When is prophylaxis for hereditary angioedema necessary?

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Objective: To determine when newer agents, such as C1 esterase inhibitor protein (C1-INH), should be considered as prophylaxis to decrease hereditary angioedema (HAE) attacks as an alternative to androgens, which have significant adverse events.

Data Sources: A literature review (PubMed, Google, and Ovid), guideline review, expert panel meeting, and group discussion were performed to decide when prophylaxis is indicated.

Study Selection: Articles addressing HAE therapy published in the peer-reviewed literature were selected.

Results: The retrieved studies demonstrate that C1-INH is effective and that the half-life makes it attractive for prophylactic use. The short half-lives of ecallantide, icatibant, and recombinant human C1-INH limit their use as prophylactic agents. Patients with severe anxiety, more than 1 attack per month, rapid progression of attacks, limited access to health care, more than 10 days lost from work or school per year, previous laryngeal swelling, more than 3 emergency department visits per year, more than 1 hospitalization per year, previous intubation, previous intensive care unit care, significant compromise in quality of life, or narcotic dependency should be considered for androgen or C1-INH prophylaxis therapy.

Conclusion: Patients with HAE with frequent attacks, severe attacks, past laryngeal attacks, excessive loss of work or school, significant anxiety, and poor quality of life should be considered for C1-INH prophylaxis, especially those who fail, are intolerant of, have adverse reactions to, or are not candidates for androgen therapy.


INTRODUCTION

Hereditary angioedema (HAE) is an autosomal-dominant disorder that is associated with a deficiency in C1 esterase inhibitor protein (C1-INH) (Fig 1). The 2 types of HAE are clinically indistinguishable. Type I is characterized by serum C1-INH levels of 5% to 30% of normal and is seen in approximately 85% of patients. Patients with type II HAE, 15% of those with HAE, have normal or elevated levels of dysfunctional C1-INH. It is estimated that 25% of patients with HAE have this disease as a result of new spontaneous mutation. A third type of HAE, formerly called type III HAE, has been identified. This type, for which estrogen-dependent and estrogen-independent forms have been described, is not associated with C1-INH deficiency; however, it has been associated with genetic defects involving factor XII. Types I and II HAE could more correctly be described as C1-INH deficiency disease. Thus, herein, the terms type I HAE, type II HAE, and C1-INH deficiency disease are used interchangeably. An update on HAE focusing on therapy is followed by a discussion of prophylaxis. The intent is to help physicians care for patients with HAE appropriately, especially when considering prophylactic therapy.

PREVALENCE

In the United States, the prevalence of C1-INH deficiency disease has been estimated to be 1:10,000 to 1:50,000. The disease occurs equally in men and women, and no differences between ethnic groups have been demonstrated. The clinical manifestations of HAE, however, are often more severe in women. This is believed to be due to hormonal influences and to the difficulties associated with using attenuated androgens in women. Studies have sug-
gested that HAE may be undiagnosed for as long as 9 years after the onset of symptoms (T.C., M. Lunn, unpublished data, 2008). This delay in diagnosis may be greater in the 25% of patients with no family history of the disease, who develop HAE because of a new mutation.

**MORBIDITY AND MORTALITY**

The morbidity and mortality associated with C1-INH deficiency disease are significant. In the United States, HAE attacks have been associated with 15,000 to 30,000 emergency department visits annually.\(^4\) Mortality, secondary to laryngeal edema and asphyxiation, has been reported in up to 30% of patients with previously undiagnosed HAE.\(^7,12\) Abdominal attacks lead to hospitalizations and unnecessary surgical procedures.\(^4,7\) Cutaneous attacks are particularly disruptive because they may be functionally disabling or disfiguring. Patients may elect to remain homebound owing to the change in appearance that facial attacks produce. 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.

