ON-DEMAND THERAPY FOR HEREDITARY ANGIOEDEMA


INTRODUCTION
Consensus guidelines currently recommend that all patients with hereditary angioedema (HAE) caused by C1-INH deficiency have access to on-demand therapy for the treatment of acute angioedema attacks. Since 2009, five new therapies have been approved by the US Food and Drug Administration (FDA) for the treatment of acute HAE attacks and another medication is pending approval. This review by Dr. Bernstein reviews the currently available acute treatments and discusses their role in the management of HAE.

Plasma-derived C1 Esterase Inhibitor (Berinert®)
In 2009, the FDA approved Berinert (CSL Behring GmbH, Marburg, Germany), a plasma-derived, nanofiltered, pasteurized C1-INH concentrate for the treatment of abdominal or facial HAE attacks. Recently, this indication has been approved to treat laryngeal attacks as well. In randomized controlled trials, Berinert given at a dose of 20 U/kg intravenously, showed a significant decrease in the median time to onset or relief for facial or abdominal attacks compared with placebo (0.5 hours vs 1.5 hours, respectively; P=0.003). In addition, median time to complete resolution of all HAE symptoms, including pain was 4.9 versus 7.8 hours for the Berinert and placebo groups, respectively; P = .02.

Ecallantide (Kalbitor®)
Ecallantide (Kalbitor, Dyax Corp, Burlington, MA) was FDA approved in 2009 for treatment of acute HAE peripheral, abdominal, and laryngeal attacks in patients aged 16 years or older. The drug works by inhibiting plasma kallikrein, a serine protease that promotes conversion of high molecular weight kinogen to bradykinin. It is administered subcutaneously at a recommended dose of 30mg as 3 separate 1-mL injections.

Placebo controlled trials of ecallantide showed a significant improvement in median symptom complex severity score compared with placebo at all anatomic locations 4 hours after dosing.

The product label contains a black box warning as anaphylaxis is a potential complication of this drug. For this reason, the medication must be administered by a healthcare professional equipped to manage anaphylaxis.

Icatibant (Firazyr®)
Icatibant (Firazyr, Shire Human Genetic Therapies, Inc, Lexington, MA) is a bradykinin-2 receptor antagonist that was approved by the FDA in 2011 for the treatment of acute attacks of HAE in adults 18 years of age and older.

In phase III clinical studies, the use of icatibant was associated with a significantly shorter median time to onset of symptom relief compared with tranexamic acid (2.0 vs 12.0 hours, respectively; P<.001). In another phase III trial in patients with moderate to very severe cutaneous or abdominal symptoms, the use of icatibant was associated with a 50% or greater reduction in symptom severity within a
median time of 2.0 hours when compared with 19.8 hours for placebo \((P=.001)\). Efficacy was also shown for the treatment of laryngeal attacks with a median time to at least a 50% reduction in symptom severity of 2.5 hours with icatibant compared with 3.2 hours for placebo. Icatibant can be self-administered as a single 30 mg subcutaneous injection and can be stored at room temperature.

**Ruconest**

Ruconest (Pharming, Leiden, the Netherlands), is a highly purified human plasma protease C1 inhibitor, is currently approved by the European Medicines Agency for treatment of acute HAE attacks and is currently under review by the FDA for approval in the US. Randomized, double blind, placebo-controlled clinical trials showed significant improvement in the median time to beginning of symptom relief and median time to minimal symptoms with Ruconest. In patients receiving Ruconest 100 U/kg, Ruconest 50 U/kg, or placebo, the median time to onset of symptom relief was 68 minutes, 122 minutes, and 258 minutes, respectively. In addition, the time to minimal clinical symptoms was 245, 247, and 1098 minutes, respectively \((P<0.01\) compared with placebo). The 50 U/kg dose has been recommended for treatment of acute HAE attacks and is pending approval.

**SUMMARY**

The purpose of on demand treatment is to prevent the mortality associated with life-threatening laryngeal attacks as well as decrease the morbidity associated with abdominal or peripheral attacks. When instituted in a timely manner, on demand therapy offers patients the potential for improved outcomes and shorter symptom duration. For this reason, consensus recommendations include the use of on demand therapy for all patients with HAE. New therapies that may help better control acute HAE symptoms are on the horizon, and will offer both physicians and patients more choices to help manage this debilitating disease.

