Clinical Medicine Insights: Cardiology

Libertas Academica
FREEDOM TO RESEARCH

OPEN ACCESS
Full open access to this and thousands of other papers at http://www.la-press.com.

REVIEW

Ecallantide for the Treatment of Hereditary Angiodema in Adults

Michael Lunn and Erin Banta

Penn State Hershey Section of Allergy and Immunology, Hershey, PA 17033, USA.
Corresponding author email: mlunn@hmc.psu.edu

Abstract: Hereditary angioedema (HAE) is a clinical disorder characterized by a deficiency of C1 esterase inhibitor (C1-INH). HAE has traditionally been divided into two subtypes. Unique among the inherited deficiencies of the complement system, HAE Types I and II are inherited as an autosomal dominant disorder. The generation of an HAE attack is caused by the depletion and/or consumption of C1-inhibitor manifested as subcutaneous or submucosal edema of the upper airway, face, extremities, or gastrointestinal tract mediated by bradykinin. Attacks can be severe and potentially life-threatening, particularly with laryngeal involvement and treatment of acute attacks in the United States has been severely limited. In December 2009 the FDA approved ecallantide for the treatment of acute HAE attacks. Ecallantide is a small recombinant protein acting as a potent, specific and reversible inhibitor of plasma kallikrein which binds to plasma kallikrein blocking its binding site, directly inhibiting the conversion of high molecular weight kininogen to bradykinin. Administered subcutaneously, ecallantide was demonstrated in two clinical trials, EDEMA3 and EDEMA4, to decrease the length and severity of acute HAE attacks. Although there is a small risk for anaphylaxis, which limits home administration, ecallantide is a novel, safe, effective and alternative treatment for acute HAE attacks.

Keywords: hereditary angioedema, ecallantide, Kalbitor®, acute, angioedema

Clinical Medicine Insights: Cardiology 2011:5 49–54

doi: 10.4137/CMC.S4434

This article is available from http://www.la-press.com.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.

Introduction

Hereditary angioedema (HAE) is a clinical disorder characterized by a deficiency of C1 esterase inhibitor (C1-INH) that results from mutations of the C1-INH gene located on chromosome 11.[1,2] It was first recognized in 1963 that C1-INH was deficient in the plasma of patients with HAE.[3] Inherited as an autosomal dominant disorder, it is unique among the inherited deficiencies of the complement system as HAE Types I and II are occur with equal frequency among both men and women. Low levels of both C1-INH proteins distinguish Type I HAE, which accounts for approximately 80% to 85% of all HAE cases. Type II HAE, which occurs in 15% to 20% of patients, results from decreased functional activity of the C1-INH gene, but with normal C1- INH levels.[4,5]

Recently, a new subtype of HAE, Type III, has been described in the literature. Type III is characterized by an X-linked dominant inheritance and initially observed exclusively in women and is associated with normal levels and function of C1-INH.[6] Most cases appear to be estrogen induced;[7] however, more recently males have been identified that appear to have type III HAE, but with normal levels of C4, C1-INH-A and C1-INH-F.

Generation of HAE attacks are caused by the depletion and/or consumption of C1 inhibitor. The role of C1-INH in regulation of the contact system activation, via inactivation of plasma kallikrein and factor XIIa, was discovered during the 1970s and 1980s.[8] Via inactivation of C1r and C1s, C1-INH is the primary regulator of the classic complement pathway activation.[9] The low plasma concentration of functionally active C1-INH permits overactivation of the kallikrein-kinin system, the classical complement pathway, the fibrinolytic system and the coagulation system, with release of vasoactive peptides among which bradykinin is considered to be most important.[10–12] Bradykinin is released by cleavage of kininogen by kallikrein and it is capable of inducing edema as a result of its effects on vasodilation and microvessel permeability.[13,14]

The exact prevalence of HAE is not known, but it has been estimated to range from 1:10,000 to 1:150,000 in the general population. This suggests that there are 2000 to 30,000 affected patients in the United States (US).[14] Patients with HAE typically begin to swell in childhood and often experience increase symptoms beginning about the time of puberty.[15]

