

# Diagnosis and Management of Hereditary Angioedema in the 21st Century

**ACAAI** American College  
of Allergy, Asthma  
& Immunology

Highlights from a symposium conducted in conjunction with the Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology held in Dallas, Texas, on November 8–11, 2007

## Pathophysiology and Clinical Presentation

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Hereditary angioedema (HAE) is a rare autosomal-dominant immunologic disorder that affects approximately half of the children of individuals with HAE. Current estimates suggest that approximately 6,000 to 10,000 individuals have been diagnosed with this disorder in the United States and Europe, and that many additional individuals may suffer its symptoms without having been diagnosed. HAE affects both males and females; hormonal differences accentuate symptoms in female patients. This is a chronic episodic disorder affecting the vascular system of the trunk, face, extremities, gastrointestinal tract, and upper airway. In a patient series studied by Dr. Frank and colleagues, 75% of patients presented with swelling of the extremities and 36% were affected in the face or throat. Thirty-two percent of patients presented with recurrent abdominal pain. These percentages indicate that many patients experience HAE at more than one anatomical site either simultaneously or serially. The frequency of HAE attacks varies widely, but in many patients averages approximately once per month.

HAE first manifests during childhood, when it is usually mild. Presumably because severe attacks are seen infrequently in primary pediatric settings, the diagnosis of HAE is commonly overlooked. In Dr. Frank's early series, adult patients reported

an average of 21 years between their recollection of initial attacks and the definitive diagnosis of HAE. A more recent European study arrived at an average of 9 years. Table 1 summarizes the discrepancy between initial presentation and diagnosis of HAE in a study of 235 patients.<sup>1</sup> The severity of HAE symptoms increases strikingly at puberty. Oral contraceptives accentuate HAE symptoms.

Episodes of HAE typically consist of 24 to 72 hours of swelling (see Table 2). Although most patients tolerate their symptoms, others experience severe abdominal pain that, by mimicking acute appendicitis or cholecystitis, may lead to unnecessary surgery if not recognized as HAE. Family history, the patient's history of prior episodes, and X-ray evidence of "thumb-printing" in areas of the bowel during acute attacks may be helpful for proper diagnosis. In the most severe cases, swelling may cause partial bowel obstruction. In many patients, but not all, attacks present

**Table 1. Age at symptom presentation and diagnosis in 226 patients with HAE**

| Age Range (yrs) | Presentation (%) | Diagnosis (%) |
|-----------------|------------------|---------------|
| 0-10            | 50               | 13            |
| 11-20           | 35               | 19            |
| 21-30           | 11               | 21            |
| >30             | 1                | 47            |

*A* symposium conducted in conjunction with the 2007 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology (ACAAI) chaired by Davis A. Kahn, MD (University of Texas Southwest Medical Center), an expert panel presented the pathophysiology, diagnosis, and emerging treatments of hereditary angioedema (HAE). The panel consisted of Michael M. Frank, MD from Duke University ("Pathophysiology and Clinical Presentation"), Mark Gompels, MD from Bristol, United Kingdom ("Diagnosis and Challenges in Interpreting Laboratory Data"), and William R. Lumry, MD from the University of Texas Health Center--Dallas, Southwestern Medical School ("Emerging Therapies for HAE").

### Learning Objectives

Upon completing this review of the symposium, the physician should:

- understand the pathophysiology and clinical presentation of HAE;
- recognize the signs and symptoms of HAE;
- understand the diagnosis of HAE including the challenges entailed in interpreting laboratory data;
- know the current treatment options together with their potential benefits and limitations; and
- be familiar with current clinical trial data regarding novel and emerging treatment options for developmental agents utilizing different theoretical targets for treating HAE.

### Target Audience

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

### Needs Assessment

HAE manifests as repeated episodes of swelling and acute pain of the face, trunk, extremities, intestinal tract, and upper airway. Abdominal involvement is particularly painful, and may mimic gall bladder or obstructive enteric disease. Misdiagnosis may result in unnecessary abdominal surgery. Attacks involving the airway are potentially fatal. At present, there is no FDA-approved medication for acute attacks of HAE in the United States.

