

Advances in Hereditary Angioedema Treatment

Considerations, Criteria, and the New Therapy Options for Treatment and Prevention of HAE Attacks



At a symposium conducted in conjunction with the 2008 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology (ACAAI), chaired by Sami L. Bahna, MD, DrPH, Professor of Pediatrics and Medicine and Chief of the Allergy and Immunology Section, Louisiana State University Health Science Center in Shreveport, an expert panel discussed new developments in the treatment of hereditary angioedema (HAE). In addition to Dr. Bahna the panel consisted of Bruce L. Zuraw, MD, from San Diego, California ("HAE: Pathogenesis and Mechanisms"); William R. Lumry, MD, from Dallas, Texas ("Clinical Characteristics of Hereditary Angioedema"); and Michael M. Frank, MD, from Durham, North Carolina ("New Therapy Options for the Treatment and Prevention of HAE Attacks").

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Highlights from a symposium conducted in conjunction with the Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology held in Seattle, Washington, November 6–11, 2008



Hereditary Angioedema: Pathogenesis and Mechanisms

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To understand the underlying mechanisms and pathophysiology of swelling in hereditary angioedema (HAE) it is useful to review the discovery of the C1 inhibitor deficiency in HAE, the identification of the mediator of swelling in HAE, the mechanism of C1 inhibitor deficiency, and the vascular permeability defect in HAE.

Discovery of the Fundamental Defect in HAE

One of the earliest portrayals of giant swelling as a distinct entity was by Marcello Donati in the 16th century. The first clear description of what we now recognize as angioedema, however, was published by Quincke in 1882. William Osler in 1888 was the first to make the key observation of the hereditary aspect of the disease, and thus is credited with being the first to identify hereditary angioedema.

Little progress was made in understanding this disease until the early 1960s. In 1962, Landerman et al. examined patients with HAE and found a deficiency of an inhibitor for plasma kallikrein in the plasma.¹ Landerman described this as a functional deficiency, but did not identify the specific protein that was deficient. Then in 1963, Donaldson and Evans published

a seminal article identifying the root cause of HAE.² Donaldson showed immunologically that HAE plasma lacked the inhibitor of C1-esterase, thus proving that patients with HAE were deficient in C1 inhibitor.

Identification of the Mediator of Swelling in HAE

While the discovery of the C1 inhibitor deficiency in HAE was important, it didn't completely explain the cause of the swelling in HAE. Incubation of plasma from HAE patients generated a factor that caused smooth muscle contraction and increased vascular permeability. The identity of this factor remained elusive, and several theories were put forth related to the role of C1 inhibitor in interrelated proteolytic path-

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Learning Objectives

Upon completion, participants should be able to:

- present the underlying mechanisms and pathophysiology of swelling in hereditary angioedema (HAE).
- describe the prevalence, clinical characteristics and presentation of HAE.
- discuss the pathophysiologic mechanisms of angioedema associated with C1 esterase inhibitor deficiency or dysfunction.
- utilize readily available complement assays to make the diagnosis of HAE and differentiate HAE Types I, II, and III, acquired C1INH deficiency, and other forms of angioedema.
- explain the impact HAE has on patients and families with this rare disorder and the urgent need for a safe and effective treatment for acute attacks and prophylaxis.
- be familiar with the new therapies being tested by five companies for the treatment of HAE, including their mechanism of action and the advantages and disadvantages of each.

Target Audience

Practicing allergists/immunologists; fellows in accredited allergy/immunology training programs; primary care physicians who treat HAE patients; physician assistants, nurse practitioners; and other allied health professionals in the field of asthma, allergy and immunology.

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Needs Assessment

HAE is a lifelong disease characterized by recurrent acute episodes often associated with substantial morbidity and high mortality. The disease seems to be rare but is probably markedly underdiagnosed. Pharmacologic therapies have not brought optimal control and have multiple adverse effects. Studies on recently developed specific therapeutic agents have shown great efficacy and minimal side effects.

CME Credits

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Off-label Uses of Products

This review contains no discussion of off-label use of products except for clinical trial data pertaining to potential uses of new and emerging treatment modalities.

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ways in plasma. C1 inhibitor is the major inhibitor of the complement C1 proteases, C1r and C1s, the proteases of the mannose-binding lectin pathway of complement, and the contact system proteases plasma kallikrein and activated Hageman factor (coagulation factor XIIa). C1 inhibitor is also a minor inhibitor of coagulation factor XIa and plasmin. Evidence suggested that the vascular permeability-enhancing factor was generated either through activation of the classic complement pathway or the contact system.

