CLINICAL
INVESTIGATION

Update on recent trials in the treatment of hereditary angioedema

Hereditary angioedema (HAE) is a rare genetic condition that manifests as painful and potentially life-threatening episodic attacks of cutaneous and submucosal swelling. It results from functional deficiency of C1 esterase inhibitor (C1-INH), which is a regulator of the complement system, contact/kinin system and coagulation system. In HAE patients, 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 noted in the disease. Until recently, therapeutic options for HAE have been very limited. Many new therapies such as C1-INH replacement drugs and medications aimed at components of the contact system such as plasma kallikrein inhibitors and bradykinin BR2-receptor antagonists, have emerged and will be the focus of this manuscript. We believe availability of new, safe and effective treatment options will change the treatment paradigm of HAE. As therapeutic options expand, selection of therapy for both prophylaxis and for acute attacks will require optimization based on patient- and drug-specific factors. In this article we provide an overview of the latest developments on therapeutic options and emerging trends in overall management of HAE.

Neelu Kalra[1] & Timothy Craig[†2]
[1]Department of Medicine, Penn State University, Hershey, PA, USA
[2]Professor of Medicine & Pediatrics, Distinguished Educator, Program Director, Penn State University, 500 University Dr, H041, Hershey, PA, 17033, USA
[†]Author for correspondence:
Tel.: +1 717 531 6525
Fax: +1 717 531 5785
E-mail: tcraig@psu.edu

Hereditary angioedema (HAE) is a rare autosomal dominant disorder resulting from a deficiency of C1-esterase inhibitor (C1-INH) or function causing episodic swelling, which most often affects the skin of extremities or mucosal tissues of the upper respiratory and GI tracts.

The disease is caused by a mutation in the gene encoding C1-INH located on chromosome 11. C1-INH, a serine protease inhibitor (serpin), is a primary regulator of the complement and kallikrein–kinin system. Deficiency of C1-INH (qualitative or quantitative) leads to unregulated activation of bradykinin. Data from various studies support that bradykinin plays an important role in mediating clinical symptomatology (pain and vascular permeability changes leading to edema) in HAE [1–3].

Two main types of HAE account for the majority of cases. Type I HAE (~80–85% of patients) is characterized by low protein levels of C1-INH; and type II HAE (15–20% of patients) is characterized by normal or elevated levels of dysfunctional C1-INH protein [4,5]. Type III HAE is a newly described subtype with some patients characterized by X-linked dominant inheritance. It is more common in females, but males have also been identified with HAE type III. For HAE type III, both estrogen-dependent and -independent forms have been described. Type III is not associated with C1-INH deficiency; however, some cases are associated with genetic defects involving factor

FUTURE SCIENCE

part of fsg

XII (Hageman factor) [6]. Type I and II HAE could perhaps more correctly be described as C1-INH-deficiency disease and are clinically indistinguishable.

It is estimated that HAE affects approximately 1:50,000 to 1:20,000 with no ethnic group differences [7]. Attacks of HAE follow an unpredictable pattern. Anatomical site, frequency and severity vary from patient to patient and within individual patients. Subcutaneous attacks commonly affect extremities but can target any part of the body. In the USA, HAE attacks have been associated with 15,000–30,000 emergency room visits annually. Mortality, secondary to laryngeal edema and asphyxiation, has been reported in up to 30% of patients who were previously undiagnosed. Abdominal attacks lead to hospitalizations and unnecessary surgeries. Some patients develop narcotic dependence due to the repetitive severe abdominal pain associated with HAE attacks; 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].

Owing to the associated morbidity, mortality and greatly reduced quality of life, treatment strategies of HAE therapy have been aimed at attack prevention (prophylaxis) and crisis management (abortive therapy).

Until recently, treatment of acute attacks of HAE in the USA has been restricted to supportive measures such as intravenous fluids and pain management. Corticosteroid, epinephrine and antihistamine are used, but are not efficacious. Fresh frozen plasma (FFP) has also been used to abort the acute attack, but there is a theoretic concern that FFP can worsen acute edema by supplying substrates involved in generation of edema. In addition, the risk of blood-borne pathogens is greater with FFP than with human-derived C1-INH. Unlike the USA, European countries have used human-derived C1-INH concentrates for many decades. Until the past few years, prophylactic therapy in the USA has been limited to attenuated androgens and antifibrinolytics, both of which have significant contraindications and side effects.

