Acute Management of Hereditary Angioedema Attacks

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KEYWORDS

• Hereditary angioedema • HAE acute attacks • Treatment of HAE
• C1-inhibitor concentrate • Icatibant • Ecallantide • rh C1-INH

KEY POINTS

- Management of acute hereditary angioedema (HAE) attacks has changed dramatically over the last decade with 4 clinically proven, options available in some countries.
- Acute treatment options include 2 plasma-derived C1 inhibitor concentrates, a recombinant C1 esterase inhibitor, a kallikrein inhibitor, and a bradykinin 2 receptor antagonist.
- Better education for patients with HAE and adoption of the principles of self-management with "on-demand" treatment have improved quality of life and outcomes for patients.

INTRODUCTION

Modern management of hereditary angioedema (HAE) includes managing the acute attack, short-term prophylaxis for procedures that place the patient at risk of an attack, and long-term management for those where the attack rate is high or impacts adversely on ability to work and conduct daily life.

Acute HAE attack management has changed dramatically over the last 10 years. For more than 2 decades, plasma-derived C1 inhibitor concentrate (pdC1-INH) was the only specific treatment available; now there are 4 clinically proven effective options available, although not all are available in every country as yet. Preferred contemporary use of the treatment options discussed herein is as "on-demand treatment," where treatment is in the hands of the patient to be used once an attack is evident. In this way, delays in treatment access are avoided. Several excellent reviews have explored this topic previously; this article summarizes, in a practical fashion, the

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attributes of each of these treatment options, listing their indications, risks and benefits, and hopefully will serve as a useful guide to those prescribing acute treatment for HAE patients.

MEDICATIONS FOR TREATING ACUTE ATTACKS

Several treatment modalities have become available for management of acute HAE attacks in the last 10 to 15 years. Most are now available to patients in North America, Europe, United Kingdom, and Australia, but few of these options exist for many patients living in developing countries.

PLASMA-DERIVED C1 INHIBITOR THERAPY

Berinert

HAE is caused by a deficiency or abnormality in C1-INH, a factor that has numerous inhibitory functions within the contact, fibrinolytic, and complement pathways. Replacement therapy with plasma-derived C1-INH has been used since 1973, with Berinert P first licensed in Germany in 1979. Berinert is nanofiltered and currently licensed for the treatment of acute HAE attacks in Europe, the United States, Australia, and numerous other countries.

Studies of efficacy

A pivotal phase III prospective, multinational, randomized, parallel-group, placebo-controlled, dose-finding, 3-arm, double-blind clinical study (I.M.P.A.C.T. 1 [International Multi-center Prospective Angioedema C1-Inhibitor]) assessed the efficacy and safety of Berinert in 124 adult and pediatric patients (6–72 years) who were experiencing an acute, moderate to severe attack of abdominal or facial HAE.[1] Two doses (10 and 20 U/kg) were compared with placebo, given by intravenous infusion (4 mL/min) within 5 hours of the onset of an attack.

Subjects treated with a 20 U/kg dose experienced a significant reduction ($P = .0025$) in the median time to onset of relief from symptoms of an HAE attack (30 minutes) as compared with placebo (90 minutes). The median time to complete resolution of HAE symptoms was significantly shorter ($P = .0237$) in the Berinert 20 U/kg group (4.9 hours) than in the placebo group (7.8 hours). The study demonstrated that a 20 U/kg dose of Berinert was significantly more efficacious than 10 U/kg or placebo.

In a subsequent study, Wasserman and colleagues[2] demonstrated that Berinert at 20U/kg dose provided rapid and effective relief for successive abdominal and facial attacks. They treated 663 abdominal attacks in 50 patients and 43 facial attacks in 16 patients. The median time to onset of relief for all attacks was 19.8 minutes, with a median time to complete resolution of 11 hours.

Cinryze

Another pd C1-INH product, Cinryze, is distributed internationally and like Berinert, is purified from human plasma. It was introduced in Europe in 1972 and was approved in 2008 by the Food and Drug Administration in the United States for prophylaxis of HAE.

Zuraw and colleagues[3] reported a randomized trial of nanofiltered C1-INH (Cinryze) for the acute treatment of HAE attacks. Sixty-eight HAE subjects were randomized to receive Cinryze or placebo within 4 hours of the onset of an episode of moderate to severe nonlaryngeal edema (laryngeal episodes were treated with open-label Cinryze). Unlike the Berinert I.M.P.A.C.T. 1 trial, a fixed dose of 1000 U of C1-INH was used in all subjects. There was a significant reduction in time to onset of relief in the treatment