Patients with hereditary angioedema have evidence of dysregulation of the classic complement pathway with persistent activation of C1, C4, and C2. One theory, therefore, postulated that active complement proteases with the cooperation of plasmin (which is activated from plasminogen) cleave C2, releasing a novel peptide (C2-kinin) that mediated the effects found in HAE plasma. There is evidence that C2-kinin does enhance permeability, and for many years it was thought to be the mediator of swelling in hereditary angioedema. Nevertheless, C2-kinin has a relatively weak effect on permeability and significant *in vivo* or *ex vivo* generation of C2-kinin from HAE plasma was never able to be demonstrated.

The alternative theory postulated that activation of the contact system during HAE attacks would result in plasma kallikrein cleaving high-molecular-weight kininogen to release the bioactive mediator bradykinin. Blister fluid from patients with HAE was shown to contain active plasma kallikrein,³ and bradykinin was shown to be generated from *ex vivo* incubated HAE plasma.⁴ Furthermore, several studies demonstrated that attacks of HAE were associated with activation of plasma kallikrein and cleavage of high-molecular-weight kininogen.^{5,6}

Confirming these earlier studies, Shoemaker and colleagues showed that the vascular permeability-enhancing activity in C1 inhibitor deficient plasma was dependent on high-molecular-weight kininogen and plasma kallikrein, but not C2.⁷ They also showed that the vascular permeability-enhancing activity could be blocked either with a kininase (an enzyme that degrades bradykinin) or a B2 bradykinin receptor antagonist. Davis et al. used a mouse model in which the C1 inhibitor gene was knocked out to further confirm that bradykinin is the mediator of swelling.⁸ The C1 inhibitor deficient mice had persistently increased vascular permeability,

and this could be reversed by exogenous C1 inhibitor, inhibition of plasma kallikrein, or either knocking out or antagonizing the B2 bradykinin receptor. Nussberger et al. then showed that bradykinin levels were increased in venous blood near the sites of angioedema in HAE patients.⁹ Taken together, these studies unequivocally show that bradykinin is the major mediator of angioedema in HAE.

Mechanism of C1 Inhibitor Deficiency in HAE

Sequencing of the C1 inhibitor gene has revealed that HAE occurs as a consequence of a mutation of the C1 inhibitor gene with a resulting functional deficiency of C1 inhibitor protein. C1 inhibitor is a member of the serine protease inhibitor (serpin) superfamily with significant homology to α 1-antitrypsin. Like other serpins, C1 inhibitor functions as a “molecular mousetrap,” rearranging and trapping the target protease when it is cleaved.¹⁰ C1 inhibitor is a suicide inhibitor, forming a 1:1 stoichiometric complex with the protease that is inhibited followed by clearance of the entire complex. In cases of overwhelming proteolytic activation, C1 inhibitor can be cleaved into an inactive form without inhibiting the protease.¹¹

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Over 150 C1 inhibitor mutations have been described, occurring throughout the gene. While all patients with HAE have decreased C1 inhibitor functional levels, type II HAE patients show normal antigenic C1 inhibitor levels. Elucidation of the underlying C1 inhibitor mutations in patients with type I and type II HAE revealed that the phenotypic difference had a structural correlate. In general, type I HAE is caused by mutations in the C1 inhibitor gene that result in either truncated proteins or proteins that cannot be secreted. In contrast, type II HAE is caused by mutations in the C1 inhibitor gene typically involving residues at or near the active site on the reactive mobile loop that result in a mutant C1 inhibitor protein that is secreted but is dysfunctional.

Mechanism by which Bradykinin Induces Angioedema

Bradykinin causes angioedema by binding to its receptor, the B2 bradykinin receptor, on vascular endothelial cells leading to increased vascular permeability. The mechanism by which bradykinin enhances vascular permeability is thought to primarily involve vascular endothelial cell cadherin (VE-cadherin). VE-cadherin forms both homotypic and heterotypic associations within one cell or across different cells thereby forming tight junctions which regulate water movement across the endothelial layer.