Better understanding of the pathophysiology of HAE attacks has led to development of novel therapeutic approaches for treatment (Table 1). In recent years, several new drugs have been approved for treatment of acute attacks and prevention of HAE attacks. It is anticipated that these agents will add significantly to improving the quality of life for patients with HAE.

Current treatment approaches
■ C1-INH replacement protein
C1-INH replacement protein is purified and concentrated from pooled human plasma and administered intravenously for purposes of short- and long-term prophylaxis. Two products are available in the USA, Cinryze® (ViroPharma) and Berinert® (CSL Behring), both were introduced recently. C1-INH by CSL Behring has been available for decades throughout Europe, and other countries [9,10]. The C1-INH concentrate by Sanquin, Cetor®, has been used in a limited number of European countries for decades and Sanquin produces the product that is distributed by ViroPharma in the USA [11]. An additional step of nanofiltration was added by Sanquin to C1-INH concentrate to produce Cinryze.

Human plasma-derived nanofiltered C1-INH: Cinryze®
Human plasma-derived nanofiltered C1-INH Cinryze (nf-C1-INH) was approved by the US FDA in October 2008 for the prevention of HAE attacks in adolescent and adult patients. Cinryze is a lyophilized intravenous preparation. This product is nanofiltered to remove viral and, potentially, prion-sized particles. In addition, it is PCR screened then subjected to multiple viral inactivation/removal steps, including pasteurization [12]. The safety of nf-C1-INH is the result of multiple steps during collection and processing that reduce the risk of blood-borne pathogens compared with fresh frozen plasma.

A randomized, double-blind, placebo-controlled study – the C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy (CHANGE) trial – was performed to assess the efficacy and safety of human nf-C1-INH in treatment of acute attacks and prevention of attacks of HAE. In the first part, nf-C1-INH was assessed for the treatment of acute attacks of facial, abdominal or genitourinary angioedema in HAE patients [13]. Subjects were randomized with intravenous study drug (nf-C1-INH 1000 IU or placebo). Patients with no significant relief within 60 min were then given a second dose of the same study drug they received initially. All patients were eligible to receive open-label Cinryze after 4 h. The time to beginning of unequivocal relief (primary end point) was measured, which was significantly shorter in the

Table 1. Hereditary angioedema treatment options.

Medication	Indication	Available in Europe	Available in the USA
Androgens	Prophylaxis	Danazol® and others	Danazol and others
C1-INH	Acute attacks	Berinert®, Cetor	Berinert
	Prophylaxis	Pending EU studies	Cinryze®
rh-C1-INH	Acute attacks	Recently approved	Repeating studies in the USA
Icatibant	Acute attacks	Firazyr®	Waiting for approval in the USA
Ecallantide	Acute attacks	Pending EU studies	Kalbitor®
C1-INH: C1-esterase inhibitor; rh: Recombinant human.			

nf-C1-INH group (median time = 2 h) than in the placebo group (median time >4 h; p = 0.026). With an alternate statistical assessment, which included patients excluded in the above statistical assessment, required by the US FDA, the primary outcome was not reached and Cinryze was not approved in the USA for acute attacks [Lev Pharmaceuticals, Pers. Comm.].

The second part of the study involved the use of nf-C1-INH as long-term prophylaxis for preventing HAE attacks in the 24-week, multicenter, double-blind, placebo-controlled, crossover trial. A total of 22 patients with a history of frequent angioedema were treated with nf-C1-INH (1000 IU) or placebo two-times per week for 12 weeks then crossed over and received the other treatment for an additional 12 weeks. The primary end point was the number of attacks on nf-C1-INH versus number of attacks on placebo, using each subject as his/her own control. The number of attacks during the nf-C1-INH treatment phase was significantly less than during the placebo treatment phase (6.1 vs 12.7; p < 0.0001). Secondary end points, including days of swelling (10.1 vs 29.6), also showed a significant benefit for the active treatment phase (p < 0.0001). Based on these data, nf-C1-INH received FDA approval for the prophylactic treatment of HAE [13].

