

Ecallantide for treatment of acute attacks of acquired C1 esterase inhibitor deficiency

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ABSTRACT

Acquired C1 inhibitor (C1-INH) deficiency exposes patients to angioedema recurrences (acquired angioedema [AAE]) mediated by bradykinin pathway activation. C1-INH replacement and specific inhibition of plasma kallikrein with ecallantide have been successful in the treatment of hereditary angioedema (HAE), a more common related disorder. C1-INH replacement has also been used in the treatment of AAE, but because of the underlying mechanism of rapid catabolism, some patients may not respond. As part of preclinical investigation of ecallantide, a potent bradykinin pathway inhibitor, we evaluated three AAE patients treated successfully with that agent. This study was designed to assess ecallantide for treatment of attacks in AAE. Three patients with AAE were treated a total of 12 times with various dosing regimens of ecallantide based on the protocols established for the studies using ecallantide in HAE (Evaluation of DX-88's Effects in Mitigating Angioedema trials). Response to therapy was also based on outcome measures determined by these protocols. Ecallantide effectively relieved symptoms in three patients with various manifestations of AAE over 12 acute episodes. Kallikrein inhibition with ecallantide appears effective in the treatment of AAE and may be an alternative for patients with resistance to C1-INH replacement therapy.

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C1 esterase inhibitor (C1-INH) deficiency is a rare disorder that most commonly presents as an inherited autosomal dominant form (hereditary angioedema [HAE]), but an acquired form of this disorder, known as acquired angioedema (AAE), is even less recognized.¹ Although the prevalence of HAE is ~1/50,000,² the prevalence of AAE has never been well defined. In contrast to HAE, AAE has no genetic predisposition and the onset of symptoms is usually later in life (fifth decade or later), although clinical presentation for both conditions can be similar.³

The mechanism of C1-INH depletion in AAE is described as an increased catabolism of C1-INH. This results in low levels of C1q, further leading to low C2 and C4 complement levels.⁴ Thus, low C1q levels is a diagnostic feature that differentiates AAE from HAE.

With the development of several new pharmaceutical biologics for the treatment of HAE, one can specu-

late whether these therapies would be effective for AAE. Current HAE therapy includes C1-INH replacement, either for acute attacks⁵ or for prophylaxis,⁶ as well as drugs that inhibit components of the kallikrein pathway.⁷

Because AAE is associated with an increased catabolism of C1-INH, some patients become refractory to C1-INH replacement. This has led to the assumption that blockade of the kallikrein pathway may be a more appropriate treatment of acute angioedema attacks in patients with AAE. We report three patients with AAE and monoclonal gammopathy of uncertain significance (MGUS) successfully treated with ecallantide, a potent inhibitor of plasma kallikrein.

METHODS

Three patients diagnosed with AAE (one patient from the United States and two patients from Italy) were treated with ecallantide, a kallikrein inhibitor. The patients were seen as part of investigational studies of HAE (Evaluation of DX-88's Effects in Mitigating Angioedema [EDEMA] trials). Written informed consent and Institutional Review Board approval were attained before enrollment. All three patients were treated with either subcutaneous or i.v. ecallantide for recurrent acute angioedema symptoms and the clinical response was noted according to the relevant study protocol.

RESULTS

Case 1

A 47-year-old white female with no significant medical history presented with a 7-month history of recur-

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rent abdominal distention and pain lasting 3–5 days that was relieved with opioids. Her symptoms averaged monthly and were accompanied by nausea and diarrhea. The patient had numerous hospitalizations and extensive workup for these complaints, including multiple diagnostic paracenteses, radiographic imaging studies, upper gastrointestinal endoscopy, liver biopsy, and exploratory laparoscopy. She was found to have C1-INH level of <3 mg/dL (normal, 11–26 mg/dL), a functional C1-INH level of 20% (normal, >68%), C4 of <3 mg/dL (normal, 16–47 mg/dL), undetectable C2 (normal, 1.6–3.5 mg/dL), and undetectable C1q (normal, 5.0–8.6 mg/dL). Antibodies to C1-INH were not assessed. A diagnosis of AAE was made. She also had an increased serum protein with a monoclonal spike consistent with MGUS. Further evaluation with a bone marrow biopsy failed to show evidence of myeloma or plasmacytoma.