Binding of bradykinin to the B2 bradykinin receptor on vascular endothelial cells activates phospholipase-C, leading to increases in intracellular calcium and DAG. This results in activation of protein kinase C, which in turn phosphorylates beta catenin and leads to an

internalization and destruction of the VE-cadherin. Additionally, activated protein kinase C also phosphorylates myosin light chain kinase promoting actin cytoskeleton contraction. Therefore, bradykinin causes the glue between the cells to disappear as well as the cells to centripetally contract. The net effect of this is to increase the gap between vascular endothelial cells allowing water to move from the vascular space into the tissue. Clinically, this is angioedema.

An important implication of this mechanism is that drugs that prevent bradykinin generation or antagonize its action only prevent additional fluid from moving out of the vascular space but do not have any effect on the removal of fluid that has already moved into the tissue. Therefore, resolution of angioedema can be slow even following effective treatment. ■

(hands, feet) swelling, central cutaneous (face, genitalia) swelling, or mucosal (lips, tongue, larynx, viscera) swelling. The edema is typically precipitated by trauma, stress, or menses. The swelling occurs slowly over 2 to 12 hours and lasts 24 to 60 hours. Many patients describe a non-pruritic rash called erythema marginatum that precedes or occurs during a swelling attack. These individuals do not have urticaria as part of their angioedema attacks.

The cutaneous swelling can be uncomfortable or even disabling (if it occurs in the hands or feet). Abdominal swelling can involve any part of the gastrointestinal tract, such as the esophagus or small or large bowels. Symptoms may include nausea, vomiting, diarrhea, and severe cramping pain. If patients can't take anything by mouth or have diarrhea dehydration may occur. They may become hemoconcentrated or have leukocytosis.

Facial and upper airway (mouth, tongue, pharynx, hypopharynx, larynx) swelling is potentially life-threatening. Symptoms may include dysphagia, voice changes, throat tightness, or stridor. If the airway is not protected or opened, the attack can be fatal.

Three types of HAE have been described. Type I, the most common (85% of HAE patients), is associated with C1 esterase inhibitor deficiency. In type II, which accounts for 15% of patients, there are quantitatively normal amounts of C1 inhibitor but it is not functional. There are genetic defects for both type I and type II HAE. Both have autosomal dominant transmission, but there is incomplete clinical expression and variable severity.

Type III was initially reported only in females and thought to be associated with estrogen, but a few males have been reported to have this disease. Individuals with type III HAE have normal C1 inhibitor level and function, but have a hereditary inheritance pattern.

Mechanism

C1 inhibitor is an important regulatory protein in the coagulation, complement and contact systems. In the contact system C1 inhibitor controls the production of bradykinin from high-molecular-weight kininogen. Uncontrolled production of bradykinin leads to fluid loss from vessels, edema and pain. In type I HAE, type II HAE, and acquired C1 inhibitor deficiency, functional C1 inhibitor is not present in sufficient quantity to regulate the activa-



Clinical Characteristics of Hereditary Angioedema

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Angioedema is defined as extravasation of plasma into deeper cutaneous tissues or mucosa. It may occur with or without urticaria. There are multiple etiologies, including IgE triggers (e.g., food, drugs, inhalants, contactants), non-IgE triggers (e.g., drugs such as nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors), physical causes (e.g., delayed pressure urticaria), medical causes (e.g., autoimmune, malignancy), and hereditary types (types I, II, and III).

The prevalence of hereditary angioedema (HAE) is difficult to assess, but is in the range of 1:10,000 to 1:50,000 individuals. It represents about 2% of angioedema cases in the United States. Angioedema attacks often begin in the second decade of life, usually with the onset of puberty, but they have been reported in infants and young children. HAE is often misdiagnosed as an allergic reaction to drugs or foods or as idiopathic angioedema. Abdominal attacks are often mistaken for bowel obstruction or inflammation, leading to unnecessary surgery. Women with

painful pelvic episodes are often misdiagnosed with endometriosis or ovarian cysts.

A family history of HAE is usually present, but the physician must explicitly ask the patient for a family medical history if the disease is suspected. About 25% of patients do not have a family history of the disease, but rather have a spontaneous genetic mutation.

Clinical Characteristics

Clinical characteristics of HAE include recurrent bouts of swelling. It is usually nonpitting, nonerythematous, and non-pruritic. There can be peripheral cutaneous

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tion of C1 esterase; therefore, in the classical complement pathway C2 and C4 are activated and consumed on an ongoing basis and the levels of C2 and C4 level go down. In most individuals with C1 inhibitor deficiency or dysfunction, there is a low C4 level even when the patient is not experiencing an attack. Because C4 can quickly and accurately be measured by most laboratories, this can be used to help to make the diagnosis of type I or II HAE.

