



Contents lists available at ScienceDirect



Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor–induced angioedema in the emergency department

Jonathan A. Bernstein, MD^{*}; Joseph J. Moellman, MD^{*}; Sean P. Collins, MD, MSc[†]; Kimberly W. Hart, MA^{*}; and Chris J. Lindsell, PhD^{*}

^{*} Department of Internal Medicine, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, Cincinnati, Ohio

[†] Department of Emergency Medicine, Vanderbilt University, Nashville, Tennessee

ARTICLE INFO

Article history:

Received for publication July 23, 2014.

Received in revised form December 8, 2014.

Accepted for publication December 9, 2014.

ABSTRACT

Background: Angiotensin-converting enzyme inhibitor–induced angioedema (ACEI-AE) is mediated by bradykinin. There remains an unmet treatment need because these patients, when presenting to the emergency department (ED), do not respond to conventional therapies, such as antihistamines and corticosteroids.

Objective: To estimate the treatment effect of ecallantide, a recombinant plasma kallikrein inhibitor, in ED patients with ACEI-AE in whom conventional therapy fails.

Methods: This was a triple-blind (patient, physician, and statistician), randomized, controlled, phase 2 study to estimate the magnitude of safety and efficacy signals for designing a definitive phase 3 trial comparing conventional therapy with ecallantide to conventional therapy with placebo. Patients were enrolled from April 1, 2010, through January 31, 2013. The primary efficacy study end point was achieving discharge criteria from the ED within 4 hours after initiating study-related treatment.

Results: Discharge criteria from the ED was met in 4 hours or less for 8 (31%) of 26 patients receiving ecallantide vs 5 of (21%) 24 patients receiving placebo (difference in proportions, 10%; 95% confidence interval, –14% to 34%). Ecallantide was well tolerated in both groups.

Conclusions: The results from this preliminary study reveal that ecallantide is safe to use and may increase the proportion of patients who meet early discharge criteria by approximately 10%. A larger phase 3 study is necessary to confirm the efficacy and evaluate the cost-effectiveness of ecallantide use for ACEI-AE in the ED setting.

Trial Registration: clinicaltrials.gov Identifier: NCT01036659

© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Angioedema secondary to angiotensin-converting enzyme inhibitors (ACEIs) has become the most common cause of angioedema in patients presenting to the emergency department (ED).^{1–3} The incidence of ACEI–induced angioedema (ACEI-AE) continues to

Reprints: Jonathan A. Bernstein, MD, Department of Internal Medicine, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, 3255 Eden Ave, ML#563, Suite 350, Cincinnati, OH 45267-0563; E-mail: Jonathan.Bernstein@uc.edu.

Disclosures: Dr. Bernstein is an investigator, consultant, and speaker for Dyax, Shire/Viropharma, and CSL Behring, and an investigator for Salix. Dr. Moellman is an investigator for Shire. The other authors have nothing to disclose.

Funding: This project was funded by a physician-initiated unrestricted proposal funded by Dyax Pharmaceuticals (Protocol #DX88-IST2). This project was also supported by grant 5UL1RR026314-03 (Institutional Clinical and Translational Science Award) from the National Center for Research Resources, National Institutes of Health.

Previous Presentation: This study was presented at the American Academy of Allergy, Asthma and Immunology Annual Meeting; March 1, 2014; San Diego, California.

<http://dx.doi.org/10.1016/j.anai.2014.12.007>

1081-1206/© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

increase in the United States because of the increased use of ACEIs for a number of chronic medical conditions. In 2008, ACEIs were the fourth most commonly prescribed medication, accounting for approximately 160 million prescriptions written annually.⁴ The prevalence of ACEI-AE is estimated at 0.1% to 4%, with most patients being older than 65 years and African American.^{5–7} Retrospective medical record review studies have reported that approximately 30% to 40% of angioedema cases seen in the ED can be attributed to ACEIs.^{8,9} The annual rate of visits to the ED for ACEI-AE is estimated at 0.7 per 100,000 ED visits.⁸ Only slightly more than half of these patients are discharged home from the ED.⁸