As a participant in the EDEMA 3 trial, the patient's acute angioedema episodes were treated and assessed based on the study protocol. She initially presented with her typical acute abdominal attack and was treated with 30 mg of ecallantide subcutaneously. She experienced symptom improvement and episode resolution within 4–8 hours of administration. She did not require any additional doses of ecallantide during this visit. The patient, however, continued to have similar attacks in the future. Each of the following 10 episodes was treated successfully with a single dose of ecallantide and no adverse effects were reported. After the 10th episode, daily danazol prophylaxis was initiated because of increased frequency of angioedema. Her symptoms have not recurred.

Case 2

A 47-year-old man was diagnosed in 1997 with acquired C1-INH deficiency by the presence of anti-C1-INH autoantibodies (favorable responses for cases 2 and 3 were previously reported by Cicardi *et al.*¹ but are presented in more detail in this article). He was later noted to also have MGUS. A bone marrow biopsy was not pursued. Rather, the M component was monitored and there was no increase noted. Since the time of AAE diagnosis, the patient had been on tranexamic acid due to high frequency of recurrent symptoms. Before this treatment he presented with intermittent facial angioedemas, which had been treated with C1-INH replacement therapy on several occasions, but with a slow response. Significant resolution was never noticeable earlier than 6 hours from infusion administration. Therefore, the patient was enrolled in the ecallantide investigational study, EDEMA0. On the treatment day, the patient presented with symptoms of viral pharyngitis without fever. He then developed edema of the upper lip, which was treated with 80 mg

of i.v. ecallantide. Within 5 minutes of administration, there was some decrease in the patient's edema, and 3 hours postinfusion there was noticeable reduction of the lip swelling. The patient did not require any additional doses of ecallantide. Over the next 2 days after treatment, the patient reported mild cheek swelling for which he was instructed to increase his dose of tranexamic acid. Four days after therapy, his symptoms resolved and no adverse effects were reported.

Case 3

A 66-year-old man with a history of coronary artery disease, hypertension (treated with losartan), and acquired C1-INH deficiency diagnosed in 1991, with demonstrated anti-C1-INH antibodies and MGUS (similar to case 2, no bone marrow biopsy was done) presented with a 1-day history of angioedema of the lower lip (favorable responses for cases 2 and 3 were previously reported by Cicardi *et al.*¹ but are presented in more detail in this article). He had a well-documented history of resistance to C1-INH replacement therapy; doses up to 12,000 U for a single attack had no clinical effect and did not result in an increase in plasma C1-INH levels. As a participant of the EDEMA0 trial, the patient was given 80 mg of i.v. ecallantide and within 15 minutes felt improvement in his lips. Within 2 hours of administration, there was a significant decrease in overall edema. Twelve hours after treatment completion, the patient's angioedema completely disappeared. The patient did not require any additional doses of ecallantide. The following day he reported some upper lip swelling; but because the episode was mild, he was started on tranexamic acid. Within 2 days his symptoms completely resolved and no adverse effects were reported.

DISCUSSION

AAE is a rare condition. It is characterized by an increased catabolism of C1-INH leading to decreased levels of C1-INH. C1-INH deficiency results in an abnormal elevation in activated C1 complement, leading to further activation of the complement cascade as well as the kallikrein cascade.⁸ AAE has been associated with B-cell malignancies as well as MGUS.⁹ MGUS occurs when plasma cells produce an excess amount of light chains, resulting in high levels of κ -light chains with normal levels of λ -light chains.¹⁰ Patients with AAE have been found to have autoantibodies to C1-INH, either through a direct effect of the associated malignancy¹¹ or possibly through other unidentified mechanisms.^{12,13}

C1-INH concentrate has been used for both prophylaxis and for treatment of HAE. In studies conducted by Waytes *et al.*, C1-INH concentrate was shown to be a safe and effective agent in both preventing HAE

attacks as well as treating acute episodes of HAE.¹⁴ The study showed normalization of C1-INH and C4 levels post-C1-INH concentrate administration. There were also significantly lower daily symptom scores of leg, laryngeal, genitourinary, and abdominal edema after the infusion.¹⁴ Additionally, randomized, double-blind, placebo-controlled studies have established that C1-INH concentrate is both efficacious and safe in the treatment of acute attacks in HAE.^{15,16}