Laboratory tests can also differentiate type I and type II HAE. In type I the C1 inhibitor level is low. In type II the C1 inhibitor level is normal but its function low. In both types the C4 level is low. In acquired C1 inhibitor deficiency there is low C1 inhibitor level, low C1 inhibitor function, low C4 level, and a low C1q level (which is normal in type I and type II HAE).

Diagnosis

Clinical suspicion is the key to making the diagnosis. This includes a family history of the disease. An algorithm published in the *Journal of Allergy and Clinical Immunology* suggests measuring C4, C1 inhibitor (antigenic) and C1q concentrations.¹² Low C4, C1 inhibitor, and normal C1q levels indicate type I HAE. If there is a low C4 level but a normal C1 inhibitor level and normal C1q level, then functional C1 inhibitor assay should be measured. If C1 inhibitor functional activity is low, the diagnosis is type II HAE. If there is a low C1q level and low C4 or low C1 inhibitor levels, the diagnosis is acquired C1 inhibitor deficiency.

An international internet survey reported by Santos et al. reveals there often is a delay in diagnosis of HAE. The survey included 313 HAE patients in five countries (average age 37 years).¹³ On average, more than one year passed between the first attack and the patient seeking medical attention, and there was an average of 8.3 years from the first attack to the time when an accurate diagnosis was made. These patients saw on average 4.4 physicians before the correct diagnosis was made. The wrong diagnosis was given 63% of the time, which led to unnecessary surgery in 21% of patients. Most patients reported two immediate family members and two extended family members with the disease. However, only 48% of the immediate and 26% of extended family members had been screened for the disease.

HAE has a significant impact on qual-

ity of life. Attacks occur without warning and can be quite disruptive. Individuals with HAE often have concomitant illnesses, such as depression or physical impairment. Medication side effects can be problematic, especially for those treated with androgens.

To assess the social and economic burden HAE places on patients with the disease an internet-based questionnaire was administered to 457 HAE patients who are members of the United States Hereditary Angioedema Association. Preliminary results from this survey were presented in three posters given at the ACAAI Annual Meeting in 2008.^{14,15,16}

Of the 457 patients (75.5% female; 92.1% Caucasian), 428 experienced a swelling attack within the previous year. On average, men reported 17 and women 29 attacks per year. Attacks lasted an average of 60 hours and lead to an average of 1.6 emergency room visits for men and 2.4 visits for women over the previous 12 months. Over 70% of patients reported their attacks to be moderate or severe.

A 12-item short-form (SF-12) health survey, conducted by Castaldo and colleagues, found that patients with HAE had lower scores on all health items, both physical and mental, compared to the normative population. The differences were statistically significant. The investigators also used the Hamilton Depression

Inventory Short Form (HDI-SF) and found that HAE patients had a higher mean HDI-SF score, which is indicative of greater depressive symptoms, versus the normative population. Nearly twice as many HAE patients took psychotropic medications versus the normative population.

The economic burden of HAE includes both direct medical costs and indirect costs from lost work and school days. The study presented in the poster by Wilson et al. found direct and indirect costs averaged \$26,000 per year for acute attacks and \$18,000 per year for chronic care. The study by Castaldo et al. found half of HAE patients missed work days, 44.4% missed school days, and 59.3% missed leisure days because of their disease. All patients reported that their educational advancement was impaired by their disease, 50% reported the disease influenced career advancement, and 70% said the disease was a consideration in their choice of job type.

In conclusion, HAE is a debilitating and potentially life-threatening condition for which no adequate acute therapy is currently approved in the United States. Diagnosis rests on knowledge, suspicion, good history taking, and listening to the patient. Making a diagnosis even in the absence of specific remedies greatly improves the mental well-being of the patient. ■



New Therapy Options for the Treatment and Prevention of HAE Attacks

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In the 1970s and 1980s androgens first began to be used as treatment for HAE, and danazol became the standard therapy. While androgens are effective for HAE, there are considerable problems associated with their use. For example, impeded androgens are not clinically effective for 48 hours. There are no intramuscular or intravenous preparations; they must be given orally. Only methylated products are active; testosterone is ineffective as therapy. Androgens are ineffective in some

people and cannot be used in children and in pregnant women. Side effects, although usually mild compared to the severity of the disease, are common.