The pathogenesis of ACEI-AE involves accumulation of excess bradykinin similar to hereditary angioedema (HAE). In contrast to patients with HAE who have *SERPINE1* gene mutations on chromosome 11 that lead to functionally abnormal C1 esterase inhibitor (C1INH) levels,^{10–13} patients with ACEI-AE produce more bradykinin because of the inhibition of C1INH. C1INH is a potent regulator of plasma kallikrein, which is important for regulating the conversion of high-molecular-weight kininogen to bradykinin.¹⁴ The 3- to 4.5-fold higher incidence of ACEI-AE in African American

compared with white individuals is believed to be due to genomic and plasma variability of proteins interfering with bradykinin catabolism.^{15–20} Not surprisingly, patients with ACEI-AE characteristically do not respond to conventional therapy, including antihistamines or corticosteroids.^{7,21} Bradykinin-targeted drugs, available for treatment of HAE due to C1INH deficiency, could be effective in ACEI-AE. Ecallantide is a novel kallikrein inhibitor approved in the United States for the treatment of HAE in persons older than 16 years. Ecallantide works by preventing the breakdown of high-molecular-weight kininogen to bradykinin.²²

To determine whether ecallantide would also be a safe and effective treatment for acute ACEI-AE, we conducted a randomized, controlled, phase 2 study in ED patients with ACEI-AE in whom conventional therapy with histamine₁ (H₁)–antihistamines and corticosteroids failed. The purpose of the study was to estimate the magnitude of the efficacy and safety signals so that a phase 3 study could be appropriately designed.

Methods

Study Design

We performed a triple-blind (patient, physician, and statistician), randomized, controlled, phase 2 trial comparing the safety and effectiveness of conventional therapy with ecallantide to conventional therapy with placebo (clinicaltrials.gov Identifier: NCT01036659). A rescue crossover design was used such that participants who did not improve with standard therapy and blinded study drug (ecallantide or placebo) were additionally treated with open-label ecallantide. An observational arm was included so sensitivity analyses could be conducted using patients who improved rapidly as a result of conventional therapy, refused consent for treatment arm, or were discovered to be pregnant (see exclusion criteria).

Study Participants and Setting

The study was performed at 2 EDs: an urban tertiary care trauma center ED and a suburban ED. The institutional review boards of both sites approved the study. Patients were screened for inclusion from 8 AM to 8 PM 7 days a week. Patients were enrolled from April 1, 2010, through January 31, 2013. Patients presenting to either of the study EDs who were diagnosed as having ACEI-AE by the treating ED physician were considered for inclusion after standard therapy had been provided by the treating ED physician. Standard therapy could include oral, intramuscular, or intravenous H₁- or H₂- antagonists, oral or intravenous corticosteroids, and epinephrine. If the patient remained symptomatic and was not improving after 2 hours or continued to worsen after standard treatment, they were screened for eligibility. Persons older than 18 years presenting within 12 hours of symptom onset and currently taking an ACEI were eligible if they had not previously been treated with ecallantide, had no other definable causes of angioedema (ie, HAE or acquired angioedema), had not received C1INHs as prophylaxis, were not treated with tranexamic acid or ε-aminocaproic acid, and had not received fresh frozen plasma within 3 days before enrollment. Women of child-bearing potential required a negative pregnancy test result before enrollment.

Study Procedures

After providing written informed consent, participants were randomized 1:1 to receive placebo or ecallantide. After consent, laboratory testing, including hematologic tests with differential, serum chemical analysis, coagulation, urinalysis, and, if a female of child-bearing age, a pregnancy test, was performed. Treatment was administered as 3 subcutaneous injections of 10 mg each (30 mg total) as recommended for its use in the treatment of HAE by the manufacturer. The injection sites had to be at least 1 in apart in a

location distal from the site of swelling but could include the participant's upper arms, thighs, and abdomen. The participant was then monitored for a minimum of 4 hours with assessments performed every 15 ± 10 minutes for the first hour and then every 30 ± 10 minutes for the remaining 3 hours.

At any time during observation in the ED, a single open-label dose of 30 mg of ecallantide (3 × 10-mg injection) could be administered if the study physician determined that a patient was at risk of severe upper airway compromise. This open-label dose could occur at any time after the blinded dose had been administered. Risk of upper airway compromise was defined as the presence of at least 1 of the following 3 clinical findings or observations: (1) worsening dyspnea, dysphagia, drooling, or stridor; (2) progression to Ishoo class IV (a system for predicting airway risk in angioedema)²³ (Table 1); or (3) unstable vital signs (systolic blood pressure <90 mm Hg, respiratory rate >28/min, and heart rate >120/min or <40/min).