**DIAGNOSING ANGIOEDEMA**


**INTRODUCTION**

Angioedema of the subcutaneous and submucosal tissues is caused by a transient increase in vascular permeability. The diagnosis as to the type of angioedema is not always straightforward. Numerous factors must be considered such as location, time to development, total duration, and family history. Taking these factors into account will help physicians distinguish between angioedema without urticaria, histamine- from non–histamine dependent angioedema, and hereditary from nonhereditary angioedema.

**Diagnosis**

The anatomic site affected can sometimes provide important diagnostic clues as to the type of angioedema. In hereditary angioedema caused by C1 inhibitor deficiency, recurrent abdominal pain caused by bowel occlusion is a common clinical finding. In angiotensin-converting enzyme (ACE) inhibitor induced angioedema, oral and perioral regions are frequently affected.

In all patients, a detailed and thorough family history should be obtained. Not all patients with HAE will show evidence of an identifiable genetic mutation or biochemical marker. In addition, patients with HAE with normal C1 inhibitor may not demonstrate factor XII mutations, thus requiring a diagnosis to be made purely on clinical grounds.

All patients with recurrent angioedema should undergo screening for deficiency of C1 inhibitor. Clinical clues to an HAE diagnosis include the absence of wheals as well as no symptomatic improvement with antihistamine therapy. Low C4 plasma levels is also consistent with a diagnosis of HAE and should be a part of routine clinical assessment when HAE is suspected. The measurement of plasma levels of C1q can help to differentiate between hereditary and acquired C1 inhibitor deficiency. In HAE, C1q is commonly normal but in acquired deficiencies, it is low 70% of the time.

**SUMMARY**

In order for proper treatment to be instituted, the type of angioedema needs to be identified. A detailed family history, physical examination, and laboratory evaluation will lead the practitioner down the right path to making a correct diagnosis.
CREATING A COMPREHENSIVE TREATMENT PLAN FOR HEREDITARY ANGIOEDEMA

INTRODUCTION
Hereditary angioedema (HAE) is a genetic condition which can cause unpredictable episodes of cutaneous or mucosal tissue swelling. These episodes can cause patients to lose function in the affected area, become temporarily disfigured, and experience acute pain (especially when the swelling occurs in the abdomen). Attacks involving the upper airway involve risk of asphyxiation and are life-threatening. This article discusses the importance of developing individualized treatment plans for patients with HAE.

MANAGING HAE
Although, HAE is potentially life-threatening it is often undiagnosed or misdiagnosed. Patients often experience a median range of 13-22 years from first symptoms to diagnosis.

Due to the potential mortality, disability and pain associated with HAE, as well as the variety of treatment options currently available, management of HAE has become increasingly complex. In order to help navigate the therapeutic landscape, an effective management plan should be implemented for every patient. Important components of the management plan should include patient education, reliable access to effective HAE-specific medications, and consistent follow-up to monitor therapeutic efficacy and safety.

Recently, several groups have developed recommendations to assist in managing patients with HAE. These consensus publications generally agree on the following:

1. On-demand treatment with an effective HAE-specific medication must be available for every HAE patient, including those on prophylactic therapy. This on-demand medication should be reliably and efficiently accessible.

2. All or nearly all HAE angioedema episodes are eligible for treatment.

3. Airway angioedema is uniquely life threatening and requires special attention.

4. Early treatment of HAE attacks is beneficial in reducing morbidity and complications.

5. Prophylactic treatment is indicated for patients in whom on-demand treatment alone is unsatisfactory.

In addition to the aforementioned recommendations, it is important for the HAE patient to be able to interact with HCPs who are not familiar with HAE. In these instances the HAE specialist can be instrumental in communicating with other health care providers regarding care of the patient.

Some specialists have developed brief letters and/or treatment action plans which help in communicating the basic elements of effective HAE treatment to other HCPs, as well as serving as a helpful reference for the patient. In addition, efforts are underway to collect worldwide clinical data from participating patients. This will allow researchers to analyze large groups of patients within this rare disorder.