Most patients with C1-INH deficiency disease experience disability due to the frequency and nature of attacks, which can have a severe impact on quality of life.\(^9\) While experiencing symptoms of an HAE attack, patients may not be able to care for themselves or their dependents, may miss many days of school or work, and may have difficulty maintaining employment.\(^7\) Approximately 44% of patients will have 1 to 4 episodes of angioedema per month.\(^7\) Death in HAE due to asphyxiation is a serious risk in patients with previously undiagnosed HAE and untreated patients.\(^13\) Attacks of HAE typically account for 20 to 100 sick days per year, with an average of 1 to 3 attacks a month, often every 10 to 14 days, each attack lasting as long as 3 to 5 days.\(^14\)

**DIAGNOSIS AND TESTING**

C1-INH deficiency must be considered if patients demonstrate recurrent angioedema without urticaria, have recurrent abdominal or laryngeal attacks, or have a positive family history of angioedema. The absence of a family history does not rule out HAE due to spontaneous mutation. Patients should be tested for serum C4 levels. This is the best screening method, and only rarely will C4 levels be within the reference range. If the suspicion for HAE is strong and the C4 level is normal, repeating the test during an attack is recommended. In this case, a normal C4 result virtually excludes HAE. Patients with late-onset symptoms and no family history of angioedema should be evaluated for acquired angioedema by testing for low levels of C1q. The diagnosis of acquired angioedema requires further evaluation for the presence of a lymphoproliferative disorder or autoimmune disease. With normal C1q levels, C1-INH deficiency disease can be determined based on levels of C4 and C1-INH (Fig 2).

**ATTACK SITES**

The clinical course of C1-INH deficiency disease is unpredictable.\(^1\) Sites of attack tend to vary from patient to patient and within individual patients. Facial swelling occurs in more than 75% of patients and may extend to the upper airways. Laryngeal attacks are the most concerning because they can be life-threatening.\(^7,13\) Patients experiencing laryngeal edema often complain of tightness of the throat, dysphonia, inability to clear saliva, and dysphagia. In advanced cases, asphyxiation may occur. Patients may also have edema of the soft palate or tongue, making swallowing and breathing difficult.\(^1^1\) One retrospective study\(^1^2\) demonstrated that untreated patients with laryngeal attacks had a mean symptoms duration of 103 hours. Symptoms peaked 8 to 12 hours after attack onset and continued unabated for 12 to 24 hours. More than half of all patients with HAE are expected to experience at least 1 laryngeal attack during their lives.\(^1^1\)

Recurrent abdominal attacks occur in more than 90% of patients. Onset of attacks may be rapid and is often accompanied by severe pain, nausea, vomiting, diarrhea, and hypovolemia. Abdominal attacks frequently require hospitalization. Recurrent abdominal attacks and associated biliary or pancreatic obstruction can lead to gallbladder disease or pancreatitis.\(^1\) The symptoms of abdominal involvement of HAE may mimic an acute abdomen, and in 1 study, nearly one-third of patients had their conditions misdiagnosed and had unnecessary surgery.\(^5,1^1\)

Cutaneous swelling is the most common symptom of HAE, with the extremities being the most frequent attack site. In a retrospective German study,\(^1^1\) 97.5% of patients reported...
swelling of hands, arms, feet, legs, and thighs. Swelling of the extremities is often disfiguring and functionally disabling.\textsuperscript{11}

Angioedema involving other anatomical sites is less common but may cause significant morbidity in some individuals. Urogenital attacks may result from intercourse, childbirth, or local trauma, such as horseback riding. When the bladder or urethra is involved, patients may experience urinary retention and pain. Headache may present with visual disturbances and may mimic migraine. Chest involvement may be associated with chest discomfort and dyspnea.\textsuperscript{11}

\section*{CURRENTLY AVAILABLE THERAPIES}

Significant differences exist between US and European interventions for HAE, largely due to a lack of approved disease-specific treatment modalities for acute HAE attacks in the United States, with the possible exception of fresh frozen plasma.\textsuperscript{15} Prophylactic therapy in the United States has historically been limited to attenuated (impeded) androgens, which have substantial contraindications and adverse effects.