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**Disclosure Statements**

Michael M. Frank, MD acknowledges speaker/consultant/research relationships with Lev Pharmaceuticals, ZLB Behring, Jerini, Pharming and Dyax, all of which have HEA-related compounds in current clinical trials.

Mark Gompels, MD acknowledges sponsorship from ZLB Behring and participation in a clinical trial sponsored by Jerini.

William Lumry, MD acknowledges consultant and research relationships with Baxter, Dyax, Jerini and Lev Pharmaceuticals.

**Off-label Uses of Products**

Because there is no FDA-approved medication for acute attacks of HAE in the United States, current treatment options are based on established practice. All other agents discussed in this review are developmental and are currently undergoing safety and efficacy evaluations in clinical trials.

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**Table 2. Historical Information about Untreated HAE Attacks**

- Time from attack onset to initial relief
  - within 12 hours in 7%
  - within 24 hours in 38%
- Time from attack onset to complete resolution
  - within 12 hours in 2%
  - within 24 hours in 7%
  - within 48 hours in 38%

with an unraised, nonpruritic, circular or diffuse eruption of the skin referred to as erythema marginatum.

Although HAE at any location may be disfiguring, it is potentially life-threatening only when it affects the airway. Unlike other forms of laryngeal edema, HAE with upper airway obstruction generally does not respond well to steroids, mast-cell stabilizers, epinephrine, or antihistaminic agents, thus threatening patients with asphyxiation if they are unable to receive timely intubation. Mortality associated with untreated acute respiratory HAE was as high as 30% based on reported family histories.

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In their initial study, Dr. Frank and colleagues found that episodes of HAE can be precipitated by stress or trauma in approximately a third of patients. Repetitive and sustained stress such as operating machinery manually or prolonged standing may increase risk for HAE attacks in this subset of patients. Patients with HAE commonly experience a prodrome of tingling in the area of the incipient attack. A retrospective questionnaire (N=31) suggests that these prodromal symptoms may

allow for pre-acute intervention, thus potentially preventing or limiting the severity of attacks and diminishing disfigurement, disability, and loss of work or school time.<sup>2</sup>

HAE is associated with abnormalities of serum complement. Type I HAE is characterized by depressed C1 inhibitor (C1-INH) production due to an inherited defective gene that often can be traced through family history. Type I HAE accounts for 80% to 85% of all patients. Individuals in this category have inherited one normal gene allele for expressing C1-INH and one abnormal allele. In Type II, which accounts for most of the remaining 15% to 20% of patients, the defective allele does not lead to an absence of gene product, but to production of non-functional protein. Virtually all patients with HAE synthesize half-normal amounts C1-INH, the product of the normal allele.

Although a family history of HAE is a major diagnostic parameter, the absence of such a history does not rule out HAE, as some patients may have had new mutations in the C1-INH gene. In Type III HAE, the pattern of abdominal and airway episodes resembles that of Types I and II, but these patients have normal C1-INH levels and functionality as well as normal plasma C4. No abnormality of the bradykinin-generating system has been noted. Abnormalities in the Factor XII gene have been identified in some patients, but the link between them and HAE-like symptoms has not yet been established. A cause of increased HAE attacks in some individuals is the use of angiotensin-converting enzyme (ACE) inhibitors for hypertension and/or congestive heart disease. Angiotensin receptor blockers (ARBs) carry a much smaller risk.

The relatively high prevalence of comorbid autoimmune disease (including inflammatory bowel disease, pancreatitis, chronic urticaria, glomerulonephritis, Sjorgen’s syndrome, thyroiditis, and systemic lupus erythematosus) in patients with HAE has also not been explained fully. In an early study of 157 patients with HAE, two-thirds of whom were women, Brickman and colleagues observed a wide variety of autoimmune diseases in approximately 20%.<sup>3</sup> In general, these diseases were mild. The common characteristic in these patients was an increase in T cells, particularly CD-4+ and CD-8+cells, that correlated with complement 4 (C4) deficiency. It is known from animal studies that C4 plays a role in the development of

normal immune function and that C4 deficiency is associated with autoimmunity.

