Original Article

Characterization of Anaphylaxis After Ecallantide Treatment of Hereditary Angioedema Attacks

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What is already known about this topic? Hypersensitivity reactions have been described in patients who received ecallantide treatment, with approximately 3% to 4% of patients who experience reactions consistent with anaphylaxis.

What does this article add to our knowledge? This article is a comprehensive retrospective review of documented cases of hypersensitivity reactions observed in the ecallantide clinical development program that meet the criteria of anaphylaxis. This is important information for allergists to ensure appropriate observation, preparation, and safety precautions for the rare occurrence of anaphylaxis when administering ecallantide.

How does this study impact current management guidelines? These data highlight the importance of ecallantide administration by a health care provider knowledgeable and prepared to treat anaphylaxis.

BACKGROUND: Ecallantide is a human plasma kallikrein inhibitor indicated for treatment of acute attacks of hereditary angioedema for patients 12 years of age and older. Ecallantide is produced in *Pichia pastoris* yeast cells by recombinant DNA technology. Use of ecallantide has been associated with a risk of hypersensitivity reactions, including anaphylaxis.

OBJECTIVE: The objective of this detailed retrospective data review was to characterize anaphylaxis cases within the ecallantide clinical trials database.

METHODS: Potential cases of hypersensitivity reactions in the ecallantide clinical development program were identified by examining reported adverse events. The National Institute of Allergy and Infectious Disease criteria were used to identify those events that were consistent with anaphylaxis; these cases were then reviewed in detail. Results from investigational antibody testing also were examined.

RESULTS: Among patients who received subcutaneous ecallantide (n = 230 patients; 1045 doses of 30 mg ecallantide), 8 patients (3.5%) had reactions that met the National Institute of Allergy and Infectious Disease criteria for anaphylaxis; none occurred on first exposure to the drug. All 8 reactions had symptom onset within 1 hour of exposure and cutaneous manifestations commonly observed in type I hypersensitivity reactions. All the reactions responded to standard management of type I hypersensitivity reactions and resolved without fatal outcomes. IgE antibody testing to ecallantide or *P pastoris* was

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Conflicts of interest: T. J. Craig is an American Academy of Allergy, Asthma & Immunology Interest section leader; past board member for American College of Allergy, Asthma & Immunology, American Lung Association of Pennsylvania, and Joint Council of Allergy, Asthma and Immunology; has received consultancy fees from CSL Behring, Dyax, Viropharma, Shire, Merck, Biocryst, Bellrose, Merck; has received research support from Viropharma, CSL Behring, Shire, Dyax, Pharming, Merck, Genentech, GlaxoSmithKline, Grifols, Novartis, Sanofi Aventis, and Boehringer Ingelheim; has received lecture fees from CSL Behring, Dyax, Shire, and Grifols; and is co-investigator of Asthmanet, National Heart, Lung and Blood Institute. H. H. Li has received consultancy fees from Salix, Shire/Viropharma, CSL Behring, and Dyax; has received research support from Shire/Viropharma; has received lecture fees from Shire/Viropharma, CSL Behring, and Dyax. M. Riedl has received consultancy fees from CSL Behring, Dyax, Shire, Isis, Biocryst, and Santarus; has received research support from CSL Behring, Dyax, Shire, Pharming, and BioCryst; has received lecture fees from CSL Behring, Dyax, and Shire. J. A. Bernstein was a principal investigator for clinical trials for, has received consultancy and lecture fees, and research support from Dyax, Shire/Viropharma, CSL Behring, and Pharming; is on the United States Hereditary Angioedema Association medical advisory board and editorial board of *The Journal of Angioedema*. W. R. Lumry has received research support from Dyax, CSL Behring, Shire/Viropharma, and Pharming; has received consultancy fees from Dyax, Biocryst, CSL Behring, and Shire/Viropharma; has received fees for participation in review activities from Biocryst; and has provided review of medical records for the Steed Law firm. A. J. MacGinnitie has received consultancy fees from Dyax, CSL Behring, and Viropharma; and has received research support from Shire. L. E. Stolz and J. Biedenkapp are employed by Dyax. Y. Chyung is employed by and owns stock/stock options in Dyax.

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Abbreviations used

−- Negative
+- Positive
Anti-ecal IgE- anti-ecallantide IgE antibody
*Anti−*P pastoris *IgE- anti−*P pastoris *IgE antibody*
bp- Blood pressure
D5W- 5% dextrose in water
ECL- Electrochemiluminescent
EDEMA- Evaluation of DX-88s Effects in Mitigating Angioedema
HAE- Hereditary angioedema
HRP- Horseradish peroxidase
HSNC- Human serum negative control
HSR- Hypersensitivity reaction
IgE-anti-ecal- Anti-ecallantide IgE antibody
IM- intramuscular
IV- Intravenous
LLOQ- Lower limit of quantitation
ND- Not determined
NIAID- National Institute of Allergy and Infectious Disease
OD- Optical density
PEF- Peak expiratory flow
PO- oral
sat- Saturation
SC- Subcutaneous
TMB- 3,3',5,5'-Tetramethylbenzidine

not consistently positive in patients who experienced apparent type I hypersensitivity reactions.
CONCLUSION: Anaphylaxis episodes after subcutaneous ecallantide exposure have clinical features suggestive of type I hypersensitivity reactions. However, anti-ecallantide or anti−*P pastoris* IgE antibody status was not found to be reliably associated with anaphylaxis. **(J Allergy Clin Immunol Pract 2015;3:206-12)**

