIV, hepatitis A, B or C, or parvovirus.⁴² These data led to the FDA approval for nfC1-INH as prophylactic therapy at 1000 units twice a week by intravenous infusion. A dose arranging study is presently being performed to access the efficacy of higher doses of C1-INH. As with acute therapy for attacks, any of the plasma derived C1-INH should be equally effective at equal doses.

Antifibrinolytic (AF) agents (epsilon aminocaproic acid and tranexamic acid) may be used when androgens are contraindicated or poorly tolerated and when other treatments have failed. Most experts recommend avoiding AF during pregnancy and lactation. AF are generally thought to be less effective than androgens.⁴¹ AF are often recommended as a drug of choice in children with severe HAE; however, off label use of C1 INH is an alternative, with the main limitation being a cost. The side effects of AF include hypotension, cardiac arrhythmias, rhabdomyolysis, thrombus formation, and associated risk of emboli. Epsilon aminocaproic acid has now been replaced with tranexamic acid (TA) because of its fewer side effects and better tolerability. In addition, TA is used for treatment of acute attacks of HAE in Europe, but is not very effective.⁴³ Because of possible teratogenic effects of tranexamic acid in animals, this drug is rarely used in the United States.²⁰

Discussion

HAE is a serious, chronic disease that requires a highly specialized approach to treatment. Traditional treatment of histamine-induced edema with epinephrine, corticosteroids, and antihistamines is still frequently used for the treatment of HAE in the United States, despite data demonstrating ineffectiveness of these medications.⁴⁴ FFP is often

used for treatment of HAE attacks and for short term prophylaxis. However, the use of FFP should be reserved for situations when C1-INH, icatibant or ecallantide are not available for acute attacks, or when C1-INH and androgens are not available for pre-procedural therapy.³⁹

New therapies of HAE have recently emerged and dramatically changed the management of HAE by switching the focus from symptomatic to more disease-specific treatments. The appropriate use of disease-specific treatments for HAE improve patients' quality of life and reduce HAE-associated morbidity and mortality while also reducing costs associated with hospitalizations and other emergency interventions. However, many of the newer treatments represent financial challenges due to high costs, which are not always balanced by the reduction of other medical expenses.⁴⁵ The cost of C1-INH can approach \$2 million USD per year if infused in an infusion room and \$655,682 USD with self-injections.⁴⁶ Future cost-effectiveness studies are needed to examine how approved therapies alter cost and quality of life.

Among the available new treatment modalities for chronic prophylactic therapy, C1-INH concentrates represent an alternative treatment for prevention of HAE attacks. FDA has approved chronic prophylactic use of nfC1-INH based on limited data, and it will be important that physicians monitor adverse events carefully. Thus far, it appears that the chronic use of C1-INH is safe and effective; however, an increased risk of thrombosis was associated with the use of C1-INH administered prophylactically via a central line.⁴⁷ Dosing should be 1000 units IV twice a week based upon half-life of C1-INH, but it is anticipated that higher doses will be more effective for preventing attacks. Rescue treatment should be prescribed since breakthrough attacks occur despite chronic prophylaxis. The main limiting factor for use of C1-INH chronic prophylaxis is cost.²⁰ Most experts recommend a trial of Danazol at 200 mg by mouth once daily as initial prophylaxis, and if the danazol is effective, tolerated well and without adverse effects, to continue this therapy. If adverse effects develop or androgens are tolerated poorly, then a trial on C1-INH should be considered. Adverse effects from C1-INH have been minimal. Multiple screening steps, viral inactivation techniques, and viral removal steps decrease the risk of potential viral transmission associated with the use of C1-INH.⁴⁸ Vaccination with Hepatitis A and B and



screening serologies to Hepatitis B, C and E, HIV and parvovirus should be done prior to initiation of C1-INH, and yearly while on therapy.^{20,42}

Compared to human derived C1-INHs, rhC1-INH (Rhucin) is unique in the absence of risk of human blood-borne pathogen transmission. As noted above, the use of rhC1-INH is contraindicated for patients allergic to rabbits because of trace rabbit protein in the product. The adverse effect profile is otherwise benign.⁴⁹ This product is reported to be unique because it is produced by transgenic rabbits, which can potentially allow an unlimited source of drug without any concerns of infectious transmission. Therapy with rhC1-INH will probably be limited to acute treatment because of the short half-life of the medication. It is anticipated to be used as an alternative in those unable or unwilling to receive blood products.

For short-term prophylaxis as off-label use before dental, surgical, or other procedures, human derived C1-INH is being used. It has a longer half-life compared to ecallantide, icatibant or rh-C1INH and fewer risks than FFP. Danazol is also effective and a less expensive alternative for short-term prophylaxis and has minimal adverse effects when used as a short course of therapy. Except during the first two trimesters of pregnancy, it can be used safely, even in children.

Presently, the HAE Association and many experts in the field are advocating for patient self-treatment of attacks at home. Attacks treated within the first 6 hours have faster relief of symptoms with less absenteeism and morbidity, and thus home therapy has advantages.¹² C1-INH can be self administered if the patient is properly trained. An alternative is infusion by health care services at home. Icatibant is approved for self-administration and has the advantage of being stable at room temperature. Ecallantide, a subcutaneous formulation, has been approved for the treatment of acute HAE attacks, but the limiting factor for the use of ecallantide is that the FDA mandates that it be administered by a health care provider knowledgeable to treat anaphylaxis. A recent retrospective observational study by Kreuz et al. reported that home therapy with subcutaneous infusion pC1-INH is effective and safe in the treatment of HAE attacks in pediatric patients⁵⁰ However, a larger, randomized study is needed to confirm these findings before this approach can be considered the standard of care for pediatric patients. The most important studies needed are

those that would compare available therapies to each other to determine which therapies are superior and safest for patients suffering from HAE.

Conclusion

New therapies of HAE have recently emerged and will likely replace FFP and antifibrinolytics. Disease-specific treatments improve patients' quality of life and reduce HAE-associated morbidity and mortality. However, high costs of these treatments are of concern and more cost-benefit analysis is needed. The route of administration will likely be one factor in future marketing directions for newer HAE drugs. Subcutaneous formulations are becoming more popular for home administration. Oral medication is presently being investigated and will add to the ease of therapy and adherence. Large Phase IV clinical trials, meta-analyses, superiority and non-inferiority trials are needed to replace interim consensus approaches for treatment of HAE. Continued international effort to promote investigational drug studies for rare diseases, such as HAE, should be encouraged.

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