C1-INH, named for its ability to inhibit the complement cascade, has multiple additional functions. C1-INH blocks products of the complement, coagulation, and contact activating systems including coagulation Factor XIa, kinin generation (kallikrein), and both plasmin and tissue plasminogen activator (t-PA) in the fibrinolytic system. Uncontrolled activation of the bradykinin-generating pathway appears to be responsible for HAE attacks.

In distinction from hereditary C1-INH deficiency or dysfunction, acquired C1 deficiency is usually associated with a monoclonal gammopathy that may signal an adenocarcinoma or a lymphoid malignancy. The gammopathy usually consists of a monoclonal antibody that blocks inhibition of the bradykinin-generating system. These patients have depressed C1q, low C4, and circulating cleaved C1-INH due to a failed effort to inhibit the enzyme.

For two decades, long-term therapy for HAE has included antifibrinolytic agents and impeded (attenuated) androgens. The first double-blind, placebo-controlled trial of epsilon amino caproic acid (EACA), a plasmin inhibitor, enrolled three women and two men ranging in age from 22 to 57 years of age. In 19 courses of treatment, only two attacks occurred, both in the same 22-year-old man. By contrast, when patients were treated with placebo, each patient suffered either four or five attacks.<sup>4</sup> However, long-term muscle toxicity, severe pain in the extremities, and a feeling of fatigue limit the use of EACA to occasional treatment in children. In general, antifibrinolytic agents may lead to such complications as thrombosis and gastrointestinal complaints including abdominal pain, although these side effects are rarely seen in patients with HAE.

Androgens are currently the mainstay of prophylactic therapy in HAE. Toxicity is usually mild but may include hair gain or loss, changes in mood, myalgia, and hepatotoxicity. Both men and women undergoing long-term androgen therapy may experience libido suppression or increase, and some women report amenorrhea. Contraindications to the use of androgens include use in children, pregnant and lactating women, and men with prostatic malignancies.

Danazol, a gonadotropin inhibitor that blocks both estrogen and testosterone synthesis, was subjected to a double-blind, placebo-controlled clinical trial in nine

patients with severe HAE. Only one attack occurred during 42 months of oral danazol therapy compared with 44 attacks during 46 months of placebo.<sup>5</sup> Danazol is associated with dose-dependent restoration of C1-INH that may reach normal levels, but normalization is not the therapeutic goal. Danazol is not useful in acute therapy. Like other attenuated androgens, it is a methylated compound that is given orally and takes up to 48 hours to induce symptom relief. There are no intramuscular or intravenous preparations. In an abdominal attack, its absorption is unreliable. Further, it is of limited use in children, as it may be associated with premature closure of epiphyses, and in pregnant women as it has been associated with infants with ambiguous genitalia.

Infused fresh frozen plasma has been reported useful in terminating acute HAE attacks because it is an exogenous source of natural C1-INH. Plasma terminates attacks in 90% to 95% of patients. However, increased symptom severity may occur in a small minority of patients, and there is no way of identifying them prior to treatment. This and the potential risk of transmitting blood-borne pathogens have limited the use of this therapy. Partially purified C1 inhibitor prepared from plasma has been shown in many studies, including one double-blind study, to terminate acute attacks.

## Diagnosis and the Challenge of Interpreting Laboratory Data

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The laboratory approaches to testing for HAE are serologic and are based on the current understanding of the complement pathway. Type I HAE is characterized by low C4 concentration, low C1-INH antigen and, therefore, low C1-INH activity. In contrast, Type II HAE consists of low C4, normal C1-INH antigen, and low C1-INH function. The rare acquired form of HAE has the same profile as Type I, but will also have low C1q levels.

As C4 is almost always low, it can be used as a screening test for the condition. It is, however, necessary to undertake confirmatory C1-INH antigen level and functionality testing in all cases in which C4 is low or when family history is compelling

for HAE. It is also necessary in cases of angioedema with no urticaria, and in those patients with angioedema and abdominal pain. There is as yet no validated routine laboratory test for Type III HAE.

