

Hereditary angioedema: Optimal therapy

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Hereditary angioedema (HAE) is an autosomal-dominant condition, characterized by episodic self-limited, occasionally life-threatening attacks of angioedema.^{1,2} Affected individuals lack sufficient functional inhibition of the first complement protein, the serine proteinase inhibitor C1INH.^{3,4} In most instances, the C1INH is absent (type I), but 15% may possess a nonfunctional C1INH (type II).⁵ These 2 types of HAE cannot be distinguished clinically. The incidence varies from 1:10,000 to 1:50,000 persons. The biological role of the C1INH is to regulate the intrinsic and contact coagulation pathways as well as the complement system.^{6,7} In the former, plasma kallikrein and coagulation factors XIa and XIIa (Hageman factor) are inhibited, and in the latter, C1r and C1s are inhibited. When C1INH is deficient or absent, bradykinin is released from the high-molecular-weight kininogen by plasma kallikrein in abnormally high amounts.⁸⁻¹¹ C1INH knockout mice have confirmed experimentally that increased vascular permeability in HAE is mediated by bradykinin via the contact system.¹²

Attacks caused by HAE involve primarily the subcutaneous tissues as well as the submucosa of the gastrointestinal and upper respiratory tracts. Laryngeal involvement may lead to asphyxiation. Consequently, mortality in untreated patients may be as high as 30%. Therapy for HAE addresses 3 areas: treatment of acute attacks and prophylaxis for both short-term before potentially triggering events, such as dental extraction, and long-term prophylaxis (chronic) to prevent recurrent severe attacks. The initial treatment for HAE, described by Spaulding¹³ in 1960, was methyltestosterone, which was thought to reduce vascular permeability. It was subsequently shown that this drug and other anabolic steroids enhanced C1INH production by the liver. Anabolic steroids can be administered for short-term and long-term prophylaxis of HAE, although they cannot generally abort an ongoing, established attack. The antifibrinolytic agents epsilon aminocaproic acid¹⁴ and tranexamic acid¹⁵ have been effective for prophylaxis as well and provide some

Abbreviations used

C1INH: C1-inhibitor

FFP: Fresh frozen plasma

HAE: Hereditary angioedema

hC1INH: Human C1-inhibitor

inhibition of acute attacks. Administration of fresh frozen plasma (FFP), which contains C1INH, has been used for the treatment of acute attacks.¹⁶ The use of FFP raised some theoretical concerns, because it also contains plasma substrates for complement-mediated inflammation and could theoretically worsen the attack, although this has not been observed in several series of such treated individuals. Recently, newer therapeutic agents targeting bradykinin include kallikrein inhibitor, Ecallantide (Dyax, Cambridge, Mass), and antagonists of the bradykinin-2 receptor, Icatibant (Jerini AG, Morristown, NJ).

Treatment of acute attacks has been effectively addressed with the advent of purified human C1INH preparations (CSL Behring, Lev Pharmaceuticals; [Table I](#)) and recombinant rabbit C1INH (Pharming Group NV, Jersey City, NJ). Initial studies with pasteurized human C1INH (hC1INH) preparations¹⁷ documented the efficacy of these preparations in the treatment of HAE. In these studies, 69% of those administered C1INH improved within 30 minutes of the C1INH infusion. By 4 hours, 95% of the subjects receiving C1INH responded, compared with only 12% of the subjects receiving placebo.¹⁸

In this issue of the Journal, the Hungarian HAE Center's experience with the administration of hC1INH (CSL Behring) over the period of a decade confirmed the safety and efficacy of this treatment for acute HAE attacks.¹⁹ A single brand of highly purified, lyophilized, human plasma-derived C1INH concentrate was administered in a dose of 500 U. Each patient was provided a 500-U ampoule for administration by the patient's physician. The patient maintained a diary for collection of attack symptomatology and treatment-response information. In the report, 61 patients including 22 children with 468 acute HAE attacks are described. Fifty-one patients with HAE were not administered the hC1INH and served as a control group. Abdominal attacks occurred most frequently (49%), followed by laryngeal edema (28%) and subcutaneous edema (13%). Information regarding the response to treatment was obtained from the patients and their diaries.

Patients were allowed to continue their usual prophylactic therapy, which included antifibrinolytic and attenuated androgen drugs. The key to the successful treatment of HAE was the early recognition of symptoms with prompt institution of therapy. Most attacks were controlled with a

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TABLE I. HAE investigative drugs

Drug	Manufacturer	Address
Beriner P (purified human C1INH) administered intravenously	CSL Behring	CSL Behring 1020 First Avenue P.O. Box 6150 King of Prussia, PA 19406
Cinryze (purified human C1INH) administered intravenously	Lev Pharmaceuticals	Lev Pharmaceuticals, Inc 675 Third Avenue, Suite 2200 New York, NY 10017
Ecaltantide (DX-88) (kallikrein inhibitor) administered subcutaneously	Dyax	Dyax Corp 300 Technology Square Cambridge, MA 02139
Icatibant (Icat) (bradykinin β 2-receptor) administered subcutaneously	Jerini AG	Jerini US, Inc 55 Madison Avenue, Suite 400 Morristown, NJ 07960
Rhucin (rhC1INH) administered intravenously	Pharming	Pharming Group NV 2500 Harborside Financial Center, Plaza 5 Jersey City, NJ 07311

single ampoule (500 U) of hC1INH. Symptomatic relief was attained in 15 minutes for laryngeal attacks and within 30 minutes for abdominal attacks. Subcutaneous edema required a more prolonged period for evidence of relief. Although the subcutaneous edema was reduced in 30 to 60 minutes, it took 24 to 48 hours for complete resolution with clearing to occur. Attacks did not progress, and there were no recurrent attacks within 72 hours of treatment administration. The average dose required per patient in this study was 1 ampoule annually. Repeat administration was required in 9 cases. Four patients required hC1INH concentrate from 1 to 15 occasions for episodic attacks over a 4-year period. There were no adverse drug reactions with repeated administration of hC1INH. Viral activity was never demonstrated in spite of extensive attempts at detection. The drugs were safe for treatment of the 22 children and when administered to 4 pregnant women.

Thus, the use of hC1INH concentrate appears safe and more expedient than FFP for treatment of acute HAE attacks and generally results in complete resolution of symptoms within 4 to 12 hours. The purified hC1INH is produced and in clinical trials for resolution of HAE attacks by ZLB Behring and Lev in the United States. Recombinant C1INH from rabbit milk is currently undergoing clinical trials directed by Pharming. Newer approaches to the inhibition of bradykinin production by Ecaltantide (Dyax) as well as inhibition of the bradykinin-2 receptor antagonist, Icatibant (Jerini AG), are also being completed. In the near future, such drugs (Table I) will be available to provide more effective treatment for HAE attacks with fewer adverse effects than the currently available treatment options, anabolic steroids.

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