Clinically, HAE is characterized by episodic recurrent episodes of subcutaneous and sub-mucosal angioedema. Swelling affects the hands and feet but also involves the genitalia, trunk, face, upper airways, larynx, and gastrointestinal tract.[16] The disease is characterized by swelling, which is not associated with urticaria, that does not respond to antihistamines, corticosteroids or epinephrine. Swelling during attacks usually subsides spontaneously in 72 hours.[17] In one study, abdominal attacks were reported in more than 93% of patients and composed almost 50% of all angioedema attacks.[18] However, skin swellings appear to be the most frequent symptoms of HAE.[19]

A positive family history of angioedema is present in most patients, although up to 25% of patients have negative family histories with a de novo C1 inhibitor mutations.[18] Thus, the absence of a family history in the presence of typical symptoms should not be a deterrent from making the diagnosis. Even within families with the same genetic aberration symptoms vary considerably and it is not unusual for one family member to have severe recurrent attacks and another to be relatively free of symptoms.

History of Treatment for Acute HAE Attacks

HAE attacks can be variable in both frequency and severity. In the United States, the treatment for acute HAE attacks has been severely limited until recently. Therapies have included fresh frozen plasma (FFP), 17α-alkylated androgens, and antifibrinolytic agents. All of which have their inherent safety and side effect profiles.[20–22] (Table 1) In October of 2009, the FDA approval of C1-INH replacement (Berinert®; CSL Behring, Melbourne, Australia) greatly improved the treatment options available for the treatment of acute attacks. More recently, in December, 2009 the United States Food and Drug Association (FDA) approval of ecallantide (Kalbitor® [previously, DX-88]; Dyax, Cambridge, MA) for acute attacks in patients 16 years of age has allowed for even greater treatment options of this rare, but potentially life threatening disorder.[23] Ecallantide has not been studied for prevention of HAE attacks as prophylactic therapy.

Pharmacology and Pharmacokinetics

Ecallantide is a small recombinant protein (7054 Da) synthesized in the yeast *Pichia pastoris* and acts as

Table 1. A comparison of both approved and frequently used treatments for acute HAE attacks in the USA.

	Method of production	Mechanism of action	Half-life	Route of treatment	FDA status
FFP (fresh frozen plasma)	Blood product	Replaces C1 esterase inhibitor	Long	IV	Used, but not approved for the treatment of acute HAE attacks
Berinert®	Plasma concentrate	C1 inhibitor	24–46.5 h	IV	FDA approved for the treatment of acute attacks
Ecallantide	Recombinant protein	Kallikrein inhibitor	1–4 h	SC	FDA approved for the treatment of acute HAE attacks

Abbreviations: HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous.

a potent, specific, and reversible inhibitor of plasma kallikrein. Ecallantide binds to plasma kallikrein and blocks its binding site, directly inhibiting the conversion of high molecular weight kininogen (HMWK) to bradykinin.[24–27]

Ecallantide is eliminated in the urine and after administration of a single 30 mg subcutaneous dose, a mean (±standard deviation) maximum plasma concentration of 586 ± 106 ng/mL was observed approximately 2 to 3 hours post-dose in healthy subjects. The mean area under the concentration-time curve was 3017 ± 402 ng*hr/mL with a mean elimination half-life of 2.0 ± 0.5 hours. Plasma clearance was 153 ± 20 mL/min and the volume of distribution was 26.4 ± 7.8 L. Body weight, age, and gender were not found to affect ecallantide exposure significantly. There is no pharmacokinetic data available in patients with hepatic or renal impairment.[27]

Dosing Strategy

Each single use vial contains ecallantide at a concentration of 10 mg/mL with a recommended dose of 30 mg, administered subcutaneously in three 10 mg (1 mL) injections. A repeat dose (30 mg) can be given if the attack persists and may be administered within a 24 hour period. Ecallantide is usually administered in the abdomen, thigh, or upper arm with each injection site separated by at least five centimeters and away from the anatomical site of attack.