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%) [12]. No events were reported to have led to death. Venous thrombosis has been reported, but is not thought to be associated with nf-C1-INH at the indicated dose [101].

The FDA-approved dose is 1000 units intravenously twice-weekly. Adverse effects associated with higher dosing are unknown. The FDA requested that post-marketing studies be performed to address, first, the optimal dose for prophylaxis in males and females, second, immunogenicity, and third, long-term safety. nf-C1-INH is not approved for pregnancy, but C1-INH is considered the safest prophylactic agent during pregnancy [14]. It is also used off-label for children with moderate-to-severe HAE [15].

The 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema recommended that home C1-INH self-infusion programs should be offered to patients. The dose, including dose per kg for prophylaxis, has not been fully established. The recommended dose is 500 units (if less than 50 kg/110 lb) or 1000 units (if greater than 50 kg/110 lb). Training patients for self-infusion is important to reduce the burden of care, but quality assurance and reassessment of technique is important to reduce adverse events. Indwelling ports used for infusion have been complicated with thrombosis and infections, and the use of nf-C1-INH by this route is expected to have similar adverse events [16].

Pasteurized plasma-derived C1-INH concentrate: Berinert®

Berinert is pasteurized 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 [9,10]. Berinert received approval from the FDA in 2009 for the treatment of acute angioedema attacks of the face and abdomen in adult and adolescent patients, but open-label data suggest that C1-INH is also effective for upper airway attacks.

The largest randomized, double-blind, prospective, placebo-controlled, dose-finding study – the International Multicentre Prospective Angioedema C1-inhibitor Trial (IMPACT) – confirmed the efficacy and safety of Berinert for the treatment of acute facial and abdominal HAE attacks. The study included 125 HAE patients who were randomized to placebo or pasteurized C1-INH (Berinert) at a dose of 10 U/kg intravenously or 20 U/kg intravenously within 5 h of attack onset [17,102]. Efficacy of the two doses was compared with placebo. Primary end point was time to onset of relief. Subjects who received 20 U/kg of drug showed a significant reduction in median time to onset of relief of attack compared with placebo (0.5 vs 1.5 h; p = 0.0025). Median time to onset of relief was not significantly shorter at 10 U/kg dose. Time to complete resolution of symptoms was also shorter with the 20 U/kg dose.

IMPACT-2 is an extension of the IMPACT-1 trial. IMPACT-2 was based on treatment with 20 U/kg bodyweight of C1-INH in 975 episodes of HAE attacks at any body location in 57 patients. The main study end points were time to onset of symptom relief, complete resolution of all symptoms and safety. The median times to complete resolution of all symptoms were reported as 8 h for laryngeal attacks, followed by 10 h for abdominal attacks, 24 h for peripheral attacks and 31 h for facial attacks [18]. No drug-related serious adverse events have been reported to date.

In clinical studies, the most common adverse reactions, reported in over 4% of the subjects who received Berinert, were headache, abdominal pain, nausea, muscle spasms, pain, diarrhea and vomiting [17]. Most of these adverse events are thought to be secondary to symptoms related to the HAE attack and not the medication.

Berinert P manufactured in the USA is made from the plasma collected from licensed sources. Rigorous donor screening is performed and each blood donor is tested for antibodies against HIV-1/2, HCV and HBsAg. In

addition, all serologically negative plasma undergo specific nucleic acid test and PCR assay for HAV, HBV, HCV, HIV-1 and human parvovirus B19 [102].

Recombinant human C1-INH: Rhucin®

Recombinant human C1-INH (rh-C1-INH; Rhucin; Pharming Technologies) is a protein produced in the milk of transgenic rabbits and is under FDA review in the USA and has just recently received EU approval. The recombinant technology yields large amounts of fully functional C1-INH protein; however, due to unique carbohydrate additions (glycosylation) the half-life of the protein is less than human-derived C1-INH and there is a possibility that anaphylaxis may occur, but anaphylaxis secondary to rh-C1-INH has not been reported.