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Although testing protocols are well established, they are not without pitfalls. For example, antisera for C4 measurements show variation depending on methodology. Antisera may be subject to interference or variation and fail to recognize C4 accurately. The resulting low values may result in a misdiagnosis. In general, C4 testing is sufficiently reliable for screening, but false negatives may occur in rare cases. One such case is interference with the assay by an IgM paraprotein associated with an acquired form of C1-INH associated with lymphoproliferative disease. It remains a prudent practice to discuss any atypical results with one's preferred laboratory.

C1-INH function can be tested via two methods. One is the Quidell binding assay that utilizes biotin-labeled C1s complex to which only functional C1-INH will bind. The bound C1-INH is then added to an avidin-coated plate. The result is labeled with an antibody against C1-INH from which the proportion of C1-INH binding can be calculated. The other method of measuring C1-INH function is the colorimetric Technoclone C1-INH functional assay. In this test, the addition of an artificial substrate for C1-esterase to fresh serum hydrolyses the esterase and produces a colored product. The intensity of the color is inversely proportional to the C1-INH in the serum sample. Both tests must be performed on fresh serum (less than 4 hours after drawing) or freshly frozen serum to avoid sample decay and to ensure that the constant activity of complement will not have consumed so much functional C1-INH that the measurable amount is falsely low.

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A statistical comparison of results from the two methods in several patients over a number of ranges yielded a correlation of approximately 0.83, a reasonable result for two procedures presumably measuring the same thing.<sup>6</sup> Nevertheless, one-time testing with both methods may yield confusingly discordant results. Fortunately, both methods showed better concordance assessed by ability to predict the presence or absence of HAE.

The Bayes' theorem states that the probability that any single test will yield positive results depends on a prior probability of the condition in the same population. Thus, in a condition such as HAE in which the prevalence is very low (approximately 1 in 50,000), false positive results are more likely than true positive results if everyone is tested.

The foregoing conclusion is supported by a clinical audit conducted on 43 patients with data suitable for assessment. When all notes and laboratory data had been reviewed, 11 diagnoses of HAE could not be substantiated. Ten of the patients were taken off all medications without adverse effects. The eleventh patient declined to discontinue treatment.<sup>7</sup> Prior selection via a clinical history improves the positive predictive value of a laboratory test. In cases in which the results of tests are inconclusive, genetic testing (gene sequencing) may have a role in confirming a diagnosis.

## New Therapies for HAE

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*A*lthough a C1-INH preparation has been available outside of the United States since 1973, there is no FDA-approved medication for the treatment of acute HAE attacks in the United States. One promising C1-INH agent was abandoned in the 1990s after 10 years of development because of the failure of a poorly designed clinical trial to demonstrate its efficacy endpoints.

Now, however, five pharmaceutical companies are in a race for approval to market novel treatments in this country. Each has a developmental compound in clinical trials made unusually difficult to design by the small disease population, its geographical diversity, age issues in exposing individuals to developmental medications, and distance from home to participating treatment centers. One consequence is that trial data are not easily compared because the protocols differ in important criteria such as minimum and maximum ages of participants, allowable time lapse from symptom onset to treatment intervention, permissibility of second or rescue dosing, response endpoints, and assessment measures.

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**Bradykinin receptor-2 (BK2) antagonism**  
Icatibant acetate (Jerini) is a subcutaneously or intravenously administered BK2-specific peptidomimetic compound designed to negate the effect of bradykinin on vascular tissue by saturating its receptors. Denied access to those receptors, bradykinin is unable to induce vascular inflammation and permeability.