Use in Special Populations

Ecallantide is labeled as pregnancy category C as it was noted to cause developmental toxicity in rats in doses approximately 8 times (based on mg/kg) the maximum recommended human dose. Therefore, it is suggested to use ecallantide with caution during pregnancy. Additionally, it is unknown whether ecallantide is excreted in human milk and caution should be also exercised when administered to nursing women.

Clinical trials did not include sufficient numbers of subjects aged 65 and over to determine response in elderly patients. Currently approved for patients 16 years of age and older, the safety and effectiveness in pediatric patients has yet to be established.

Safety and Tolerability

In 255 patients between the ages of 10 and 78 years with HAE treated with either intravenous or subcutaneous ecallantide, the most adverse effect was headache (16.1%). Additional side effects included nausea (12.9%), fatigue (11.8%), diarrhea (10.6%), upper respiratory tract infection (8.2%), injection site reactions (7.4%), nasopharyngitis (5.9%), vomiting (5.5%), pruritus (5.1%), upper abdominal pain (5.1%), and pyrexia (4.7%).[27] As noted, the above data is combined from all patients treated with ecallantide either intravenously in the EDEMA1® trial[28] or via subcutaneous administration documented in the EDEMA3® and EDEMA4® trials.[29,30] As ecallantide is a recombinant product, it is free of potential human or animal contaminants.[31]

During clinical trials, hypersensitivity reactions, including anaphylaxis, occurred in patients receiving ecallantide. In the aforementioned 255 HAE patients treated with intravenous or subcutaneous, 10 patients (3.9%) experienced anaphylaxis. In the subgroup of patients (n = 187) receiving subcutaneous administration, 5 patients (2.7%) experienced anaphylaxis. The symptoms associated with these anaphylactic reactions included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and

hypotension and all occurred within the first hour after dosing. Thus, Kalbitor®, has a black box warning for this hypersensitivity risk. Other adverse reactions suggestive of hypersensitivity reactions included pruritus (5.1%), rash (3.1%), and urticaria (2.0%). Therefore, it is recommended that patients should be observed for an appropriate period of time after administration, and the medication should only be used in the presence of healthcare workers who are trained in the treatment of anaphylaxis. Prior to prescribing, physicians are obligated to discuss this potential adverse reaction extensively with their patients.

A few patients treated with ecallantide developed antibodies to the medication. Overall, 7.4% of patients seroconverted to anti-ecallantide antibodies with rates increasing over time. Neutralizing antibodies to ecallantide in vitro were noted in 4.7% of patients. Additionally, anti-*P. pastoris* IgE antibodies were also detected.[27]

FDA Approval and Clinical Studies

The safety and efficacy of ecallantide was evaluated in 2 randomized, double-blind, placebo-controlled trials (EDEMA4® and EDEMA3®) in 168 patients with HAE.[29,30] Patients having an acute attack of hereditary angioedema, at any anatomic location, with at least 1 moderate or severe symptom, were treated with 30 mg subcutaneous ecallantide or placebo. As patients could participate in both trials, there were a total of 143 unique patients between the two trials. In both trials, the effects of ecallantide were evaluated using the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). These measures evaluated the severity of attack symptoms at all anatomical locations (MSCS score) and response to therapy (TOS) (Tables 2 and 3). A decrease in the MSCS score reflected an improvement in symptoms and TOS is a measure of symptom response to treatment. During the EDEMA4® and EDEMA3® trials, safety was also assessed documenting headache, nausea, and diarrhea were the most common adverse effects (Table 4).

EDEMA4® was a randomized, double-blind, placebo-controlled trial in which 96 patients were randomized to receive ecallantide 30 mg subcutaneous or placebo for acute attacks of HAE. The primary endpoint was the change from baseline in MSCS score at 4 hours, and the TOS at 4 hours was a key secondary endpoint. Results showed that patients treated with ecallantide demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients with placebo (Table 2).

Table 2. Change in MSCS score and TOS at 4 hours in EDEMA4.