\subsection*{Acute Treatment}

Patients with acute HAE attacks in the United States are most commonly treated with supportive therapy until symptoms resolve, including intravenous fluids, pain management, intubation, and tracheotomy as indicated. Corticosteroids, antihistamines, and epinephrine are often used but are not efficacious in aborting acute HAE attacks. Fresh frozen plasma has been used successfully, but, in addition to its potential to transmit viral diseases, there has been concern that it may exacerbate symptoms by supplying additional substrates to generate edema and perpetuate loss of regulatory control.\textsuperscript{15}

\subsection*{Prophylactic Treatment}

For HAE prophylaxis in the United States, attenuated androgens (eg, danazol, stanozolol, and oxandrolone) are commonly used, whereas antifibrinolytics (eg, aminocaproic acid and tranexamic acid) are rarely used, principally because of their adverse effect profile and lesser effectiveness. Androgens presumably act by inducing the hepatic synthesis of C1-INH or increased degradation of kinins and are effective for short- and long-term prophylaxis. However, they are slow acting (requiring approximately 48 hours before onset of significant effect) and are not useful in terminating acute attacks. Androgens administered for at least 2 to 3 days before scheduled surgical or dental procedures are used to reduce the risk of acute HAE episodes that can be precipitated by such procedures.

Danazol has been used for more than 30 years as prophylactic treatment for HAE. In most cases, an induction dose (eg, 400–600 mg/d) is initially administered for several weeks. The individual dose is then tapered to the minimum believed to be effective in attack prevention. Typically, maintenance doses vary from 50 to 200 mg/d or every other day, although some patients may need up to 800 mg/d.\textsuperscript{1,4} Patients often require adjustment of their dose owing to new triggers and associated changes in their disease burden. Long-term prophylaxis with danazol must include consideration of its associated adverse effects, including virilization, weight gain, amenorrhea, decreased libido, myalgia, fatigue, headaches, hemorrhagic cystitis, arterial hypertension, and hepatic necrosis or cholestasis.\textsuperscript{1,4,16,17} Additional hepatotoxic effects have also been reported, including induction of hepatocellular adenoma and carcinoma.\textsuperscript{16} Attenuated androgens are contraindicated in children and during pregnancy. Many patients find the adverse effects to be intolerable and are unwilling to take androgens or are anticipated to become nonadherent; however, the true incidence of nonadherence is not known. Finally, androgen therapy is ineffective in some patients.

Antifibrinolytics are rarely used for prophylactic therapy in the United States. Presumably, these agents act by inhibiting the conversion of plasminogen to plasmin, resulting in a C1 inhibitor–sparing effect. Their use is associated with reductions in the number and severity of HAE attacks in only 30% of patients.\textsuperscript{4} Aminocaproic acid is used as a drug of last resort for children because it has significant adverse effects and is of limited clinical utility. Aminocaproic acid is associated with thrombosis, postural hypertension, muscular pain, and weakness. Tranexamic acid is not commonly used in the United States because it is not approved for use in HAE.\textsuperscript{18}

\section*{NEW THERAPEUTIC OPTIONS FOR HAE}

Several new agents are under investigation for treating HAE. Availability of these agents is anticipated to change the treatment paradigm for C1-INH deficiency disease.

\subsection*{Ecallantide}

Developed for intravenous or subcutaneous delivery and with a half-life of approximately 2 hours, ecallantide (DX-88) is a small-protein kallikrein inhibitor that has been evaluated for short-term treatment in 4 phase 1 studies in healthy adults and in 3 phase 2 studies and 2 phase 3 studies in patients with moderate to severe HAE. One hundred seventy-five patients, encompassing more than 300 HAE attacks involving all anatomical sites, have been treated with ecallantide.\textsuperscript{19}

In a phase 2 study (Evaluation of DX-88’s Effect in Mitigating Angioedema [EDEMA 2]), Schneider and colleagues\textsuperscript{19} evaluated the efficacy and tolerability of ecallantide, 5, 10, 20, or 40 mg/m\textsuperscript{2} intravenously, in 48 patients. Significant improvements in symptoms of HAE attacks within 4 hours were reported (72.5% vs 25% for patients receiving placebo; \(P = .02\)). The most common adverse effects were headache, diarrhea, nausea, upper respiratory tract infection, vomiting, abdominal pain, allergic rhinitis, cough, and sinusitis. Of possible concern is that 4 patients experienced severe or life-threatening short-term dosing reactions.