Another group of drugs used for HAE prophylaxis are fibrinolysis inhibitors. Like androgens, they do not show an effect for 48 hours. They are inconvenient to take and toxic side effects are common. Fresh frozen plasma, although widely used, may prove dangerous in some patients.

The treatment of HAE is poised to

undergo a major change as five pharmaceutical companies test and prepare to introduce new therapies for HAE. The five new therapies for HAE include two purified C1 inhibitor preparations. The FDA has approved one of these drugs, C1 inhibitor (human) (Cinryze; ViroPharma), for prophylaxis. The second purified C1 inhibitor (Berinert P) is made by CSL Behring. A recombinant C1 inhibitor is under development by Pharming. The company Dyax is working on a kallikrein inhibitor (ecallantide [DX-88]). Finally, the company Jerini (now a unit of Shire Deutschland) is making a bradykinin receptor type 2 antagonist (icatibant [Firazyr]). Preliminary data from placebo-controlled trials suggest that all of the drugs are effective.

Studies of all five drugs involved a preliminary screening visit at which the diagnosis was confirmed. Patients had low C1 inhibitor (antigenically or functionally) and low C4 with a normal C1q. All studies attempted to enroll individuals who were early in attacks. It was hoped to enroll patients four to six hours from the start of an attack so that attacks were not resolving spontaneously. All of the studies assumed that patients would maintain medications they were taking chronically. The dose of androgens was not changed once an attack started. All studies suggested that narcotic treatment for abdominal pain was not acceptable or was deemed a treatment failure. The type of attack acceptable for the treatment protocol varied from study to study. Some allowed peripheral edema attacks. Some did not. Some allowed facial attacks. Some did not. For some studies the FDA has allowed C1 inhibitor to be used as the rescue medication.

**Historical Perspective:
C1 Inhibitor Isolated from Plasma**

In the 1970s, several organizations that had developed purification procedures for the isolation of IgG from plasma attempted to develop a therapy for HAE by turning their attention to purification of C1 inhibitor. One of these was the American Red Cross, which began to make experimental batches from plasma in 1974. Frank and colleagues reported the biochemical effect of the preparation in 8 patients with HAE and the effectiveness of the preparation in the treatment of HAE attacks in 5 patients.¹⁷ The American Red Cross planned to make C1 inhibitor available to the patient population. However, with the onset of the AIDS epidemic in the U.S. in

1980 the plans were halted.

In the 1990s, Waytes et al. conducted two double-blind, placebo-controlled studies with a C1 inhibitor preparation made by an Austrian company, Immuno.¹⁸ In the first study prophylactic infusions of either C1 inhibitor or placebo were administered every three days. In the active treatment group, the level of C1 inhibitor rose quickly and declined slowly. The half-life of the protein was shown to be about 40 hours. For these very severe patients who were hospitalized at the time of entry in the study the response to therapy was at least 60%.

The second study was conducted in outpatients with acute attacks of HAE. Within 30 minutes of administration, none of the patients receiving placebo improved, but many of the patients receiving C1 inhibitor had started to show improvement (Table 1). By 240 minutes, all of the patients receiving C1 inhibitor had improved.

In the 1970s, CSL Behring began work on a C1-esterase inhibitor (Berinert P). It was first licensed as a non-pasteurized product in Germany in 1979 and as a pasteurized product in 1985. Bork and colleagues have extensively studied this drug, which has been approved in Europe as a licensed product or for compassionate use since the early 1980s.

In a study conducted in 2005, Bork et al. showed that this C1-esterase inhibitor provides relief in many patients within 30 minutes.¹⁹ In addition, the duration of attacks was reduced and vomiting, pain, and diarrhea were reduced.

The Dutch Red Cross was making batches of C1 inhibitor prepared from

plasma as early as 1972. Agostoni et al. reported that the preparation was effective in the treatment of HAE in a case report in 1978 and in a longer report in 1980. In 2003, the Dutch Red Cross spun off the preparation to a company called Sanquin. This product was acquired by Lev Pharmaceuticals, and with the addition of a nanofiltration step developed into the current drug C1 inhibitor (human) (Cinryze). In October 2008, it was approved by the FDA for prophylaxis.