Participants who had worsening of their symptoms based on a severity score assessment (Table 1) after 2 hours were administered an open-label dose of subcutaneous ecallantide (3 × 10-mg injections for a total of 30 mg). If after an additional 2 hours, participants had a worsening of their symptoms, they were administered a second open-label dose. Observations were considered completed once a participant had been monitored for 4 hours after the last dose received or on discharge home from the ED. Seven days after enrollment, participants were followed up by telephone to determine the occurrence of adverse events or relapse of angioedema symptoms. Figure 1 summarizes the study design and enrollment.

Study End Point

The primary efficacy study end point was achieving objectively defined ED discharge criteria within 4 hours of initiating treatment. A participant was considered eligible for ED discharge when all the following criteria were fulfilled: stable vital signs (oxygen saturation >92%, systolic blood pressure <160 mm Hg or >90 mm Hg, diastolic blood pressure <100 mm Hg, heart rate <100/min or >50/min, and respiratory rate <20/min), which are routine criteria used in the ED to determine whether a patient can be safely discharged; no evidence of stridor, dysphagia, dyspnea, or drooling; and edema at or below Ishoo class I at the time of evaluation for discharge. This end point did not always reflect actual discharge home because patients may have had to be admitted for concomitant unrelated medical problems.

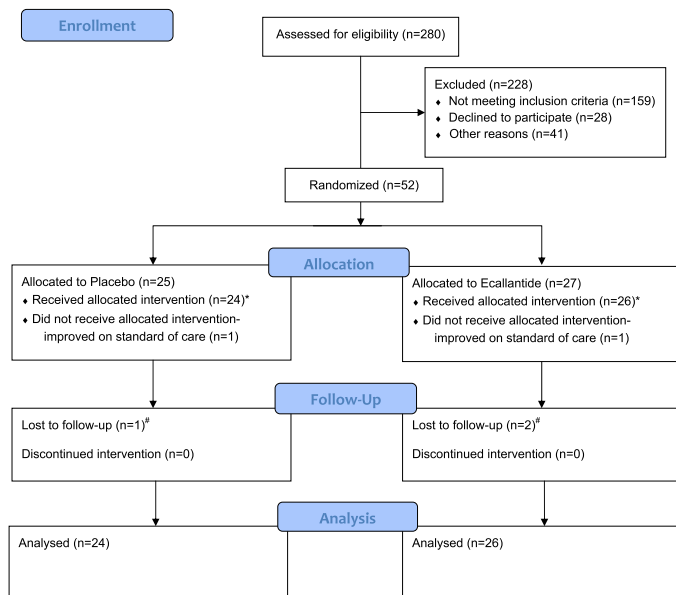
Participants who required open-label treatment with ecallantide at 4 hours or less were assumed to be treatment failures and did not meet ED discharge criteria at 4 hours. Safety was assessed by the adverse event rate and need for rescue therapy. All adverse events and their causality were regularly reviewed by an independent data safety monitoring board throughout the study.

Statistical Analysis

Statistical analyses were conducted on an intent-to-treat basis. The goals of this study were to estimate the adverse event rate for

Table 1
Angioedema classification and assessment

Classification of angioedema defined according to Ishoo et al ²³
Class I: Facial rash, facial edema, lip edema
Class II: Soft palate edema
Class III: Tongue edema
Class IV: Laryngeal edema
Symptom complex response assessment
Significant improvement is when a symptom complex is "a lot better."
Improvement is when a symptom complex is "a little better."
Same is when a symptom complex is unchanged.
Worsening is when a symptom complex is "a little worse."
Significant worsening is when a symptom complex is "a lot worse."



* Treatment was administered as soon after subjects signed an informed consent and the pharmacy was able to randomize and prepare the medication which was typically within 30 minutes; three subcutaneous injections of 10 mg each (30mg total) were administered as recommended for its use in the treatment of hereditary angioedema by the manufacturer. The injection sites were at least one inch apart in a location distal from the site of swelling but could include the participant's upper arms, thighs, and abdomen.

*Subjects were unable to be contacted after 3 attempts using phone number provided.

Figure 1. CONSORT 2010 flow diagram.