The successful use of C1-INH concentrate in HAE has also been established in more recent publications^{17,18}; however, very limited data are available for its role in AAE. Studies have shown some variability in the efficacy of this product in patients with AAE (Table 1).¹⁹⁻²¹ Bork *et al.*, looked at the effect of C1-INH concentrate therapy in AAE.²⁰ Their patient was initially administered 500 U of the C1-INH concentrate for acute lip swelling and abdominal symptoms, followed by an additional 500 U for persistent edema. There was resolution of the angioedema post-therapy, but the patient required 1000 U of the C1-INH concentrate every 5 days for an entire year. Although in the first few months there was a reduction in both severity and frequency of symptoms, the patient developed resistance to this therapy within 10 months of treatment and was taken off the C1-INH concentrate after 12 months.²⁰

The partial or complete resistance to the C1-INH concentrate in AAE patients may be explained by the biochemical heterogeneity of the autoantibodies or complement activating factors. This likely results in variable, albeit increased, C1-INH catabolism leading to inconsistent responses in treatment.²¹ One additional study had reported the successful use of C1-INH concentrate (1000 U i.v.) in five patients with AAE, three of which were treated for acute symptoms and two for prophylaxis. However, the duration of the therapy and the follow-up period posttreatment in this subset were not described.²²

Attenuated androgens (danazol and stanozolol) enhance liver production of C1-INH and are only used for prophylaxis from angioedema exacerbations. However, adverse effects such as acne, hirsutism, hepatotoxicity, and weight gain limit the use of androgens.²³ With long-term use, androgen prophylaxis has been inadequate in some AAE patients.²⁰ This is not surprising because the fundamental defect is not one of C1-INH production as it is in HAE.

Other therapies for AAE prophylaxis include the antifibrinolytic agents, tranexamic acid, and ϵ -amino-caproic acid. These agents block the lysine-binding sites on the plasminogen and plasmin molecules preventing them from binding to fibrin and thus inhibiting fibrinolysis.²⁴ Because patients with AAE are noted to have persistent activation of this fibrinolytic system, agents such as tranexamic acid allow for effective

Table 1 Clinical data on AAE patients treated with C1-INH concentrate

Patient*	Gender	Age (yr)	Presence of Autoantibodies to C1-INH	Symptom(s)	Dose of C1-INH Concentrate	Symptom Resolution after C1-INH Concentrate Therapy
A	M	70	Yes	Laryngeal edema	3000 U	No response
B	F	64	Yes	Prophylaxis for surgery	1500 U	Good response
C	M	56	Yes	Laryngeal edema	3000 U	Partial response
D	F	70	Yes	Laryngeal edema	3000 U	Partial response
E	M	73	Yes	Laryngeal edema	2000 U	Good response
F	Unknown	Unknown	Yes	Lip edema	1000 U	Good response
G	Unknown	Unknown	Yes	Laryngeal edema	2000 U	No response
H	M	55	Yes	Lip swelling, abdominal pain	1000 U	Good initial response, but no response long term

*Source for patients: A-E, Ref. 21; F-G, Ref. 19; H, Ref. 20. AAE = acquired angioedema; C1-INH = C1 inhibitor.

tive counteraction.²⁵ These agents are well tolerated and adverse effects are fairly uncommon.²⁶ However, nausea and vomiting have been noted from tranexamic acid²⁷ and rhabdomyolysis from ϵ -aminocaproic acid.^{28–31} Although there have been isolated case reports showing an increased risk of thrombosis with the use of antifibrinolytics,^{32–36} there have not been any double-blind randomized controlled clinical trials that have confirmed these findings.