In the prophylactic study of C1 inhibitor (human), patients were randomized to placebo or the drug (1000 units twice a week) at week 0. At the end of 12 weeks patients taking C1 inhibitor (human) were switched to placebo and those taking placebo were switched to the drug. HAE attacks were treated with open-label C1 inhibitor (human) as rescue therapy. Almost all patients on C1 inhibitor (human) improved. Overall, the patients on active treatment had less swelling and less frequent use of rescue therapy. Frequency, severity, and duration of attacks were all reduced with the drug (Figure 1).

The recombinant C1 inhibitor (conestat alfa), developed by Pharming, is produced in rabbit milk. The human gene is introduced into rabbits under regulatory control of the bovine αS1-casein promoter and is secreted in the milk. The human protein is then purified from the milk.

EcCallantide, which is manufactured by Dyax, is a reversible inhibitor of plasma kallikrein. Kallikrein is the protein that cleaves high-molecular-weight kininogen to generate bradykinin. EcCallantide is a

Table 1.
Length of Time to the Response to C1 Inhibitor Concentrate or Placebo

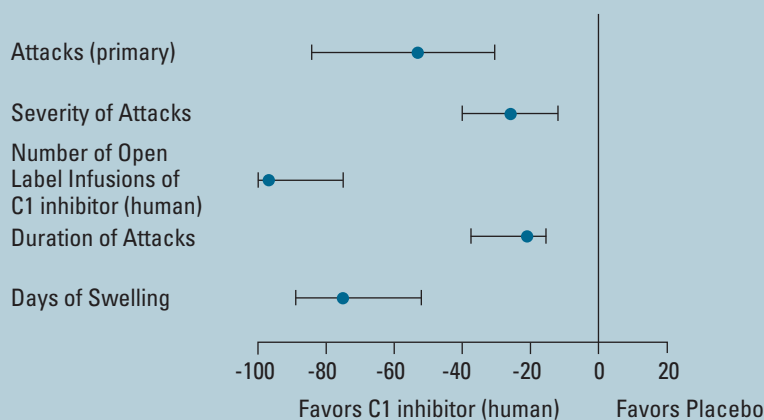
| Location of Edema | Response in ≤30 minutes | | Response in <240 minutes | |
|--------------------|---|----------|--------------------------|-----------|
| | C1 Inhibitor | Placebo | C1 Inhibitor | Placebo |
| | <i>no. of responses/no. of attacks (% responding)</i> | | | |
| Abdomen | 25/35 (71) | 0/34 | 35/35 (100) | 2/34 (6) |
| Larynx | 3/4 (75) | 0/4 | 4/4 (100) | 1/4 (35) |
| Face | 7/7 (100) | 0/8 | 7/7 (100) | 1/8 (12) |
| Extremities | 9/16 (56) | 1/16 (6) | 13/16 (81) | 3/16 (19) |
| First 3 locations* | 33/44 (75) | 0/40 | 44/44 (100) | 4/40 (10) |
| All locations* | 38/55 (69) | 1/49 (2) | 52/55 (95) | 6/49 (12) |

*For single attacks involving more than one location, the location with the earliest response was used for statistical analysis.

Waytes, Rosen, Frank. *NEJM*. 1996; 334:1630-1634.

Figure 1.

Secondary Endpoints Results: Median of within Patient Percent Differences (95% CI)



60-amino-acid peptide derived from a Kunitz domain backbone with seven unique amino acids. It has a very rapid on rate and a slow off rate. Unlike the serum C1 inhibitors, it can be given intravenously or subcutaneously. It is a very rapid inhibitor of kallikrein and also inhibits less strongly other plasma mediator pathways. In studies of treatment of acute attacks conducted by Dyax, patients improved on the drug compared to placebo.

The drug icatibant, being developed by Jerini (Shire Deutschland), is a potent, specific, reversibly competitive antagonist of the bradykinin B₂ receptor. The drug is effective when administered subcutaneously. The acute treatment trials included patients with broad HAE manifestation (abdominal, cutaneous, and laryngeal attacks). The company conducted two clinical trials, called FAST 1 (in the U.S., Canada, Australia, and Latin America) and FAST 2 (in Europe and Israel). The FAST 2 trial compared icatibant to one of the plasmin inhibitors and showed statistically significant improvement with the drug. The drug was approved for use in Europe. The FAST 1 trial, which compared icatibant to placebo, missed its efficacy endpoint. The company has faulted the trial design of FAST 1 with the failure to achieve the endpoint.

