Overview of ecallantide in the treatment of hereditary angioedema types I and II

Hereditary angioedema is a rare disease characterized by unpredictable attacks of swelling in any anatomic location. Hereditary angioedema attacks lead to significant morbidity and can occasionally cause mortality. Treatment for acute attacks includes intravenous C1 esterase inhibitor replacement and, in Europe, subcutaneous bradykinin inhibitor (icatibant). In December 2009, a new medication aimed at the bradykinin cascade called ecallantide received approval from the US FDA for the treatment of acute attacks of hereditary angioedema. Ecallantide is a 60-amino acid recombinant protein that is a potent and specific plasma kallikrein inhibitor. Ecallantide is subcutaneously administered and not plasma derived. In the Phase III EDEMA3 and EDEMA4 studies, subjects treated with ecallantide had statistically significant evidence of clinical improvement at 4 and 24 h when compared with subjects treated with placebo. Ecallantide is an alternative to C1 esterase inhibitor and icatibant for the treatment of acute attacks of hereditary angioedema.

KEYWORDS: C1 esterase inhibitor ■ ecallantide ■ hereditary angioedema ■ pharmacology ■ plasma kallikrein

Erin Banta[1] & Timothy J Craig[†]

[1]Pennsylvania State University, Section of Allergy Asthma & Immunology, 500 University Drive, Hershey, PA 17033, USA
[†]Author for correspondence: Department of Medicine & Pediatrics, Pennsylvania State University, 500 University Drive, H041, Hershey, PA 17033, USA
Tel.: +1 717 531 6525
Fax: +1 717 531 5785
tcraig@psu.edu

Hereditary angioedema (HAE) is a rare, debilitating and potentially fatal disease characterized by unpredictable, acute exacerbations of nonpitting edema without urticaria. The prevalence of HAE is between one in 10,000 and one in 50,000 individuals. HAE has traditionally been divided into two subtypes inherited in an autosomal dominant pattern. Both types involve mutations of the C1 esterase inhibitor (*C1-INH*) gene located on chromosome 11. Type I HAE, which accounts for 85% of cases, is distinguished by a deficiency in C1-INH. Type II HAE, accounting for 15% of cases, is characterized by decreased function of C1-INH [1]. Recently, a third type of HAE has been described in the literature [2] and, in this type, patients appear to have normal antigenic and functional C1-INH levels, but are clinically indistinguishable from HAE [1,3]. The pathophysiology of type III is unknown. This article will focus on treatment of types I and II HAE.

C1 esterase inhibitor is a member of the serpin family and plays a major role in the inhibition of complement proteases and contact system proteases. It is also involved in the inhibition of the fibrinolytic protease plasmin and coagulation protease factors XIa and XII. Deficiency or decreased activity of C1-INH leads to increased levels of plasma kallikrein, which cleaves high-molecular-weight kininogen. This reaction causes the release of bradykinin, which then leads to increased vascular permeability and angioedema [4].

A typical untreated HAE attack increases gradually, but steadily, in severity for the first 24 h and resolves after approximately 2–5 days. Attack location and severity are not predictable, but the extremities are most frequently affected [5]. More than half of HAE patients will have laryngeal angioedema in their lifetime and these attacks are life-threatening [6]. Disease morbidity is significant with peripheral exacerbations causing pain, decreased motor function and lost days of work. Abdominal exacerbations cause pain, nausea and vomiting, and often lead to unnecessary surgeries prior to diagnosis [7].

Overview of the market

Hereditary angioedema therapy targets both the treatment of acute attacks and prevention of these attacks through the use of prophylactic medications. Ecallantide is a subcutaneously administered recombinant protein inhibitor of plasma kallikrein and was approved by the US FDA on 2nd December 2009, for treatment of acute attacks of HAE in patients 16 years of age and older [8,9]. Ecallantide is pregnancy category C. Further details are outlined below. The other available treatments for acute attacks are intravenously administered with the exception of icatibant, which is available in Europe. Options include plasma-derived C1-INH and fresh-frozen plasma (FFP). In countries where alternate therapies are available, FFP should

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not be used. Plasma-derived C1-INH therapy is FDA approved for the treatment of acute facial and abdominal attacks in the USA and has been used for decades in Europe. It is not FDA approved for peripheral or laryngeal attacks. It has been demonstrated in randomized controlled trials to lead to the onset of symptom relief 30 min after administration of a 20 U/kg dose (IMPACT-1) [10]. C1-INH carries the rare side effect of anaphylaxis and since it is plasma derived there is a risk of viral transmission [1]. Three steps are taken to reduce the risk of viral transmission with C1-INH. The first two steps involve repeated testing for transmissible viruses and the third step is an inactivation/removal step. There have been no reported cases of viral transmission with plasma-derived C1-INH [3]. It is likely that in the near future another option for acute attacks will be recombinant C1-INH. Recombinant C1-INH administered intravenously has been demonstrated in a Phase III study to improve the time to onset of relief and time to complete relief when administered for acute attacks [101] and is now under review by the FDA. This product received favorable review from the EMA's Committee for Medicine and Products for Human Use (CHMP) and will be marketed in the EU for the treatment of acute attacks [102].