Although drugs such as tranexamic acid and danazol have been used for prophylaxis only, other therapies such as icatibant and ecallantide target acute angioedema exacerbations by inhibiting bradykinin along the kallikrein pathway. The kallikrein system plays a critical role in the pathogenesis of angioedema. C1-INH regulates the conversion of plasma prekallikrein to kallikrein, and it also facilitates the conversion of high molecular weight kininogen to bradykinin. C1-INH deficiency leads to increased bradykinin production, resulting in increased vascular permeability.³⁷ The fact that serum bradykinin levels rise substantially during an acute angioedema episode³⁸ led to the premise that bradykinin is the primary mediator in causing angioedema. This was confirmed by studies using C1-INH knockout mice.³⁹

Icatibant and ecallantide are now being used to treat acute HAE attacks. Icatibant is a bradykinin B₂-receptor antagonist that inhibits normal bradykinin function, resulting in decreased vascular permeability.⁴⁰ Several studies have illustrated significant improvement of acute angioedema symptoms in HAE patients with the use of icatibant.^{41,42} Icatibant, which has been available in Europe and Brazil, has recently been approved in the United States.

Ecallantide, the focus of this article, is a recombinant peptide highly specific in inhibiting plasma kallikrein. Kallikrein is necessary for the formation of bradykinin from high molecular weight kininogen. Blocking bradykinin release halts progression of angioedema by reversing the enhanced vascular permeability associated with C1-INH deficiency.

Multiple prospective studies have shown the use of ecallantide in HAE patients. These include three phase II trials (EDEMA0-2) and one phase III trial (EDEMA 3).⁴³ EDEMA0 was an open-label study conducted in Europe involving nine HAE patients whose acute angioedema attacks were treated with escalating doses of i.v. ecallantide (20, 40, and 80 mg). Initial symptom improvement occurred between 0.4 and 4 hours with complete resolution between 2 and 72 hours posttherapy.^{44,45}

EDEMA1 was a double-blind placebo-controlled single-dose study in which 49 patients with HAE were treated with escalating doses of i.v. ecallantide (5, 10, 20, and 40 mg). Significant symptom improvement was noted within 4 hours posttreatment. A greater re-

sponse was noted in the ecallantide group compared with placebo (72.5% versus 25%, respectively), with a value of $p = 0.017$.^{46,47}

EDEMA2 was an open-label multiple-dose study that used both i.v. and subcutaneous ecallantide to treat acute HAE attacks in 240 HAE patients. The initial study was based on both i.v. (5, 10, and 20 mg) and subcutaneous dosing (30 mg); however, all of the patients were switched to the subcutaneous protocol after the trial was started. This was because of the comparable efficacy between i.v. and subcutaneous dosing reported in phase I trial studies.^{48,49} Each patient was eligible to receive a maximum of two treatments per acute attack (up to 20 attacks). Onset of symptom improvement was noted within 4 hours post-ecallantide administration.⁵⁰

EDEMA3 was a multicenter double-blind randomized placebo-controlled trial involving 72 patients with HAE. The acute attacks were treated with subcutaneous ecallantide at a dose of 30 mg. The primary end point was the treatment outcome score⁵¹ at 4 hours after ecallantide administration. The study also looked at the change in mean symptom complex severity (MSCS) score⁵¹ at 4 hours as a secondary end point. It was concluded that both scores were significantly better with ecallantide when compared with placebo.⁵²

Ecallantide was well tolerated by participants of the EDEMA trials. The adverse effects were mainly mild in nature and included headache, nasal congestion, diarrhea, and rhinitis to name a few.^{52,53} Although uncommon, anaphylaxis with the use of ecallantide has been reported.⁵⁴

Ecallantide was considered as treatment for angioedema in AAE because its mechanism of action is unrelated to the presence of C1-INH antibodies or C1-INH levels. C1-INH replacement therapy may not be a favorable option in refractory AAE patient, and other alternate therapies should be considered. This case series is the first to describe the use of ecallantide in treating acute AAE episodes. All three patients in our case series achieved symptom resolution within hours of ecallantide administration. The drug was tolerated without serious adverse events. As of the date this article was written, all three patients are doing well.

In summary, ecallantide may be advantageous in the treatment of acute attacks of AAE and should be considered as a first- or second-line agent. The paucity of AAE would make randomized control trials comparing C1-INH and ecallantide or icatibant difficult to conduct. In the United States, testing for presence of anti-C1-INH antibodies in AAE patients is not available and represents another obstacle. Additional studies involving AAE patients would help distinguish which patients would benefit by the different forms of therapies.