The first report of successful treatment of HAE with icatibant to appear in the scientific literature pertained to an uncontrolled pilot study undertaken in Germany, where it was developed. Fifteen patients were treated with either subcutaneous or intravenous icatibant for a total of 20 acute episodes. Overall, intervention with icatibant reduced the mean time to onset of symptom relief by 97% compared with historical data on untreated attacks. Interestingly, plasma bradykinin concentrations measured 4 hours after either injection or infusion decreased by more than 60% relative to baseline, when the median level was seven times the normal level.<sup>8</sup>

Prior to the publication of the foregoing pilot study, however, the final results of two pivotal randomized, double-blind, and controlled trials of icatibant in acute HAE attacks were announced by the drug's manufacturer.<sup>9</sup> One For Angioedema Subcutaneous Treatment (FAST 1) trial was conducted in the United States, Canada, Argentina, and Australia. It randomized 56 patients to receive either a single fixed 30 mg dose of icatibant or placebo. FAST 2 randomized 74 patients in Germany and Israel to receive either a single fixed 30 mg dose of icatibant or tranexamic acid as an active control. Treatments were administered subcutaneously, usually on the abdominal wall. Both trials were limited to patients 18 years of age and above with Type I or Type II HAE and serologically confirmed C1-INH antigen deficiency or low activity. All patients were experiencing at least moderate peripheral, abdominal, or laryngeal symptoms and were able to seek treatment within 4 to 6 hours of symptom onset. The trials were conducted simultaneously.

In both trials, treatment with icatibant was associated with statistically significant improvement in secondary outcomes (time to onset of symptom relief from skin swelling, skin pain, and abdominal pain) compared with placebo/active control with the single exception of relief from abdominal pain in FAST 1 ( $p=0.056$ ). However, only in FAST 2 did improvement in the primary endpoint – median time to onset of symptom relief using the Visual Analog Scale (VAS) – achieve statistical significance (2 hours vs. 12 hours;  $p<0.001$ ). In FAST 1, treatment with icatibant was clinically relevant but not statistically significant for the same primary endpoint (2.5 hours vs. 4.8 hours;  $p=0.131$ ) due to an unexpectedly high response to placebo among patients with abdominal pain as measured by VAS. (This discrepancy between the two trials is currently in discussion between the trial directors and the FDA.) The median time to complete symptom relief, or end of attack, as determined by VAS was statistically significant in both trials ( $p=0.035$  for FAST 1 and  $p<0.001$  for FAST 2).

Adverse effects of icatibant in these trials were limited to injection-site erythema, warmth, and pruritis that resolved usually within 30 minutes.

Icatibant has been awarded orphan drug status by the FDA. Based on the foregoing data, it has been granted a priority review with final FDA action expected in April, 2008.

### Recombinant plasma kallikrein antagonist

DX-88 (Ecallantide® by Dyax) is a recombinant plasma kallikrein inhibitor that has two actions pertinent to HAE: (i) it blocks the effect of kallikrein on high molecular weight kininogen to prevent the synthesis of bradykinin and (ii) it blocks the positive feedback loop from kallikrein through the Factor XIIa pathway. Like icatibant, DX-88 has been awarded both orphan drug and fast-track status by the FDA. It has been under very active development in the United States, having been through eight completed trials in HEA populations with two more currently in progress. There are also two trials designed for a cardiovascular surgery indication that will provide additional safety data.

The third Evaluation of DX-88's Effects in Mitigating Angioedema (EDEMA3) trial was a pivotal double-blind, placebo-controlled trial designed to assess the efficacy and safety of DX-88 for the treatment of acute HAE attacks. The double-blind phase was followed by a repeat dosing phase. EDEMA4, a Phase III trial with an open-label extension, is a confirmatory study that is currently in progress.

EDEMA3 enrolled 71 patients at least 10 years of age who were experiencing moderate to severe HEA attacks at any site. Initially, patients were randomized to receive either DX-88 30 mg or placebo by subcutaneous injection. Patients were evenly matched in the two cohorts with the exception that the number experiencing laryngeal symptoms was larger in the active group (N=7) than in the placebo arm (N=3). Patients who completed the one-time randomized phase were permitted open-label treatment with DX-88 for subsequent acute episodes. In EDEMA3, the efficacy of DX-88 was assessed using two HAE-specific patient-reported outcome scales: the Treatment Outcome Score (TOS) (range -100 to 100) and the Mean Symptom Complex Severity Score (MSCS) (range 0-3).<sup>10</sup> The primary outcome was the change in TOS at 4 hours following treatment. MSCS at 4 hours and time to symptom relief were the secondary endpoints.