In the phase 3 study (EDEMA 3), 72 patients received either ecallantide or placebo. The primary end point was a treatment outcome score based on an evaluation of change in symptoms. The mean treatment outcome score was signifi-
diagnosed with HAE (n = 4 patients). Mean time to onset of symp-
toms was shorter in patients administered icatibant subcu-
taneously, and treatment resulted in mean time to symptom
relief onset of 1.16 hours. Icatibant use resulted in marked
improvements in skin swellings and abdominal attacks. How-
ever, rebound HAE attacks, successfully treated with rescue
medications, were seen in 4 patients (5 attacks). Marked
decreases in plasma bradykinin levels were seen 4 hours after
intravenous or subcutaneous icatibant administration, sug-
gest a feedback mechanism. Subcutaneous icatibant was
associated with local reactions, such as itching, urticarial
wheal, erythema, and mild pain. All reactions resolved spon-
taneously within a few hours.

On the basis of these data, subcutaneous icatibant was
evaluated in 2 phase 3 studies for treating patients with
HAE.\textsuperscript{20} FAST 1 (For Angioedema Subcutaneous Treatment) was a double-blind, randomized, placebo-controlled study conducted in 56 patients with moderate to severe HAE, and FAST 2 was a double-blind, randomized, comparator-controlled study conducted in 74 patients with acute HAE. Median time to clinical symptom improvement was shorter for patients receiving icatibant in FAST 1 without statistical significance (2.5 vs 4.6 hours for placebo; \(P = .14\)). Statistical significance was achieved for median time to clinical symptom improvement in FAST 2 (2 vs 12 hours for tranex-
amic acid; \(P < .001\)). Time to first symptom improvement was stastically significant in both studies (FAST 1: 0.8 vs 16.9 hours for placebo, \(P < .001\); FAST 2: 0.8 vs 7.9 hours for tranexamic acid, \(P < .001\)). No clinically relevant adverse events were reported for icatibant in either study.

In 2008, icatibant received a nonapprovable letter from the FDA because the primary outcome did not reach statistical significance. The agent has been approved for use in Europe, and new phase 3 clinical studies are anticipated to be started in the United States this year.

\textbf{Cinryze}

A nanofiltered, highly purified human C1-INH (C1-INH-nf) replacement therapy (Cinryze; ViroPharma Inc, Exton, Penn-
sylvania) has been developed for C1-INH deficiency disease.
Nanofiltration, via 2 serial filters (Planova; Asahi Kasei Med-
cial Co Ltd, Westbury, New York), provides additional mar-
gins of safety against enveloped and nonenveloped viruses and is effective for the removal of prions.\textsuperscript{20}

C1-INH-nf has been evaluated in 2 phase 3 US clinical
trials, 1 for short-term treatment and 1 for prophylactic treat-
ment of HAE. The short-term trial was a randomized, double-
blind, placebo-controlled study using intravenous C1-INH-nf
for the treatment of HAE abdominal, urogenital, or facial
attacks (B. Zuraw, W. Lumery, D. Hurewitz, unpublished
data, 2008). The primary end point was time to onset of
unequivocal relief of the HAE symptom. The median time to
the beginning of unequivocal relief was significantly shorter
with C1-INH-nf (2 hours) than with placebo (>4 hours, \(P =
.03\)). Thirty-one HAE attacks treated with open-label C1-
INH-nf (including 18 laryngeal attacks) had a 100% response
rate. Seven individuals were given C1-INH-nf prophylacti-
cally before surgical or dental procedures, and none experi-
enced angioedema during or immediately after the proced-
tures.