REFERENCES

- Cicardi M, and Zanichelli A. Acquired angioedema. *Allergy Asthma Clin Immunol* 6:14, 2010.
- Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: A current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 100(suppl 2):S30–S40, 2008.
- Cicardi M, Zingale LC, Pappalardo E, et al. Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. *Medicine* 82:274–281, 2003.
- Melamed J, Alper C, Cicardi M, and Rosen FS. The metabolism of C1inhibitor and C1q in patients with acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 77:322–326, 1986.
- Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion* 38: 540–549, 1998.
- Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, et al. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 49:1987–1995, 2009.
- Levy JH, and O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Investig Drugs* 15:1077–1090, 2006.
- Gigli I, Mason JW, Colman RW, and Austen KF. Interaction of plasma kallikrein with the C1- inhibitor. *J Immunol* 104:574–581, 1970.
- Fremaux-Bacchi V, Guinépain MT, Cacoub P, et al. Prevalence of monoclonal gammopathy in patients presenting with acquired angioedema type 2. *Am J Med* 113:194–199, 2002.
- Breitbart S, and Bielory L. Acquired angioedema: Autoantibody associations and C1q utility as a diagnostic tool. *Allergy Asthma Proc* 31:428–434, 2010.
- Chevallier A, Arlaud G, Ponard D, et al. C1 inhibitor binding monoclonal immunoglobulins in three patients with acquired angioneurotic edema. *J Allergy Clin Immunol* 97:998–1008, 1996.
- Mandle R, Baron C, Roux E, et al. Acquired C1 inhibitor deficiency as a result of an auto-antibody to the reactive center region of C1 inhibitor. *J Immunol* 152:4680–4685, 1994.
- Alsenz J, Bork K, and Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 316:1360–1366, 1987.
- Waytes A, Rosen F, and Frank M. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 334:1630–1634, 1996.
- Craig T, Levy R, Wasserman R, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 124: 801–808, 2009.
- Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C 1 inhibitor concentrate in treating hereditary angioedema. *Transfusion* 38: 540–549, 1998.
- Bork K, and Barnstedt S. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 161:714–718, 2001.
- Zuraw B, Busse P, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 363:513–522, 2010.
- Alsenz J, Lambris J, Bork K, and Loos M. Acquired C1 inhibitor (C1-INH) deficiency type II. Replacement therapy with C1-INH and analysis of patients' C1-INH and anti-C1-INH autoantibodies. *J Clin Invest* 83:1794–1799, 1989.
- Bork K, and Witzke G. Long-term prophylaxis with C1-inhibitor (C1-INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 83:677–682, 1989.
- Cicardi M, Bisiani G, Cugno M, et al. Autoimmune C1 inhibitor deficiency: Report of eight patients. *Am J Med* 95:169–175, 1993.
- Levi M, Choi G, Picavet C, Hack CE. Self administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 117:904–908, 2006.
- Cicardi M, Castelli R, Zingale L, and Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema; comparison of treated and untreated patients. *J Allergy Clin Immunol* 99:194–196, 1997.
- Verstrate M. Clinical application of inhibitors of fibrinolysis. *Drugs* 29:236–261, 1985.
- Cugno M, Cicardi M, and Agostoni A. Activation of the contact system and fibrinolysis in autoimmune acquired angioedema: A rationale for prophylactic use of tranexamic acid. *J Allergy Clin Immunol* 93:870–876, 1994.
- Dunn C, and Goa K. Tranexamic acid: A review of its use in surgery and other indications. *Drugs* 57:1005–1032, 1999.
- Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs* 29: 236–261, 1985.
- Seymour BD, and Rubinger M. Rhabdomyolysis induced by epsilon-aminocaproic acid. *Ann Pharmacother* 31:56–58, 1997.
- Brown J, Wollmann R, and Mullan S. Myopathy induced by epsilon-aminocaproic acid. Case report. *J Neurosurg* 57:130–134, 1982.
- Vanneste J, and van Wijngaarden G. Epsilon-aminocaproic acid myopathy. Report of a case and literature review. *Eur Neurol* 21:242–248, 1982.
- Britt C, Light R, Peters B, and Schochet SS Jr. Rhabdomyolysis during treatment with epsilon-aminocaproic acid. *Arch Neurol* 37:187–188, 1980.
- Cooper J, Abrams J, Frazier O, et al. Fatal pulmonary micro thrombi during surgical therapy for end stage heart failure: Possible association with anti-fibrinolytic therapy. *J Thorac Cardiovasc Surg* 131:963–968, 2006.
- Scott R, and Garrido E. Spontaneous thrombi of an intracranial aneurysm during treatment with epsilon aminocaproic acid. *Surg Neurol* 7:21–23, 1977.
- Fodstad H, and Liliequist B. Spontaneous thrombosis of ruptured intracranial aneurysms during treatment with tranexamic acid. (AMCA): Report of three cases. *Acta Neurochir Wien* 49:129–144, 1979.
- Ryding E, and Lundberg P. Tranexamic acid and intracranial thrombosis. *Lancet* II:49, 1976.
- Davies D, and Howell D. Tranexamic acid and arterial thrombosis. *Lancet* I:49, 1977.
- Gorczyński R, and Jacqueline S. Soluble mediators of immunity II: Complement. *Clinical Immunology*. TX: Landes Bioscience, 101–102, 2001.
- Nussberger J, Cugno M, Amstutz C, et al. Plasma bradykinin in angio-oedema. *Lancet* 351:1693–1697, 1998.
- Han E, MacFarlane R, Mulligan A, et al. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 109:1057–1063, 2002.
- Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (icatibant). *J Allergy Clin Immunol* 119:1497–1503, 2007.
- Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 363:532–541, 2010.
- Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 119:1497–1503, 2007.