Treatment with DX-88 was associated with a significantly higher mean TOS at 4 hours compared with placebo ( $p=0.021$ ), marking an affirmative outcome for the primary endpoint. Improvement in MSCS at 4 hours favored DX-88 treatment ( $p=0.024$ ) as did time to onset of overall symptom improvement (149 minutes vs. more than 240 minutes;  $p=0.044$ ), thus

confirming the efficacy of DX-88 with respect to the secondary endpoints.<sup>11</sup> Adverse events in the double-blind portion were more frequent in DX-88-treated patients (56% vs. 33%). Such events were mild except for three Grade III toxicities in patients treated with the active agent and four Grade III toxicities in patients who received placebo. One hundred thirty-four acute HAE attacks were treated during the open-label extension with one treatment-related serious adverse event. These results were similar to those of a smaller trial in which patients were randomized to receive one of four doses of DX-88 or placebo during acute episodes. Treatment at all dose levels was associated with significantly more rapid symptom relief within 4 hours than placebo.<sup>12</sup>

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### Recombinant human C1 esterase inhibitor

Rhucin®, a recombinant human C1 esterase inhibitor derived from the mammary secretions of a transgenic rabbit, has had a less linear developmental path. Although it has been granted orphan drug status by the FDA, its application for marketing approval in Europe was originally rejected and is now under appeal at the EMEC. The Phase III trial from which data were presented in Europe is now followed by a Phase III trial in the United States and Canada, the completion of which was announced by the manufacturer on August 30, 2007. Although the data from the North American trial have not yet appeared in the scientific literature, preliminary data suggest that Rhucin® (Pharming Group NV) is both efficacious and safe when used to treat patients with acute HAE symptoms.

The double-blind North American trial recruited 28 patients who were randomized in equal numbers to receive either the active medication or placebo. Patients in the treatment cohort experienced unanimous response compared with a 36% response rate among patients in the placebo

trial arm. The median time to onset of relief, the trial's primary endpoint, was significantly shorter in the treatment group (60 minutes vs. 508 minutes;  $p=0.019$ ) as was the time to minimal symptoms (368 minutes vs. 1,209 minutes;  $p=0.0038$ ), the secondary endpoint. No treatment-related adverse events were reported among patients randomized to receive Rhucin®.<sup>13</sup>

### Plasma-derived human pasteurized C1-INH concentrate

A product of ZLB Behring, this has been used to treat more than 300,000 acute HAE attacks in Europe over a period of 20 years. Recently, however, it has been under evaluation in the Phase III double-blind and placebo-controlled International Multi-center Prospective Angioedema C1-INH Trial (IMPACT) as a means of achieving approval in the United States and the United Kingdom. Recruitment of 125 patients at 45 centers in 15 countries made IMPACT the largest Phase III dose comparison trial (10 units or 20 units per kilogram of body weight) to be conducted in HAE. The trial enrolled individuals 6 years of age and older who have serologically-determined C1-INH deficiency and documented histories of acute facial or abdominal attacks. The primary clinical endpoint was reached in the fall of 2007. Although the results have yet to appear in a scientific publication, the efficacy data were announced in a corporate press release of November 26, 2007.

*Recruitment of 125 patients at 45 centers in 15 countries made IMPACT the largest Phase III dose comparison trial (10 units or 20 units per kilogram of body weight) to be conducted in HAE.*

The trial's primary efficacy endpoint was the time from treatment to the onset of relief from facial or abdominal symptoms as reported by participating patients. The larger dose of C1-IHN concentrate was associated with a median time to onset of relief of 30 minutes compared with 90 minutes for patients receiving placebo. Although this was reported as having been statistically significant, the  $p$  value was not included in the press release.