The prophylactic trial was a 6-month, double-blind, place-
bo-controlled, multicenter, crossover study with 3 months of
placebo use and 3 months of active therapy (B. Zuraw, W.
Lumery, D. Hurewitz, unpublished data, 2008). The primary
end point was the number of attacks while taking C1-INH-nf
was statistically significantly less than with placebo (6.1 vs
12.7, \(P < .001\)). Secondary end points, including days of swelling (10.1 vs
29.6), also showed a statistically significant benefit for the
active treatment phase (\(P < .001\)). There were no significant
adverse events, and the safety of C1-INH-nf builds on the
experience in Europe, where C1-INH concentrate has been
used for 36 years.\textsuperscript{23–25}

In October 2008, the FDA approved Cinryze for the
prophylactic treatment of HAE. The FDA-approved dose is
1,000 U (two 500-U vials) every 3 to 7 days intravenously.
The short-term treatment trial data are currently under review
by the FDA.

\textbf{Berinert}

Berinert P (CSL Behring, King of Prussia, Pennsylvania) is
an intravenous pasteurized C1-INH product (P-C1-INH).
It has been available in Europe for more than 20 years, it has an
excellent safety record, and there have been no reported cases
of viral transmission associated with its use. Results of IM-

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PACT 1 (International Multi-center Prospective Angioedema C1-Inhibitor Trial), a phase 2/3 study, have recently been reported.\textsuperscript{26} This double-blind, placebo-controlled study randomized 125 patients with abdominal or facial attacks to P-C1-INH (10 or 20 U/kg) or placebo. In this study, the median time to patient-reported onset of symptom relief was 30 minutes for 20 U/kg vs 90 minutes for placebo ($P = .003$). The results for the 10-U/kg dose were not statistically significant. Similar efficacy results were reported for IMPACT 2, a randomized, double-blind study in which P-C1-INH was administered to 39 patients experiencing HAE attacks at a variety of body locations.\textsuperscript{26} P-C1-INH is currently under review by the FDA for the treatment of acute attacks of HAE.

**Rhucin**

Rhucin (Pharming Group NV, Leiden, the Netherlands) is a recombinant human C1-INH (rhC1-INH) produced in transgenic rabbits. Phase 2 and 3 studies have investigated the use of rhC1-INH for treating patients with acute attacks of moderate to severe HAE.\textsuperscript{20} In the phase 2 study of acute attacks, 100 U/kg of intravenous rhC1-INH achieved symptom relief in 30 and 60 minutes as determined by physician and patient, respectively. Median time to symptom relief was 4 hours; no relapses were reported. In the phase 2/3 study, rhC1-INH, 100 U/kg, was evaluated in a randomized, placebo-controlled, double-blind study. An interim analysis indicated significant superiority of rhC1-INH over placebo for the primary end point of time to beginning of relief ($P < .001$) and the secondary end point of time to minimal symptoms ($P = .004$).

In December 2007, the European Medicines Agency provided a negative opinion for rhC1-INH. The opinion stated that the available studies were too small to show how effective rhC1-INH is in treating more severe forms of the disease, and there was insufficient evidence to confirm the clinical benefits of rhC1-INH in repeated use.

Topline results from a North American phase 3 trial of rhC1-INH were announced in June 2008. In this trial, 39 patients experiencing an HAE attack were randomized to receive 100 or 50 U/kg of rhC1-INH or placebo. Median time to first symptom relief, the primary end point, was significantly shorter with both doses of Rhucin vs placebo (approximately 68 minutes for 100 U/kg; approximately 100 minutes for 50 U/kg; and 258 minutes for placebo; $P < .01$).\textsuperscript{27} No serious treatment-related adverse events were reported. Pharming has indicated future plans to file a Biologics License Agreement with the FDA.

**DISCUSSION**

To consider treatment options for HAE properly, it is important to first evaluate the nature and frequency of HAE attacks, the associated disease burden of each patient, and the risk for morbidity and mortality. Patients should be evaluated based on their individual history, needs, disease burden, and expectations. Important consideration must be given to the progression and types of attacks, access to emergency care, and the history of emergency department/physician visits, hospitalizations, and intubation due to HAE attacks.