Table 2

Demographic and presenting characteristics^a

Characteristic	Placebo (n = 24)	Ecallantide (n = 26)
Age, mean (SD), y	56 (17)	57 (17)
Race		
African American	23 (95.8)	22 (84.6)
White	1 (4.2)	4 (15.4)
Non-Hispanic	24 (100)	26 (100)
Female	15 (62.5)	11 (42.3)
ACEI use for <6 months	4 (16.7)	13 (50.0)
Internal swelling at presentation		
Not experiencing	1 (4.2)	1 (3.8)
Mild	3 (12.5)	2 (7.7)
Moderate	9 (37.5)	10 (38.5)
Severe	11 (45.8)	13 (50.0)
Internal pain at presentation ^{b,c}		
Not experiencing	7 (30.4)	10 (38.5)
Mild	5 (21.7)	6 (23.1)
Moderate	8 (34.8)	4 (15.4)
Severe	3 (13.0)	6 (23.1)
Medical history		
Hypertension	23 (95.8)	26 (100)
Myocardial infarction	2 (8.3)	3 (11.5)
Coronary artery bypass grafting	2 (8.3)	2 (7.7)
Atrial fibrillation	2 (8.3)	1 (3.8)
Congestive heart failure	2 (8.3)	6 (23.1)
Stroke	1 (4.2)	3 (11.5)
Diabetes mellitus	6 (25.0)	9 (34.6)
Renal disease	3 (12.5)	2 (7.7)
Liver disease	1 (4.2)	1 (3.8)
Vital signs at presentation, mean (SD)		
Systolic blood pressure	139 (23)	145 (23)
Diastolic blood pressure	83 (13)	87 (14)
Heart rate	85 (14)	85 (19)
Respiratory rate	18 (3)	17 (3)
Oxygen saturation	97.1 (2.8)	97.3 (1.8)
Minutes from symptom onset to presentation, median (IQR)	264 (80)	154 (292)

Abbreviation: IQR, interquartile range.

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bOne patient is missing data.

^cSymptoms included choking, hoarseness, altered speech, or breathing.

Efficacy

Objective discharge criteria were met in 4 hours or less for 5 (21%) of the 24 patients receiving placebo and for 8 (31%) of the 26 patients receiving ecallantide (difference in proportions, 10%; 95% CI, −14% to 34%) (Fig 2). Open-label treatment with ecallantide was required by 13 (54%) of the 24 patients in the placebo group and 11 (42%) of the 26 patients in the ecallantide group. Of the 13 patients in the placebo

Table 3

Physician assessment of patient at baseline

Variable	No. (%) of patients	
	Placebo (n = 24)	Ecallantide (n = 26)
Baseline symptoms		
Swelling	15 (62.5)	15 (57.7)
Rash or erythema	7 (29.2)	9 (34.6)
Drooling	3 (12.5)	4 (15.4)
Dysphagia	6 (25.0)	8 (30.8)
Stridor	0	2 (7.7)
Dyspnea	0	0
Ishoo class of edema		
I	15 (62.5)	13 (50.0)
II	3 (12.5)	1 (3.8)
III	5 (20.8)	9 (34.6)
IV	1 (4.2)	3 (11.5)
Overall severity		
Mild	4 (16.7)	3 (11.5)
Moderate	15 (62.5)	18 (69.2)
Severe	5 (20.8)	5 (19.2)

safety and to estimate the potential efficacy for designing a phase 3 study. Both safety and efficacy outcomes are binary and are summarized as proportions. To estimate the magnitude of effect, differences in proportions with 2-sided 95% confidence intervals (CIs) are provided. This study was designed to enroll 50 participants. On the basis of historical data, we expected that patients treated with placebo would have a 20% discharge rate at 4 hours, whereas those treated with ecallantide would have a 50% discharge rate at 4 hours. A 2-sided 95% continuity corrected CI around the difference in proportions would be extended $\pm 29\%$ with a sample size of 50. All statistical analyses were conducted using SPSS statistical software, version 21.0 (SPSS Inc, Chicago, Illinois).