A synthetic subcutaneously administered bradykinin receptor antagonist (icatibant) is also under investigation for treatment of acute attacks. One trial (FAST-1) showed no significant difference in time to improvement with the treatment of an acute attack with icatibant when compared with placebo. Another randomized controlled trial (FAST-2), which led to icatibant's approval in Europe, did demonstrate significant benefit in time to improvement over tranexamic acid [11]. Another Phase III randomized controlled trial is currently being performed in the USA. FFP has also had reported benefit in uncontrolled studies [12,13], but remains controversial owing to the potential risk of generation of bradykinin and exacerbation of edema with the addition of contact system proteins. General use of FFP for HAE attacks or prophylaxis is not recommended. It is generally understood that corticosteroids and antihistamines are not effective in the treatment of acute attacks of HAE since the mechanism of HAE is secondary to bradykinin and not to histamine. Epinephrine may obviate the need for intubation, but otherwise has been demonstrated to have only transient benefit [3] and has not been assessed in a double-blind study of HAE.

Short-term prophylaxis may be indicated in patients with known triggers such as dental work, surgical procedures or invasive medical procedures. In these cases, C1-INH, FFP or androgens may be administered prior to the provoking event. These triggers may be potentiated by underlying mediators of inflammation. It has been demonstrated that patients with C1-INH deficiency and angioedema have elevated levels of both circulating and local bradykinin [14,15]. Patients with angiotensin-converting enzyme inhibitor-induced angioedema have similarly elevated bradykinin levels [16]. Some studies have indicated that these patients also have elevated C-reactive protein and fibrinogen levels [17]; although these results have not been consistent [18]. Recent studies have demonstrated that plasma F1+2 and D-dimer are both elevated at baseline in patients with HAE and rise with attacks of angioedema [19].

Long-term prophylaxis is indicated in patients who experience multiple and severe episodes. Approved agents for long-term prophylaxis currently include oral androgens and intravenous nano-filtered C1-INH [5,20,21].

Introduction to ecallantide

Ecallantide is a potent and specific plasma kallikrein inhibitor that blocks generation of bradykinin. It is a 60-amino acid recombinant protein generated by phage display technology, which has been demonstrated to ameliorate the symptoms of acute HAE attacks in a placebo-controlled trial [22,23].

Chemistry

Ecallantide is a 60-amino acid recombinant protein produced by the yeast *Pichia pastoris*. It is a reversible and potent inhibitor of plasma kallikrein. Ecallantide is formulated as a 10 mg/ml clear and colorless, sterile, preservative-free and nonpyrogenic solution in phosphate-buffered saline, pH 7.0. Each vial contains 10 mg ecallantide. Ecallantide should be stored at refrigerated temperatures and protected from the light. The recommended dose of ecallantide is 30 mg (3.0 ml), administered subcutaneously at three different locations as divided 10 mg doses. The injection sites should be distant from the location of angioedema [24,103].

Pharmacodynamics

Ecallantide delays thrombin generation *in vitro* [25]. Prolongation of activated partial thromboplastin time following intravenous dosing of ecallantide was seen at doses of 20 mg/m^2 or

more. In healthy subjects intravenously administered with 80 mg activated partial thromboplastin, time values were prolonged twofold over baseline. These values returned to normal by 4 h postdose [24]. Prolongation of activated partial thromboplastin time has not been associated with increased risk of bleeding [20].

Electrocardiogram monitoring of patients in the randomized, placebo-controlled trial EDEMA4 revealed no change in heart rate-corrected QT interval, heart rate or any other components of electrocardiogram in patients treated with ecallantide [24,26,103].