Pharming, a Dutch company, has recently completed another Phase III study to obtain approval to use rh-C1-INH for acute attacks of HAE in the USA; however, further studies in the USA seem to be necessary prior to approval. In a Phase I clinical trial, 12 asymptomatic HAE patients received Rhucin [19]. Rhucin was administered intravenously in two divided administrations in doses ranging from 6.25 to 100 U/kg. There was an increase of plasma level of C4 and inhibition of C4 cleavage. The half-life of Rhucin was dose dependent and the longest half-life of approximately 3 h was observed at the dose 100 U/kg. Owing to the short half-life, Rhucin is expected to be more effective in the treatment of acute HAE attacks, than for prophylaxis. Adverse effects were minimal; however, one patient with rabbit allergy developed anaphylaxis secondary to residual rabbit proteins in Rhucin [Pharming, Pers. Comm.].

In an open-label, Phase II clinical trial, 13 severe angioedema attacks in nine patients were treated with Rhucin 100 U/kg [20]. The mean time to onset of symptom relief was 1 h and median time to onset of relief was 30 min. Time to minimum symptoms score was achieved at a mean of 6–12 h. 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 study of rh-C1-INH for acute attacks of HAE, 39 HAE patients were randomized to two different doses of rh-C1-INH 100 or 50 U/kg or placebo. Primary end point was time to onset of relief. Median time to onset was 68 min at the rh-C1-INH dose of 100 U/kg, 122 min at a dose of 50 U/kg and 258 min for placebo [21].

Recombinant human C1-INH has undergone separate Phase III clinical trials in Europe and North America to assess its efficacy and safety in treatment of acute HAE attacks, the double-blind, randomized, placebo study (Phase III) in Europe was stopped earlier

than anticipated due to ethical reasons since there was significant difference in efficacy of median time for onset to symptom relief demonstrated with rh-C1-INH versus placebo (62 vs 508 min; p = 0.0009) [22,23]. rh-C1-INH will soon be marketed in many countries in the EU.

Rhucin appears to be safe and effective and only contraindicated in those with hypersensitivity to rh-CI-INH or rabbits [21]. One subject who failed to disclose history of rabbit allergy developed hives and wheezing [22]. 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.

■ Inhibition of the kinin pathway

Plasma kallikrein inhibitor: ecallantide

Ecallantide (Kalbitor®, DX-88, Dyax Corp.), is a selective reversible inhibitor of plasma kallikrein. It is a 60 amino acid recombinant protein, identified by bacteriophage display technology and produced in the yeast *Pichia pastoris*. Ecallantide inhibits kallikrein by binding with high affinity to kallikrein, thereby preventing bradykinin generation and edema progression in acute HAE. Ecallantide was approved in the USA for treatment of acute HAE attack in patients aged over 16 years in December 2009 [24]. It is administered as subcutaneous injection.

Two randomized, double-blind, placebo-controlled Phase III trials termed as Evaluations of DX-88's Effect in Mitigating Angioedema (EDEMA) trials were conducted to assess efficacy of ecallantide for the treatment of HAE in patients with moderate-to-severe HAE attacks. Two patient-reported outcome measures were used to assess symptom severity and to measure overall response (improvement or worsening) relative to baseline. The instruments are the mean symptom complex severity (MSCS) and the treatment outcome score (TOS). Patients who presented within 8 h of moderate or worse attack at any location were randomized 1:1 to receive either ecallantide 30 mg or placebo by subcutaneous injection. The first trial (EDEMA 3) involved 72 patients with the primary end point measured as a TOS at 4 h. TOS represents a comparison of symptoms between two times using a scale that ranges from 100 (significant improvement) to -100 (significant worsening). Patients treated with ecallantide showed significant improvement compared with placebo-treated patients with TOS scores of 49.5 ± 59.4 versus 18.5 ± 67.8 in placebo-treated patients (p = 0.037) [25]. The improvement in TOS score was demonstrated at 24 h as well (p = 0.044).

EDEMA 4, a second trial with similar study design to EDEMA 3 was conducted involving 96 patients with acute HAE symptoms. The primary end point

was MSCS measured at 4 h. The MSCS score is a patient-evaluation of symptoms at a specific time measured by a score range of zero (none) to five (severe). Lower MSCS from baseline was interpreted as improvement. Ecallantide-treated patients reported a significant decrease from baseline MSCS score as compared with placebo. At 4 h, mean decrease was 0.81 for ecallantide versus a decrease of 0.37 in placebo (p = 0.01). At 24 h, the mean symptom scores also showed a decrease to 1.5 in patients who received ecallantide versus 1.1 in the placebo-treated patients (p = 0.039) [25].