Results

Treatment Arm

Fifty patients were enrolled in the study: 24 in the placebo group and 26 in the ecallantide group. The mean (SD) age in the placebo group was 56 (17) years, and the mean (SD) age in the ecallantide group was 57 (17) years. Of the 50 patients, 45 (90%) were African American and 26 (52%) were female. Of the 50 patients, 43 (86%) presented with moderate or severe internal swelling, and 21 (42%) presented with moderate or severe internal pain. Complete demographic and presenting characteristics are presented in Table 2. During the physician assessment at baseline, 43 (86%) presented with moderate or severe overall severity, and 28 (56%) had Ishoo class I edema. Complete physician assessments of symptoms are presented in Table 3. When compared with the placebo group, patients who received ecallantide had a greater proportion of Ishoo class III and IV symptoms, with similar proportions of overall disease severity. All patients were administered conventional therapy that consisted of corticosteroids and H₁-antihistamines, and 1 patient in the ecallantide group received epinephrine before enrollment.

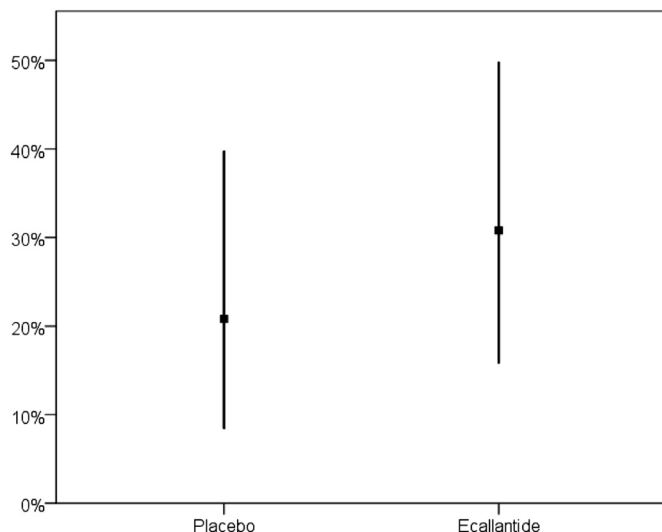


Figure 2. Proportions of patients meeting discharge criteria in four hours or less with 95% confidence intervals for the placebo and ecallantide groups.

group, 2 (15%) required a second open-label dose, one for relapse and one for failure to respond. No patients in the ecallantide group required a second open-label dose. Most of the open-label doses were administered because of an incomplete treatment response or for failure to respond to treatment. However, 1 patient in the placebo group and 1 patient in the ecallantide group received the first open-label dose due to severe upper airway compromise.

Safety

Ecallantide was well tolerated. No local site reactions were reported in either group. Most patients reported at least one adverse event. Adverse events related to their angioedema were reported by 6 (25%) of the 24 patients in the placebo group and 4 (15%) of the 26 patients in the ecallantide group (Table 4). Serious adverse events included hospitalization for longer than 24 hours because of worsening of angioedema, chest pain, recurrence of angioedema, and supraventricular tachycardia for patients in the placebo group and hospitalization for longer than 24 hours because of angioedema, gastric pain, and chest pain for patients in the ecallantide group. None of the adverse events or serious adverse events were deemed to be related to drug.

Discussion

Patients with ACEI frequently present with angioedema of the gastrointestinal tract, face, lips, tongue, and neck that requires

Table 4

Proportion of patients with adverse events, adverse events related to angioedema, and serious adverse events

Event	Placebo, No. (%) (n = 24)	Ecallantide, No. (%) (n = 26)	Difference in proportion (95% CI), %
Any adverse event	18 (75.0)	17 (65.4)	−9.6 (−34.8 to 15.6)
Any related adverse event ^a	6 (25.0)	4 (15.4)	−9.6 (−31.8 to 12.6)
Adverse event only	12 (50.0)	15 (57.7)	7.7 (−19.9 to 35.3)
Serious adverse event ^b	6 (25.0)	2 (7.7)	−17.3 (−37.4 to 2.8)

Abbreviation: CI, confidence interval.

^aAdverse events were related to angioedema but were not considered to be related to treatment with ecallantide.