Pharmacokinetics & metabolism

In prior studies, ecallantide displayed linear pharmacokinetics and was dose proportional up to 96 mg intravenously. In studies with 30 mg subcutaneous administration to healthy subjects, mean peak concentrations (586 ± 106 ng/ml) occurred 2–3 h after dosing. The mean area under the concentration–time curve was 3017 ± 402 ng*h/ml. After administration, plasma concentration declined with a mean elimination half-life of 2.0 ± 0.5 h (FIGURE 1). Plasma clearance was 153 ± 20 ml/min and volume of distribution was 26.4 ± 7.8 l. Bodyweight, age and gender were not noted to significantly affect ecallantide kinetics. Ecallantide undergoes renal elimination without prior metabolism. Studies have not been performed in patients with hepatic or renal impairment [103].

Clinical efficacy

EDEMA3 and EDEMA4 were both randomized, double-blind, placebo-controlled trials that investigated ecallantide 30 mg administered subcutaneously for the treatment of moderate-to-severe attacks of HAE. A total of 143 unique subjects with HAE were enrolled. At the time of treatment, subjects reported moderate-to-severe symptoms of angioedema at any anatomic location. Patients had the opportunity to enroll in both trials, resulting in data for 168 treatments [24,26,103].

Patient response to treatment was evaluated using two validated patient-reported outcome scoring systems, the mean symptom complex severity (MSCS) score and the treatment outcome score (TOS) [26]. Both scoring systems evaluate symptoms that occur in the upper aerodigestive tract, abdominal (gastrointestinal/abdominal) and/or peripheral (genital/buttocks, face and cutaneous) attack locations. The MSCS score is a comprehensive point-in-time measure of symptom severity. At the time of presentation with a moderate-to-severe attack, patients identified all active symptom complexes and rated their severity (1 = mild, 2 = moderate and 3 = severe). At 4 and 24 h postdose, patients again rated the severity of all symptom complexes on a categorical scale (0 = normal, 1 = mild, 2 = moderate and 3 = severe). New symptom complexes were identified as they arose and severity was assigned as described here. Patients defined mild, moderate or severe symptoms based on provided descriptions. Severity ratings were averaged to obtain the MSCS score. A decrease in MSCS score reflects on improvement in symptoms.

The TOS is a comprehensive measure of response to therapy. Patient's assessment of response as compared with baseline was collected at 4 and 24 h postdose and recorded on a categorical scale (significant improvement 100], improvement [50], same [0], worsening [-50] and significant worsening [-100]) for each symptom complex. The response to each symptom complex was weighted by the baseline severity and then averaged for the TOS. An increase in TOS reflects improvement in symptoms [27].

EDEMA4 included 96 patients randomized to receive ecallantide 30 mg subcutaneously or placebo for a moderate-to-severe acute attack of HAE. In this trial, a change in MSCS score from baseline to 4 h was the primary end point and TOS at 4 h was a secondary end point. One ecallantide-treated patient and three placebo-treated

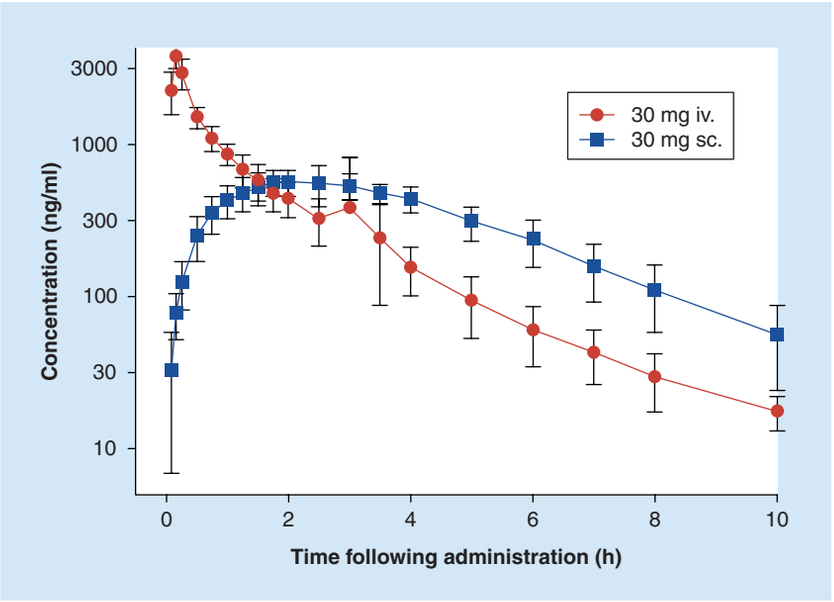

Figure 1. Mean ecallantide plasma concentration following intravenous and subcutaneous administration.
iv.: Intravenous; sc.: Subcutaneous.
Reproduced with permission from Dyax Corp. [103].