Ecallantide was well tolerated with the most common reported side effects being headache, nausea, fatigue and also upper respiratory infections. Hypersensitivity including anaphylaxis has been reported. Throughout the study, ten (3.9%) out of 255 patients treated with ecallantide developed hypersensitivity consistent with anaphylaxis with reactions occurring within 60 min of dose. It prompted a black box warning for the risk of anaphylaxis and the drug should only be administered by healthcare professionals with appropriate medical support to manage anaphylaxis and HAE. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and HAE and patients should be closely monitored [24,26]. Phase IV postmarketing surveillance studies to monitor the incidence of these reactions will be conducted [Dyax, Pers. Comm.].

Ecallantide represents a novel treatment option for patients with HAE [27]. The recommended dose of ecallantide to treat an angioedema attack is 30 mg, administered as three 1 ml subcutaneous injections. Maximum ecallantide levels are reached 2–3 h following subcutaneous injection, and the half-life is approximately 2 h [24].

Bradykinin-receptor antagonism: icatibant

Icatibant (Firazyr®, Shire, formerly Jerini AG), is a potent selective competitive antagonist for the bradykinin B2 receptor. It is a synthetic decapeptide and is structurally similar to bradykinin. Icatibant is approved in Europe for acute treatment of HAE attacks [103].

The For Angioedema Subcutaneous Treatment (FAST)-1 and -2 trials were randomized, double-blinded trials conducted for approval of icatibant in the USA and Europe. The primary end point was time to onset of symptom relief determined by patient reported visual analog. FAST-1 was placebo-controlled and was conducted in north America, Argentina and Australia. In FAST-1, 56 patients with severe cutaneous and abdominal attacks were randomized to receive subcutaneous icatibant or placebo. The treatment with icatibant significantly shortened the time to onset of symptom relief, 0.8 versus 16.9 h in icatibant-treated and placebo groups, respectively (p < 0.001), but it failed

to show statistical difference in median time to significant symptom relief, 2.5 versus 4.6 h in icatibant and placebo groups (p = 0.142).

In FAST-2, 74 patients with acute HAE attacks from Europe and Israel were randomized in a double-blind study to receive 30 mg subcutaneous injection of icatibant or tranexamic acid. Significant improvement was demonstrated in patients treated with icatibant. The time to onset of symptom relief was 0.8 versus 7.9 h (p < 0.001) and the median time to significant symptom improvement was 2.0 versus 12.0 h in patients treated with icatibant and tranexamic acid.

After randomization, future attacks in subjects from either trial were treated in an open-label fashion. Most of the attacks in both extension trials required treatment with only a single injection of icatibant (87.1% in FAST-1 and 91.0% in FAST-2). No drug-related serious adverse events were reported. Most common side effects reported in clinical studies were limited to localized mild erythema and edema at the site of injection, with occasional minor burning sensations, itching or pain, which resolved within a few hours.

In summary, in the FAST-1 trial, there was no significant difference in the primary end point for patients given icatibant versus patients given placebo. In the FAST-2 trial, the time to clinically significant relief of symptoms was significantly shorter for patients given icatibant than for patients given tranexamic acid. The early use of rescue medication may have confounded the result of icatibant in the FAST-1 trial, which resulted in FDA nonapproval of icatibant in the USA. Owing to this, a repeat Phase III trial was conducted and the results are presently pending. By contrast, the EMA granted a marketing authorization to Firazyr (icatibant) for treatment of acute HAE attacks in countries of the EU.

Future perspective

In the USA, two novel medications are pending FDA approval to treat acute attacks of HAE. Rhucin, a rh-C1-INH produced by Pharming, is repeating studies directed by the FDA in the USA. It is already approved for use in the EU. Icatibant (Firazyr), a bradykinin B2-receptor antagonist produced by Shire from the EU, has just completed Phase III trials and approval is being sought for the use of icatibant for on-demand therapy of acute HAE attacks in the USA; it is already approved in the EU [28].