^bSerious adverse events included hospitalization for longer than 24 hours because of worsening of angioedema, chest pain, recurrence of angioedema, and supraventricular tachycardia for the placebo group and hospitalization for longer than 24 hours because of angioedema, gastric pain, and chest pain for the ecallantide group.

emergency care, including intubation to prevent asphyxiation and death.^{14,24–28} Because there are no currently available biomarkers that measure bradykinin or metabolites, which could differentiate ACEI-AE from other forms of histamine-mediated angioedema, the diagnosis is made largely by history and physical examination. If ACEI-AE is suspected, it is recommended that the ACEI treatment be immediately discontinued to prevent progression and recurrence of angioedema.³ However, discontinuation of use of the drug does not usually result in rapid resolution of angioedema, and frequently the angioedema can persist and even progress for 24 to 48 hours or longer despite standard therapy with antihistamines and corticosteroids.³

A 5-year medical record review of all patients with angioedema seen at community and tertiary care hospital EDs found that patients diagnosed as having ACEI-AE tend to be 65 years or older and have unilateral angioedema symptoms in the absence of urticaria or itching.²⁹ Moreover, hospital admission for angioedema is strongly related to a patient having ACEI-AE and especially those with a lack of improvement despite treatment with conventional therapy.²⁹ These studies suggest that ACEI-AE is associated with significant morbidity and health care use, supporting the development of novel therapies targeted to treat this condition. There is a significant unmet need for therapies that target bradykinin production in the management of ACEI-AE, such as Ecallantide. The Evaluation and Management of Angioedema in the Emergency Department guidelines reflect this gap in treatment by emphasizing the need for a real-time biomarker to measure bradykinin or metabolites to confirm nonhistaminergic angioedema and more effective treatment approaches for patients with ACEI-AE.³⁰

The results of this phase 2 study reveal a trend that patients receiving standard therapy plus ecallantide met criteria for discharge home from the ED within 4 hours after initiating treatment when compared with standard therapy plus placebo. Furthermore, ecallantide is to use in the ED for the treatment of ACEI-AE because no significant adverse events were noted throughout the trial. Of interest, a number of patients enrolled in this study reported associated rash and erythema associated with angioedema that were not characterized as hives. As previously reported, manifestation of rash or urticaria is uncommon.³¹ However, it is possible to speculate that the rash and erythema was a manifestation of increased bradykinin release because rashes are commonly reported in patients presenting with HAE.³²

The absence of a statistically significant difference between ecallantide and placebo may be explained by the small number of patients enrolled in this study. Another explanation may be related to enrolling patients with ACEI-AE with milder lip involvement. Twice as many patients receiving ecallantide (n = 12) were classified as having Ishoo class III or IV in severity compared with patients receiving placebo (n = 6). Inclusion bias is also possible given the relatively small sample size, although the sample was similar to patients with ACEI-AE who were included in a retrospective medical record review of 100 patients who presented to the ED with ACEI-AE.³³ Despite these limitations, the 10% difference is similar to that found in another study of ecallantide for treatment of ACEI-AE and suggests that this may be a robust estimate on which to base the design of a phase 3 study (clinicaltrials.gov Identifier: NCT01343823).

The use of a second open-label dose of ecallantide for those patients who did not respond or appeared to be worsening by 2 hours may have obfuscated our ability to determine the effect of ecallantide over several hours. The rationale to provide an open-label dose was based on previous HAE trials that incorporated a severe upper airway compromise dose for patients with symptoms suggestive of laryngeal edema.

A multicenter, phase 2, double-blind study investigating ecallantide at 3 different doses (10, 30, or 60 mg) compared with placebo in patients with ACEI-AE unresponsive to conventional therapy was recently published.³⁴ Similar to our study, the primary

end point was defined as meeting predetermined discharge criteria within 6 hours after study drug administration. This study, which was based on the design of our study, was discontinued after an interim analysis revealed no statistical difference between active drug and placebo. Although that study did not permit administration of a second dose of ecallantide, it was still subject to many of the other same limitations cited in our study. The lack of efficacy supports our recommendations for more rigorously designed future studies to definitively ascertain whether there is a role for using medications designed to inhibit bradykinin production or block its activity in the treatment of ACEI-AE. For such studies, it is reasonable to speculate that earlier administration of ecallantide to these patients may better delineate a clinically significant difference between active treatment and placebo.

Conclusions

In summary, the results of this study indicate that novel HAE therapies, such as ecallantide, may increase the proportion of patients who meet early discharge criteria by approximately 10% and are safe to use. Subsequent larger studies that are powered to detect a 10% difference in outcomes and that control for other potential confounders are required to confirm the efficacy of ecallantide in ACEI-AE. In addition, whether a 10% improvement in discharge rate reflects cost-effectiveness of this treatment for ACEI-AE to prevent hospitalizations and intensive care unit admissions should be ascertained.