	Ecallantide	Placebo
Change in MSCS score at 4 hours		
Number	47	42
Mean	–0.8 ± 0.6	–0.4 ± 0.8
P-value	0.010	
TOS at 4 hours		
Number	47	42
Mean	53.4 ± 49.7	8.1 ± 63.2
P-value	0.003	

Abbreviations: MSCS, Mean Symptom Complex Severity; TOS, Treatment Outcome Score.

EDEMA3® was a randomized, double-blind, placebo-controlled trials in which 72 patients were randomized to receive ecallantide or placebo for acute attacks of HAE. The primary endpoint was the TOS at 4 hours, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hours. As in EDEMA4®, patients treated with 30 mg of ecallantide demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients treated with placebo (Table 3).

Based on EDEMA4 and EDEMA3 trials, Kalbitor® (ecallantide) was FDA approved for treatment of acute HAE attacks on December 1, 2009 in patients 16 years of age and older.

Limitations in Clinical Application

As noted above, there were a few side effects noted including nausea, fatigue, diarrhea, upper respiratory

Table 3. Change in MSCS score and TOS at 4 hours in EDEMA3.

	Ecallantide	Placebo
Change in MSCS score at 4 hours		
Number	36	36
Mean	–0.88 ± 1.11	–0.51 ± 0.68
P-value	0.01	
TOS at 4 hours		
Number	36	36
Mean	46.8 ± 59.3	21.3 ± 69.0
P-value	0.004	

Abbreviations: MSCS, Mean Symptom Complex Severity; TOS, Treatment Outcome Score.

Table 4. Adverse reactions occurring at ≥3% and higher than placebo in 2 placebo in EDEMA3® and EDEMA4® in patients treated for acute HAE attacks.

Adverse reaction	Ecallantide (n = 100)	Placebo (n = 81)
Headache	8 (8%)	6 (7%)
Nausea	5 (5%)	1 (1%)
Diarrhea	4 (4%)	3 (4%)
Pyrexia	4 (4%)	0
Injections site reaction	3 (3%)	1 (1%)
Pharyngitis	3 (3%)	0

tract infection, injection site reactions, nasopharyngitis, vomiting, pruritus, upper abdominal pain, and pyrexia. None of which should preclude the clinician from offering this treatment option to their hereditary angioedema patients as the benefits appear to outweigh the risks. However, the risk of anaphylaxis could be a limiting factor in clinical use as it has to be administered in a clinical setting supervised by health care professionals. It has been well documented that treatment of HAE attacks early decrease the severity and length of attacks. Ideally, treatment of an attack would occur in any setting at the onset of symptoms and at the patient's convenience. This is currently not an option with ecallantide and has the potential to delay timely treatment.

Conclusion

The recommended dose for the treatment of acute HAE attacks is 30 mg administered subcutaneously with a maximum of 2 doses (60 mg) in a 24 hour period. The current wholesale price (2010) for Kalbitor® is $9,540.00 per 30 mg treatment. ($3,180.00/10 mg vial). Therefore, cost of treatment can be a barrier to treatment based on insurance coverage. Additionally, there remains controversy on when to initiate chronic replacement therapy in individuals with HAE versus treatment isolated to acute attacks. Cost is a factor, but chronic treatment for HAE with C1-Inhibitor replacement may lead to more expense. The cost is dependent on the frequency of attacks and ultimately the number of doses used.