Theoretical Advantages and Problems

Each of the five new drugs under development for HAE has theoretical advantages, as well as problems. For example, they

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all appear to be effective in acute attacks of HAE. The plasma products carry a minor risk of infection. However, no infection has been observed with the current products. Both products start with blood from healthy donors and go through potent virus reduction purifications. The product is the normal physiologic protein. Since patients are all heterozygotes, allergy to the administered product is unlikely. One disadvantage is the current need to administer the drugs intravenously.

With the recombinant C1 inhibitor, glycosylation differs from the normal C1 inhibitor; some patients may have an allergic reaction to the backbone sugars. A disadvantage of the drug is its short half-life. Because it is not a serum product, one potential advantage is a limitless supply.

The kallikrein inhibitor and the bradykinin receptor antagonist are both foreign peptides, and therefore there is some risk of an allergic reaction with repeated administration. Both have a short half-life. Both drugs can be administered subcutaneously, which is an advantage. They are relatively inexpensive to make and there is no risk of infection. ■

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Advances in Hereditary Angioedema Treatment

Considerations, Criteria, and the New Therapy Options for Treatment and Prevention of HAE Attacks

If you wish to receive CME credit and confirmation of your participation, please complete the Self-Assessment Test and the Program Evaluation and mail a photocopy of the completed material to The American College of Allergy, Asthma and Immunology, 85 West Algonquin Road, Suite 550, Arlington Heights, IL 60005, or FAX your Self-Assessment Test to (847) 427-1294. If you attended the 2008 Annual Scientific Meeting and received CME credits for attending the live symposium, you are not eligible to receive credit from this monograph. Your answers will be graded, and you will be advised of passage (or failure). A minimum score of 80% must be achieved in order to earn a certificate of credit. Credits for this CME post-test are available until February 15, 2010.

Self-Assessment Test

Prepared by Sami L. Bahna, MD, DrPH, Professor of Pediatrics and Medicine and Chief of the Allergy and Immunology Section at Louisiana State University Health Sciences Center in Shreveport.

For each question or incomplete statement, please select one answer that is correct and enter your choice on the answer sheet on the reverse.

1. What is the hereditary pattern of HAE?
 - a. X-linked
 - b. autosomal dominant
 - c. autosomal recessive
 - d. polygenic
2. The pathogenesis of HAE includes the following, except:
 - a. C1-INH dysfunction
 - b. C2-kinin activation
 - c. bradykinin production
 - d. prostaglandin synthesis inhibition
3. In contrast to IgE-mediated angioedema, HAE is characteristically associated with:
 - a. severe itching
 - b. rapid onset and short duration
 - c. rarely fatal
 - d. often remit during pregnancy
4. What is the least expensive screening laboratory test for HAE?
 - a. CH50 assay
 - b. AP50 assay
 - c. C1q functional assay
 - d. C4 level
5. In contrast to hereditary C1 inhibitor dysfunction, the acquired type is typically associated with:
 - a. low C1q level
 - b. antibodies to kallikrein
 - c. antibodies to bradykinin
 - d. antibodies to C4
6. Which of the following treatments is most effective for acute HAE?
 - a. epinephrine subcutaneously
 - b. corticosteroids intramuscularly
 - c. a plus b
 - d. none of the above
7. New therapeutic approaches for HAE include the following except:
 - a. C1 inhibitor
 - b. plasmin inhibitor
 - c. bradykinin receptor inhibitor
 - d. kallikrein inhibitor
8. Which of the following drugs should be avoided in patients with HAE?
 - a. angiotensin-converting enzyme inhibitors
 - b. testosterone
 - c. estrogen
 - d. antifibrinolytic agent
9. Which of the following is not an effect of bradykinin?
 - a. increased vascular permeability
 - b. activates a specific receptor on the vascular endothelium
 - c. activation of protein kinase C
 - d. hypertension
10. Which of the following new drugs for HAE is administered subcutaneously?
 - a. kallikrein inhibitor
 - b. bradykinin receptor antagonist
 - c. both
 - d. neither

Continued on reverse.

Answer Sheet

Please place your answers to the test questions in the appropriate box.

| | | | | | | | | | |
|----|----|----|----|----|----|----|----|----|-----|
| 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. |
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1. How well organized was this publication? (1 = poor; 2 = fair; 3 = good; 4 = excellent) _____

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3. Overall, how would you rate the importance of this publication? (4 = very; 3 = moderate; 2 = little; 1 = not at all) _____

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