patients received severe upper airway compromise doses (second dose of open-label ecallantide 30 mg subcutaneously administered within the first 4 h) and were therefore excluded from analysis. In addition, three placebo-treated patients were excluded as they were missing their 4 h data. There was a significant change in the MSCS score from baseline for patients treated with ecallantide compared with placebo at 4 h (mean ± standard deviation for ecallantide: -0.8 ± 0.63; placebo: -0.4 ± 0.82; p = 0.010, comparing distributions) (Table 1). Ecallantide was also associated with a significantly larger TOS at 4 h (mean ± standard deviation for ecallantide: 53.4 ± 49.7; and placebo: 8.1 ± 63.2; p = 0.003, comparing distributions). This improvement continued through the 24 h assessment for both treatment groups (MSCS score: p = 0.039, comparing the distributions and TOS: p = 0.029, comparing the distributions) [26,103].

EDEMA3 included 72 patients who were also randomized one-to-one to receive ecallantide or placebo for attacks of HAE. The primary end point for this trial was the TOS at 4 h and the change in MSCS score was a secondary end point. Again, there was a significant improvement from baseline in the ecallantide group with a mean TOS of 46.8 ± 59.3 compared with 21.3 ± 69.0 for the placebo group (p = 0.004) (Table 2). The mean change in MSCS score at 4 h was -0.88 ± 1.11 in the ecallantide group and 0.51 ± 0.68 in the placebo group (p = 0.014). At 24 h the TOS and MSCS scores continued to reflect improvements in the ecallantide group over the placebo group (TOS: p = 0.007 and MSCS score: p = 0.041). In addition, more patients from the placebo group (13 out of 36; 36%) required medical intervention to treat unresolved symptoms within 24 h compared with the ecallantide-treated group (five out of 36; 14%) [28].

The data that led to approval of ecallantide for treatment of acute laryngeal attacks were accumulated during the treatment of swelling of the upper aerodigestive tract, which includes the lips, palate, tongue, mouth, throat and larynx. The description of symptoms for this area included swelling or tightening, pain, soreness, aching, choking, tingling, hoarseness, altered speech, difficulty breathing, difficulty swallowing, burning or thirst [103].

Postmarketing surveillance

Phase IV studies are underway to monitor and report adverse events and to clarify the frequency of anaphylaxis.

Safety & tolerability

A total of 255 patients aged 10–78 years old with HAE were assessed for adverse reactions to ecallantide administered either intravenously or subcutaneously. Of the total group, 3.9% of patients (ten out of 255) experienced anaphylaxis, as defined by the criteria of the National Institute of Allergy and Infectious Disease (NIAID) [24,29]. Symptoms included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing and hypotension, and all occurred within 1 h of dosing. Of the 187 patients treated with subcutaneous ecallantide, 2.7% (n = 5) experienced anaphylaxis [24]. Some patients receiving multiple doses of ecallantide developed antidrug antibodies, but the relationship between these antibodies and adverse events is not clear [8]. At the onset of the EDEMA4 trial, one patient treated with ecallantide tested positive for ecallantide antibodies and developed neutralizing antibodies at day 7. This patient did not have adverse events associated with treatment and continued to respond to therapy. No patients from this trial seroconverted to anti-ecallantide IgE antibodies [26].

The most common other adverse reactions seen among patients treated with either intravenous or subcutaneous ecallantide (255 patients) included headache (16.1%), 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%). Injection site reactions were described as including local pruritus, erythema, pain, irritation, urticaria and/or bruising [24].

Table 1. Efficacy outcomes at 4 h in EDEMA4.

Treatment	Number	TOS (mean ± standard deviation)	MSCS (mean ± standard deviation)
Ecallantide	47	53.4 ± 49.7	-0.8 ± 0.63
Placebo	42	8.1 ± 63.2	-0.4 ± 0.82
p-value	–	0.003	0.010

MSCS: Mean symptom complex severity; TOS: Treatment outcome score.

Table 2. Efficacy outcomes at 4 h in EDEMA3.

Treatment	Number	TOS (mean ± standard deviation)	MSCS score, change from baseline (mean ± standard deviation)
Ecallantide	36	46.8 ± 59.3	-0.88 ± 1.11
Placebo	36	21.3 ± 69.0	-0.51 ± 0.68
p-value	–	0.004	0.014

MSCS: Mean symptom complex severity; TOS: Treatment outcome score.