Key words: *Hypersensitivity; Anaphylaxis; Allergy; Hereditary angioedema; Ecallantide; HAE*

Hereditary angioedema (HAE) is a rare disease characterized by prolonged, unpredictable attacks of nonpitting, nonpruritic edema of the subcutaneous (SC) tissue and mucosa. It is caused by a deficiency in functional C1-inhibitor, a serine-protease inhibitor of the plasma kallikrein-kinin, coagulation and complement systems. Swelling occurs most commonly in the face, extremities, gastrointestinal tract, and genitalia.[1] Swelling of the laryngeal area is of serious medical concern because it can result in airway compromise and asphyxiation.[2,3] During an HAE attack, unregulated plasma kallikrein activity results in excessive production of bradykinin, a potent vasodilator that causes the symptoms of swelling and pain characteristic of an HAE attack.[4-6]

Ecallantide (KALBITOR; Dyax Corp, Burlington, Mass) is a recombinant protein inhibitor of human plasma kallikrein produced in the yeast *Pichia pastoris*.[7,8] It is indicated for the treatment of acute attacks of HAE of patients 12 years of age and older.[9] The safety and efficacy of ecallantide were demonstrated in 2 randomized, double-blinded, placebo-controlled phase 3 studies, Evaluation of DX-88s Effects in Mitigating Angioedema (EDEMA) 3 Double Blind (EDEMA3®-Double Blind) and EDEMA4® (Dyax Corp, Burlington, Mass).[10-12] In both studies, clinical efficacy was evaluated by using 2 validated, HAE-specific, patient-reported outcomes: the Treatment Outcome Score and the Mean Symptom Complex Severity score.[13] The Treatment Outcome Score is a measurement of symptom response to treatment, and the Mean Symptom Complex Severity score is a point-in-time measurement of symptom severity. When using both measurements, 30 mg of SC ecallantide was superior to placebo in relieving symptoms and in decreasing the severity of attacks.[10,11] Symptom relief was durable, with sustained symptom relief observed up to 24 hours after ecallantide treatment.[10,11]

The use of ecallantide is associated with anaphylaxis in 3% to 4% of treated patients.[9] The drug, therefore, should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE.[9] In this analysis, we conducted a retrospective review of cases of anaphylaxis reported during the clinical development program for ecallantide to ascertain if these cases represent type I hypersensitivity reactions. The analysis included all the patients treated with either SC or intravenous (IV) ecallantide during clinical trials: EDEMA0, EDEMA1, EDEMA2, EDEMA3 (Double-Blind and Repeat-Dosing arms), EDEMA4, and DX-88/19. Only the SC formulation of ecallantide is currently approved and available for clinical use in the United States.

METHODS

This analysis included all cases of potential hypersensitivity reactions identified in the ecallantide HAE clinical development program (EDEMA0, EDEMA1, EDEMA2, EDEMA3 [Double-Blind and Repeat-Dosing], EDEMA4, and DX-88/19). Ecallantide was administered by IV in EDEMA0 and EDEMA1; either IV or SC in EDEMA2; and only SC in EDEMA3 (Double Blind and Repeat-Dosing arms), EDEMA4, and DX-88/19. A change in the ecallantide manufacturing process occurred during EDEMA2 in which an additional purification step was added. This step decreased the amount of residual *P pastoris* host cell protein in the drug product. All SC doses of the drug were produced with this additional purification step. IV doses of ecallantide administered in EDEMA0, EDEMA1, and portions of EDEMA2 did not include the additional purification step, and, therefore, the residual amounts of *P pastoris* differed between the SC and IV doses. All the studies were institutional review board-approved, and all the patients provided written informed consent. For inclusion in the clinical studies, patients had to be $\geq$10 years old, except in EDEMA0, in which the subjects were $\geq$18 years of age, with moderate-to-severe acute HAE attacks (DX-88/19 also included mild attacks).

Identification and adjudication of hypersensitivity reactions

The database listing of treatment emergent adverse events, defined as those events with onset during or after ecallantide dosing, was searched for cases that had adverse event terms that may be associated with type I hypersensitivity reactions. These terms included "adverse drug reaction," "anaphylaxis," "anaphylactic reaction," "anaphylactoid reaction," "hypersensitivity," "erythema," "flushing," "hot flush," "pharyngeal edema," "laryngeal