43. Levy J, and O'Donnell P. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Investig Drugs* 15:1077-1090, 2006.
44. Gonzales-Quevedo T, Caballero T, Cicardi M, et al. The synthetic Kunitz domain protein Dx88 to treat angioedema in patients with hereditary angioedema. *Int. Immuno Pharmacol* 2:1318, 2002 (Abs).
45. Cicardi M, Gonzales-Quevedo T, Caballero T, et al. DX-88 a recombinant inhibitor of human plasma kallikrein. Efficacy and safety in hereditary and acquired angioedema. *Mol Immunol* 40:197-198, 2003.
46. Williams T, Schneider L, Lumry W, et al. DX-88: A double blind placebo controlled study in hereditary angioedema (HAE) the EDEMA1 study. *Ann Allergy Asthma Immunol* 94:109, 2005.
47. Schneider L, Lumry W, Vegh A, et al. Critical role of kallikrein in hereditary angioedema pathogenesis: A clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol* 120:416-422, 2007.
48. Gunawardena K. An open-label study of the pharmacokinetic and safety profiles of subcutaneous versus intravenous formulations of ecallantide (DX-88), a potent recombinant protein inhibitor of human plasma kallikrein. Presented at the annual meeting of the American College of Asthma, Allergy and Immunology, Anaheim, CA, 2005.
49. Ian J, Lawrie A, Prurdy G, et al. DX-88, a novel kunitz-type inhibitor of human plasma kallikrein with potential therapeutic use. *Blood* 100:88b-89b, 2002.
50. Lumry W, Ritchie B, Beck T, et al. Interim results of EDEMA2, a multicenter, open-label, repeat-dosing study of intravenous and subcutaneous administration of ecallantide (DX-88) in hereditary angioedema. *J. Allergy Clin Immunol* 117:S179, 2006.
51. Vernon M, Rentz A, Wyrwich K, et al. Psychometric validation of two patient reported outcome measures to assess symptom severity and changes in symptoms in hereditary angioedema. *Qual Life Res* 18:929-939, 2009.
52. Cicardi M, Levy R, McNeil D, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 363: 523-531, 2010.
53. Cicardi M, Zingale L, Zanichelli A, and Deliliers DL. Established and new treatments for hereditary angioedema: An update. *Mol Immunol* 44:3858-3861, 2007.
54. Caballero T, and López-Serrano C. Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J Allergy Clin Immunol* 117:476-477, 2006. □

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