Table 3 represents safety data from EDEMA3 and EDEMA4, listing adverse reactions that occurred in at least 3% of patients treated with subcutaneous ecallantide. These reactions occurred with greater frequency than with placebo. The most common adverse reactions included headache (8%), nausea (5%), diarrhea (4%), pyrexia (4%), injection site reaction (3%) and nasopharyngitis (3%) [24].

Ecallantide is currently in pregnancy category C. There are no well-controlled trials of ecallantide in pregnant women. Studies performed in rats indicate that an intravenous dose 13-times the maximum recommended human dose (MRHD) led to increased numbers of early resorptions as well as a higher percentage of resorbed conceptuses per litter. These rats also experienced mild maternal toxicity. Rats given an intravenous dose eight-times the MRHD on a milligram/kilogram basis did not display development toxicity. Embryo-fetal development was not affected in rats given subcutaneous doses up to 2.4-times the MRHD and rabbits given intravenous doses up to six-times the MRHD [103].

Regulatory affairs

Approval was granted for ecallantide (Kalbitor®) on 2nd December 2009. Dyax Corp. has agreed to do a postmarketing study for adverse events. A risk evaluation and management strategy program is in place to ensure safety information is appropriately communicated. The risk evaluation and management strategy program consists of a medication guide and a communication plan.

Conclusion

Hereditary angioedema is a rare, heritable disease characterized by unpredictable attacks of swelling that can be life threatening. In most patients, these attacks lead to significant morbidity and possible mortality. Currently available treatments for acute attacks include plasma-derived C1-INH, FFP and icatibant in Europe. C1-INH and FFP are administered intravenously and, being plasma products, carry the possible risk of viral transmission. Ecallantide is a recombinant protein that inhibits plasma kallikrein and has been demonstrated in randomized, controlled, double-blind studies to improve symptoms of acute attacks of HAE within 4 h. The advantages of ecallantide are that it can be administered subcutaneously, is a recombinant protein and does not carry a risk of viral transmission. Adverse events have included hypersensitivity reactions at a rate of 2.7% with subcutaneous administration, which is not much different from that seen with subcutaneous aeroallergen immunotherapy, which has systemic reaction rates cited in the literature between 0.2 and 23% [30]. However, the risk associated with both intravenous and subcutaneous studies approaches 4% with no deaths. Other adverse events were generally mild. Owing to the risk of anaphylaxis, it is recommended that ecallantide be administered in-office with an observation period of 60 min. Furthermore, both physicians and patients should be aware of the risk of anaphylaxis and its signs and symptoms. It is worth noting that in EDEMA4, no patients treated with ecallantide developed symptoms suggestive of hypersensitivity. Ecallantide is an effective treatment for acute attacks of HAE.

Future perspective

Researchers continue to look for predictors for acute attacks. In the coming years we may be able to use prodromal symptoms to help predict attacks. Some studies have demonstrated that many HAE patients experience prodromal symptoms, including fatigue, rash, muscle aches, nausea and vomiting, which often begin more than 12 h before the onset of angioedema [11,12]. Early identification of HAE attacks may allow physicians to intervene with treatment before

Table 3. Safety data for hereditary angioedema patients treated in EDEMA3 and EDEMA4.

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
Injection site reaction	3 (3%)	1 (1%)
Pharyngitis	3 (3%)	0

significant swelling, pain, respiratory distress and temporary disability occur. For now, rapid intervention at the first onset of signs and symptoms of swelling remains an important method of controlling the morbidity and mortality of this disease.

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Executive summary

Mechanisms of action

- Ecallantide is a recombinant protein inhibitor of plasma kallikrein.

Pharmacokinetic properties

- Ecallantide has a peak concentration 2–3 h after subcutaneous dosing.
- Bodyweight, age and gender were not noted to significantly affect ecallantide exposure.
- Ecallantide undergoes renal elimination.
- The half-life of ecallantide is 2.0 ± 0.5 h.

Clinical efficacy

- Ecallantide significantly improved symptoms of acute hereditary angioedema attacks compared with placebo at 4 h in randomized, placebo-controlled trials.
- Ecallantide is strategically placed for use in the office since the therapy is given subcutaneously and requires only a 60 min observation period. Physicians administering ecallantide should be ready and educated to treat anaphylaxis in case it occurs.

Safety & tolerability

- Ecallantide hypersensitivity is a possible serious reaction occurring in 2.7% of patients treated subcutaneously. No data are available for breastfeeding women and limited data are available in patients over 65 years of age.

Drug interactions

- No drug–drug interactions have been observed or are expected.

Dosage & administration

- The recommended dose of ecallantide is 30 mg (3 ml), administered subcutaneously in three 10 mg (1 ml) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 h period.

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