Because HAE symptoms in acute attacks typically intensify over time, the secondary endpoint of IMPACT was the proportion of subjects with increased intensity between 2 and 4 hours after treatment compared with baseline. Compared with placebo, treatment with the higher dose of C1-INH concentrate significantly improved the intensification of symptoms ( $p=0.001$ ). Although the lower dose was also superior to placebo, the difference did not reach statistical significance.<sup>14</sup>

#### Nanofilter-purified human plasma-derived C1 esterase inhibitor

Although the risk of transmitting blood-borne pathogens limited the use of fresh frozen plasma for treatment acute HAE attacks, new nanofiltration techniques now enable scientists to consider the use of plasma-derived C1-INH. Cinryze™ by Lev Pharmaceuticals is the first such product to reach Phase III trials. It is undergoing evaluation as C1-INH replacement therapy for both acute HAE episodes and long-term HAE prophylaxis.

C1-inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating Efficacy (CHANGE) is a two-part Phase III trial addressing the acute setting in Part A and prophylaxis in Part B. The results of Part A were presented at the ACAAI meeting in November, 2007. Although Part B has now been completed and the data forwarded to the FDA as an amended request for regulatory approval, they have not yet been presented in a scientific setting.

In Part A of CHANGE, 71 patients were randomized for treatment with a single dose or either Cinryze™ or saline by infusion. All patients had documented HAE without evidence of anti-C1-INH antibodies. Sixty-eight patients had eligible acute HAE attacks with moderate or severe pain and C4 levels thought to be consistent with acute HAE attacks. These 68 patients comprised the efficacy dataset. Thirty-five and 33 patients, respectively, were randomized to the treatment and placebo cohorts. Following treatment, subjects were asked to report their pain status at a specific anatomical site (abdomen, genitourinary, or face) every 15 minutes up to a total of 4 hours. This was termed the defining symptom. Three consecutive reports of improvement in the defining symptom constituted “unequivocal relief,” and the time to the first of those three reports was used as the time to the onset of unequivocal relief. The median time to

unequivocal relief was the primary endpoint. Secondary endpoints included the presence or absence of unequivocal relief of the defining symptom within 4 hours following initial treatment, time to complete resolution of the attack, and the ability of Cinryze™ to raise C1-INH and C4 levels. Lev Pharmaceuticals has reported statistically significant efficacy results for both primary and secondary endpoints<sup>15</sup>; however, the trial data have been embargoed temporarily pending publication in a refereed journal. Subjects who experienced no relief of symptoms within 4 hours were given open-label Cinryze™ for rescue. Individuals who presented with laryngeal edema were not randomized, but were treated with open-label Cinryze™.

*Lev Pharmaceuticals has reported statistically significant efficacy results for both primary and secondary endpoints; however, the trial data have been embargoed temporarily pending publication in a refereed journal.*

In the last 2 years, Cinryze™ has been given approximately 3,500 times for acute HAE attacks, short-term prophylaxis, and long-term replacement therapy. No drug-related side effects have been reported. Importantly, there are no reports to date of seroconversion for hepatitis B or C, parvovirus, or the human immunodeficiency virus (HIV).

#### Conclusion

HAE, although uncommon, is a painful, disabling, disfiguring, and potentially life-threatening episodic disorder. Currently there is no FDA-approved medication for the treatment of acute symptoms. This paper summarizes the current status of each of four developmental agents competing to be first to market with FDA and EMCA approval by presenting up-to-date data from randomized clinical trials.

Because of orphan status and priority regulatory review, one or more of these products may be available to the sufferers of this disease as early as the opening months of 2008.

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# Diagnosis and Management of Hereditary Angioedema in the 21st Century

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 2007 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 March 1, 2009.