Further research is underway to identify new alternative therapeutic targets such as inhibition of coagulation factor XII and subcutaneous C1-INH.

As outlined previously, in the past several years many new therapies have emerged in HAE management for prophylaxis and acute therapy of HAE. Several

additional therapies are likely to be approved in the years to come. It is anticipated that availability of effective and safe treatment options will not only reduce mortality, but also improve quality of life for HAE patients. Introduction of these new therapeutic agents will also allow physicians to manage and individualize HAE care appropriately. It will be interesting to see, with the expanding HAE therapies, how the treatment paradigm of HAE will evolve during the next 5 years.

Executive summary

- Hereditary angioedema (HAE) is a rare but serious disease characterized by painful, recurrent attacks of swelling affecting the hands, feet, face, abdomen, urogenital tract and the larynx. It carries important medical, social and financial implications.
- Lack of reliable and effective medical therapies in the USA and non-European countries have often led to inadequate treatment of acute attacks and use of medications with multiple side effects.
- Treatment of both acute and prophylaxis of HAE has evolved due to approval of several new drugs such as Cinryze® for prophylaxis treatment in the USA and Berinert® and Kalbitor® for acute attacks in the USA. In Europe, Firazyr® has been approved for acute attacks and is an alternative to the use of C1-esterase inhibitor in the EU.
- Long-term prophylaxis is important to limit the number of attacks needing acute treatment. Prophylaxis should be recommended for treating HAE in those patients with a significant disease burden that justifies the risk, cost and therapeutic burden of prophylactic therapy.
- Since 2008, Cinryze is indicated for routine prophylaxis against HAE attacks in adolescents and in adults with HAE. Controversy exists as to when to use Cinryze, especially since androgens are effective, inexpensive and often well tolerated at low doses. It appears appropriate to use Cinryze for patients with HAE with severe disease, or those that fail to be controlled with androgens or patients with adverse events or intolerance to androgens or when androgens are contraindicated. In general, patients with relatively severe (≥1 attack/month) HAE are potential candidates for prophylactic treatment.
- It is also likely that low-dose anabolic androgen therapy will continue to be useful in patients who tolerate these drugs.
- The debate is when to use chronic prophylactic therapy instead of on-demand use of Kalbitor or C1-INH (Berinert, Cetor®) for an acute attack. Similar to nf-C1-INH, both Kalbitor and pC1-INH are expensive, but the use in the vast majority of patients would be far less than twice-weekly and, thus, result in cost savings. In addition, since therapy is intermittent, the adverse effects and therapeutic burden would be potentially less except in those with severe disease. Guidelines based on objective evidence are necessary to help educate physicians and patients on which therapy is most appropriate for each individual.
- On-demand therapy for acute attacks should be arranged for patients on chronic prophylaxis since neither androgens nor nanofiltered C1-INH are 100% effective and breakthrough attacks should be expected. In most cases of mild-to-moderate disease, it appears that on-demand therapy for acute attacks may be the only required therapy for the majority of patients with HAE.

Bibliography

Papers of special note have been highlighted as:
- of interest

1   Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of 'spontaneous' formation of bradykinin. *J. Allergy Clin. Immunol.* 72, 54–60 (1983).

2   Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE 3rd. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J. Clin. Invest.* 109, 1057–1063 (2002).

3   Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *J. Allergy Clin. Immunol.* 104, 1321–1322 (1999).

4   Zuraw BL, Christiansen SC. Pathogenesis and laboratory diagnosis of hereditary angioedema. *J. Allergy Asthma Proc.* 30, 487–492 (2009).

5   Banerji A, Shaffer AL. The spectrum of chronic angioedema. *J. Allergy Asthma Proc.* 30, 11–16 (2009).

6   Bork K, Barnstedt S, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 356, 213–217 (2000).

7   Bowen T, Cicardi M, Farkas H *et al.* Canadian 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema *J. Allergy Asthma Clin. Immunol.* 6, 24 (2010).

- **The most up to date consensus and anyone caring for hereditary angioedema patients should read this.**

8   Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann. Allergy Asthma Immunol.* 104(4), 314–320 (2010).