Disease burden includes the impact that HAE has on an individual’s activities of daily living, such as the functional impairment that patients experience in missing days at work or school, the effect on family and lifestyle, anxiety and depression secondary to HAE, and potential dependency on analgesics. On the basis of these factors, we developed “HAE therapy considerations” that serve as a way to determine whether patients can be managed with episodic/rescue therapy or whether prophylactic therapy should be recommended (Fig 3).

These consideration criteria reflect an advance in the approach to treatment of HAE and build on the previously published consensus documents. The Canadian Hungarian 2007 consensus document\textsuperscript{28} recommends prophylaxis for patients who experience more than 1 severe event per month, are disabled more than 5 days per month, or have a history of airway compromise. However, it is recognized that the number of events experienced does not predict the severity of the next event or whether the next event will be an airway event. The British consensus document\textsuperscript{3} stresses that the threshold for treatment and the development of an appropriate treatment plan should be a joint decision between physician and patient. There is recognition of the role of individualized therapy and the burden HAE places on quality of life. Gompels et al\textsuperscript{5} propose that maintenance treatment should be considered in patients with more than 1 episode of severe abdominal pain in 1 year or any head or neck swellings, frequent peripheral or genital swellings, or a requirement for analgesics. On the basis of these factors, we developed “HAE therapy considerations” that serve as a way to determine whether patients can be managed with episodic/rescue therapy or whether prophylactic therapy should be recommended (Fig 3).

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**Figure 3.** Hereditary angioedema (HAE) therapy considerations for prophylaxis with the goal of therapy to enable each patient with HAE to live as normal a life as possible. These therapy considerations are proposed for guidance only. Therapy decisions should be based on close consultation between physician and patient on what the best course of therapy should be for a patient’s particular needs, problems, and concerns. Pregnant women and children younger than puberty are best managed without androgens. ICU indicates intensive care unit.
C1-INH more than once a year. All consensus documents underscore the risk inherent in HAE and concur in the recognition that fatal episodes have occurred and may occur in patients who previously have had only mild or benign attacks.

There has also been progress in recognizing the impact of HAE on a patient in terms of the nature of individual attacks and activities of daily living. The Canadian consensus, for example, references 5 incapacitated days per month or 60 per year as a criterion for consideration of prophylaxis. This number (5 days per month) of absences and decreased productivity are considered excessive in the United States because workers rarely have more than 2 weeks of vacation and less than half get sick days. Thus, this degree of absenteeism may jeopardize employment. The HAE therapy considerations presented in Figure 3 represent an evolution that will assist health care providers and their patients in making more informed decisions on the appropriate therapeutic approach to HAE.

CONCLUSIONS
HAE is a serious disease causing significant morbidity and mortality and greatly reduced quality of life. Attacks may be disabling and life-threatening. The goal of treatment should be to assist patients in minimizing the detrimental impact of HAE on daily life. It is imperative that the clinical presentation of HAE be recognized early in the disease course so that appropriate, effective therapy can be administered. Currently available therapies are often inadequate. Danazol, currently the most commonly used HAE prophylactic agent in the United States, may be associated with serious adverse effects, especially with long-term use. Several new therapies that specifically target the pathways implicated in C1-INH deficiency disease are under investigation. Prophylactic therapy with C1-INH-nf, a disease-specific treatment that corrects the underlying cause of HAE, has been FDA approved and is presently available. We believe that the ultimate availability of effective and safe treatment options will change the treatment paradigm for HAE. The present situation in the United States is similar to that observed in Europe in the early 1970s before the availability of C1-INH concentrate. At that time, the only therapies for C1-INH deficiency disease were androgens and antifibrinolytics, neither of which was effective at interrupting an acute attack. The introduction of C1-INH concentrate provided a treatment for acute HAE and offered the possibility of prophylaxis for selected patients. The imminent availability of new therapeutic options, including icatibant, Rhucin, ecallantide, and Berinert P, for HAE in the United States and Europe should result in more effective therapy for patients and the opportunity to offer individualized care to those affected by C1-INH deficiency.

REFERENCES


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