## Self-Assessment Test

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. Which of the following statements is NOT true?
  - a. Acute HAE can be life-threatening
  - b. HAE affects at least 6,000 to 10,000 individuals in the US and Europe.
  - c. HAE is almost always painful and may be disfiguring.
  - d. Abdominal symptoms of acute HAE may mimic cholecystitis or appendicitis.
  - e. None of the above.
2. Which of the following statement is/are true?
  - a. Initial acute attacks of HAE typically appear in the first decade of life.
  - b. Acute HAE attacks typically increase in severity at puberty.
  - c. The time elapsed between initial symptoms of acute HAE and definitive diagnosis may exceed two decades.
  - d. Acute HAE of the upper airway usually responds to mast cell stabilizers but not to epinephrine, antihistamines, or steroids.
  - e. All of the above.
  - f. All of the above except (d).
3. Currently,
  - a. Attenuated androgens are the preferred treatment for acute HAE attacks.
  - b. There is no FDA-approved therapy for acute HAE attacks.
  - c. Attenuated androgens are used appropriately only in adult males.
  - d. Epsilon aminocaproic acid (EACA) has been demonstrated in placebo-controlled trials to be efficacious as HAE prophylaxis only in pre-pubescent males.
  - e. None of the above.
4. Type I HAE is characterized by
  - a. High C4 concentration.
  - b. High C1-INH antigen.
  - c. High C1-INH activity.
  - d. All of the above.
  - e. None of the above.
5. Type II HAE is characterized by
  - a. Low C4 concentration.
  - b. Normal C1-INH antigen.
  - c. Low C1-INH functionality.
  - d. All of the above.
  - e. All of the above except (b).
6. Confirmatory testing for C1-INH antigen level and functionality is required for the diagnosis of HAE when the patient's C4 level is low OR:
  - a. Family history is compelling for HAE.
  - b. The patient presents with angioedema without urticaria.
  - c. The patient presents with angioedema and abdominal pain.
  - d. All of the above.
  - e. All of the above except (b).
7. New developmental strategies for treating acute attacks of HAE include
  - a. Bradykinin receptor-2 blockade.
  - b. Plasma kallikrein antagonism.
  - c. C1 esterase inhibitor supplementation.
  - d. All of the above.
  - e. None of the above.
8. The CHANGE trial provides evidence of rapid symptom relief in acute attacks of HAE using
  - a. A nanofiltered human plasma-derived C1 esterase inhibitor.
  - b. A recombinant human C1-INH inhibitor.
  - c. A plasma-derived human pasteurized C1-INH concentrate.
  - d. Fresh frozen plasma
  - e. None of the above.
9. The IMPACT study
  - a. Demonstrated no rapid relief from symptoms of acute HAE using a plasma-derived human pasteurized C1-INH concentrate.
  - b. Demonstrated rapid onset of symptom relief using a kallikrein inhibitor.
  - c. Is designed principally as an efficacy and safety demonstration of a plasma-derived human pasteurized C1 inhibitor for drug regulators in the US and the UK.
  - d. None of the above.
10. The EDEMA3 trial
  - a. Involved a kallikrein inhibitor in acute HAE attacks.
  - b. Demonstrated significantly more severe adverse events among patients treated with the trial drug than in the control population.
  - c. Demonstrated efficacy only of the secondary endpoints.
  - d. All of the above.
  - e. None of the above.

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. |
|----|----|----|----|----|----|----|----|----|-----|

## Program Evaluation

1. How well organized was this publication? (1 = poor; 2 = fair; 3 = good; 4 = excellent) \_\_\_\_\_

2. How would you rate the clarity of this publication? (1 = poor; 2 = fair; 3 = good; 4 = excellent) \_\_\_\_\_

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

4. Do you intend to make any changes in your practice or patient care as a result of this publication? \_\_\_\_\_ Yes \_\_\_\_\_ No

If Yes, how? Comment \_\_\_\_\_

5. Did this publication include proper disclosure of speakers' potential conflict of interest and relationship with industry? \_\_\_\_\_ Yes \_\_\_\_\_ No

6. Did this publication include proper disclosure of speakers' discussion of FDA Off-Label use of medications or products? \_\_\_\_\_ Yes \_\_\_\_\_ No

If NO, please comment \_\_\_\_\_

7. Was this a fair and balanced publication? Please comment on the scientific rigor, fairness, and balance of the material.

Comment \_\_\_\_\_

8. What related topics would you find useful for future ACAAI programs and publications? \_\_\_\_\_

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