9   Epstein TG, Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs* 68, 2561–2573 (2008).

10   Bernstein JA. Hereditary angioedema, a current state of the art review VII: current status of emerging therapies. *Ann. Allergy Asthma Immunol.* 100(Suppl. 2), 41–46 (2008).

11   Zuraw BL. Hereditary angioedema: a current state of the art review IV: short and long term treatm*ent of hereditary angioedema. Ann. Allergy Asthma Immunol.* 100(Suppl. 2), 13–18 (2008).

12   Zuraw BL, Busse PJ, White M *et al.* Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N. Engl. J. Med.* 363(6), 513–522 (2010).

13   Zuraw BL, Schaefer O, Grant JA *et al.* Results of a randomized double-blind placebo controlled study of nanofiltered C1-inhibitor for the treatment of HAE attacks. *Ann. Allergy Asthma Immunol.* 105, A100 (2010).

14   Czaller I, Visy B, Csuka D, Füst G, Tóth F, Farkas H. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 152(1), 44–49 (2010).

15   Farkas H, Varga L, Szeplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. *Pediatrics* 120, e713–e722 (2007).

16   Longhurst HJ, Farkas H, Craig T *et al.* HAE international home therapy consensus document. *Allergy Asthma Clin. Immunol.* 6(1), 22 (2010).

17   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.* 124, 801–808 (2009).

■   **The first double-blinded, placebo-controlled, dose-ranging study assessing the efficacy of C1-inhibitor protein (C1-INH); healthcare providers prescribing C1-INH should review this article.**

18   Levy RL, Wasserman RL, Bewtra AK *et al.* C1 esterase inhibitor concentrate for treatment of acute attacks of hereditary angioedema: interin results of an ongoing prospective, open label study in North America after 640 attacks (IMPACT 2). *J. Allergy Clin. Immunol.* 123(Suppl. 2), 99 (2009).

19   Van Doorn MB, Burggraaf J, van Dam T *et al.* A Phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. *J. Allergy Clin. Immunol.* 116(4), 876–883 (2005).

20   Choi G, Soeters MR, Farkas H *et al.* Recombinant human C1-inhibitor in the treatment of acute angioedema attacks. *Transfusion* 47(6), 1028–1032 (2007).

21   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.* 126(4), 821–827 (2010).

■   **This article should be read if the healthcare provider prescribes recombinant human C1-inhibitor.**

22   Bernstein JA. Hereditary angioedema: a current state-of-the-art review, VIII: current status of emerging therapies. *Ann. Allergy Asthma Immunol.* 100(2), S41–S46 (2008).

23   Zuraw BL. HAE therapies: past present and future. *Allergy Asthma Clin. Immunol.* 6, 23–28 (2010).

24   Cicardi M, Levy RJ, McNeil DL *et al.* Ecallantide for the treatment of acute attacks in hereditary angioedema. *N. Engl. J. Med.* 363(6), 523–531 (2010).

25   Levy R, McNeil D, Li H, Hsu FL, Horn P, Roberts J. Results of a 2-stage, Phase 3 pivotal trial EDEMA3:a study of subcutaneous DX-88 (Ecallantide), a plasma kallikrein Inhibitor, in patients with hereditary angioedema (HAE). *J. Allergy Clin. Immunol.* 121, S231 (2008).

26   Caballero T, Lopez-Serrano C. Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J. Allergy Clin. Immunol.* 117(2), 476–477 (2006).

27   Bernstein JA, Qazi M. Ecallantide: its pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Expert Rev. Clin. Immunol.* 6, 29–39 (2010).

28   Cicardi M, Banerji A, Bracho F *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N. Engl. J. Med.* 363(6), 532–541 (2010).

■   **Essential reading for anyone prescribing icatibant.**

■ **Websites**

101   FDA Alert on thrombosis associated with C1-esterase inhibitor (Cinryze®) 9 June 2009. www.fda.gov/BiologicsBloodVaccines/ GuidanceComplianceRegulatoryInformation/ ComplianceActivities/Enforcement/ UntitledLetters/ucm174489.htm

102   CSL Behring. Berinert prescribing information. www.berinert.com/patient/prescribing-information.aspx

103   EMA. CHMP assessment report for Firazyr®. www.ema.europa.eu/humandocs/PDFs/ EPAR/firazyr/H-899-en6.pdf