There have been major advances in the treatment options available for acute HAE attacks in the United States over the past year. The hope is that those advances correlate with an increase in the quality of life for patients with HAE. Safety remains a concern with a small risk of anaphylaxis, in addition to the lack of availability for home administration and ecallantide's potential for immunogenicity. Unique aspects for ecallantide include subcutaneous administration which is a significant advantage for individuals with poor peripheral venous access. In conclusion, ecallantide remains a novel, safe, and effective treatment for acute HAE attacks.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Bock SC, Skriver K, Nielsen E, Thoegersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, c DNA, cloning, and chromosomal localization. *Biochemistry*. 1986;25:4292–301.
2. Theriault A, Whaley K, McPhaden AR, Boyd E, Connor JM. Regional assignment of the human C1-inhibitor gene to 11q11–11q13.1. *Human Genet*. 1990;84:477–9.
3. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor C1-esterase. *Am J Med*. 1963;35:37–44.
4. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2000;105:541–6.
5. Bowen B, Hawk JJ, Sibunka S, Hovick S, Weiler JM. A review of the reported defects in the human C1 esterase inhibitor gene producing hereditary angioedema including four new mutations. *Clin Immunology*. 2001;98:157–63.
6. Bork K, Barnstedt S, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356:213–7.
7. Binkley K, Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol*. 2000;106:546–50.
8. Schapira M, Scott CF, Colman RW. Contribution of plasma protease inhibitors to the inactivation of kallikrein in plasma. *J Clin Invest*. 1982;69:462–8.
9. Davis AE III. C1 inhibitor and hereditary angioneurotic edema. *Annu Rev Immunol*. 1988;6:595–628.
10. Cugno M, Cicardi M, Bottasso B, Coppola R, Paonessa R, Mannucci PM, et al. Activation of the coagulation cascade in C1-inhibitor deficiencies. *Blood*. 1997;89:3213–8.
11. Arlaud GJ, Rossi V, Thielens NM, Gaboriaud C, Bersch B, Hernandez JF. Structural and functional studies on C1r and C1s: new insights into the mechanisms involved in C1 activity and assembly. *Immunobiology*. 1998;199:303–16.
12. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet*. 1998;351:1693–7.
13. Colman RW, Schmaier AH. Contact system: A vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes. *Blood*. 1997;90:3819–43.
14. Davis AE III. Mechanism of angioedema in first complement component inhibitor deficiency. *Immunol Allergy Clin North Am*. 2006;26:633–51.
15. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med*. 2001;161:2417–29.

16. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976;84:586–93.
18. Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1 inhibitor gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106:1147–54.
19. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119: 267–74.
20. Sloane DE, Lee CW, Sheffer AL. Hereditary angioedema: safety of long-term stanozolol therapy. *J Allergy Clin Immunol*. 2007;120:654–8.
21. Rosen FS, Austen KF. The neurotic edema. *N Engl J Med*. 280(1979): 1356–7.
22. Donaldson VH. Therapy of the neurotic edema. *N Engl J Med*. 286(1972):835.
23. Zuraw B, Yasothan U, Kirkpatrick P. Ecallantide. *Nat Rev Drug Disc*. 2010;9: 189–90.
24. Ley AC, Markland W, Ladner RC. Obtaining a family of high-affinity, high specificity protein inhibitors of plasmin and plasma kallikrein. *Mol Divers*. 1996;2:119–24.
25. Markland W, Ley AC, Ladner RC. Iterative optimization of high-affinity protease inhibitors using phage display. 2. Plasma kallikrein and thrombin. *Biochemistry*. 1996;35:8058–67.
26. Levy JH, O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Investig Drugs*. 2006;15: 1077–90.
27. Kalbitor prescribing information. Accessed 1/20/11 http://www.kalbitor.com/hcp/rems/pdf/KalbitorFullPrescribingInformation.pdf.
28. Schneider L, Lumry W, Vegh A, Williams AH, Schmalbach T. Critical role of kallikrein in hereditary angioedema pathogenesis: A clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol*. 2007; 120:416–22.
29. Levy R, McNeil D, Li H, Hsu FI, Horn P, Roberts J. *J Allergy Clin Immunol*. February 2008;121(2 Suppl 1):S221.
30. Levy RJ, Lumry WR, McNeil DL, Li HH, Campion M, Horn PT, et al. *Ann Allergy Asthma Immunol*. 2010;104:523–9.
31. Epstein TG, Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs*. 2008;68:2561–73.

Publish with Libertas Academica and every scientist working in your field can read your article

"I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely."

"The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I've never had such complete communication with a journal."

"LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought."

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

http://www.la-press.com