Acknowledgments

We thank Jillian Picard, Sarah Holmes, Laura Heusing, the data safety and monitoring board members (Linda Levin, PhD, Emanuel Villareal, MD, and Michael Policastro, MD), and the numerous coordinators, clinical scientist associates, and ED subinvestigators who participated in this trial.

References

- [1] Bernstein JA, Moellman J. Emerging concepts in the diagnosis and treatment of patients with undifferentiated angioedema. *Int J Emerg Med*. 2012;5:39.
- [2] Bernstein JA, Moellman JJ. Progress in the emergency management of hereditary angioedema: focus on new treatment options in the United States. *Postgrad Med*. 2012;124:91–100.
- [3] Moellman JJ, Bernstein JA. Diagnosis and management of hereditary angioedema: an emergency medicine perspective. *J Emerg Med*. 2012;43:391–400.
- [4] Boyang B, Kelton CML, et al. ACE Inhibitor and ARB Utilization and Expenditures in the Medicaid Fee-For-Service Program from 1991 to 2008. *J Manag Care Pharm*. 2010;16:671–679.
- [5] Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of angioedema associated with enalapril. *Arch Intern Med*. 2005;165:1637–1642.
- [6] Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension*. 2008;51:1624–1630.
- [7] Zuraw BL, Bernstein JA, Lang D. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and ACE inhibitor associated angioedema. *J Allergy Clin Immunol*. 2013;131:1491–1493. 3e1–3e25.
- [8] Banerji A, Clark S, Blanda M, LoVecchio F, Snyder B, Camargo CA Jr. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. *Ann Allergy Asthma Immunol*. 2008;100:327–332.
- [9] Banerji A, Oren E, Hesterberg P, Hsu Y, Camargo CA Jr, Wong JT. Ten-year study of causes of moderate to severe angioedema seen by an inpatient allergy/immunology consult service. *Allergy Asthma Proc*. 2008;29:88–92.
- [10] Bafunno V, Divella C, Sessa F, et al. De novo homozygous mutation of the C1 inhibitor gene in a patient with hereditary angioedema. *J Allergy Clin Immunol*. 2013;132:748–750. e3.
- [11] Lopez-Lera A, Favier B, de la Cruz RM, Garrido S, Drouet C, Lopez-Trascasa M. A new case of homozygous C1-inhibitor deficiency suggests a role for Arg378 in the control of kinin pathway activation. *J Allergy Clin Immunol*. 2010;126:1307–1310. e3.
- [12] Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106:1147–1154.
- [13] Roche O, Blanch A, Duponchel C, Fontan G, Tosi M, Lopez-Trascasa M. Hereditary angioedema: the mutation spectrum of SERPING1/C1NH in a large Spanish cohort. *Hum Mutat*. 2005;26:135–144.
- [14] Campo P, Fernandez TD, Canto G, Mayorga C. Angioedema induced by angiotensin-converting enzyme inhibitors. *Curr Opin Allergy Clin Immunol*. 2013;13:337–344.
- [15] Adam A, Cugno M, Molinaro G, Perez M, Lepage Y, Agostoni A. Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors. *Lancet*. 2002;359:2088–2089.
- [16] Blais C Jr, Rouleau JL, Brown NJ, et al. Serum metabolism of bradykinin and des-Arg9-bradykinin in patients with angiotensin-converting enzyme inhibitor-associated angioedema. *Immunopharmacology*. 1999;43:293–302.
- [17] Burkhart DG, Brown NJ, Griffin MR, Ray WA, Hammerstrom T, Weiss S. Angiotensin converting enzyme inhibitor-associated angioedema: higher risk in blacks than whites. *Pharmacoepidemiol Drug Saf*. 1996;5:149–154.
- [18] Byrd JB, Touzin K, Sile S, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. *Hypertension*. 2008;51:141–147.
- [19] Cilia La Corte AL, Carter AM, Rice GI, et al. A functional XPNPEP2 promoter haplotype leads to reduced plasma aminopeptidase P and increased risk of ACE inhibitor-induced angioedema. *Hum Mutat*. 2011;32:1326–1331.
- [20] Duan QL, Nikpoor B, Dube MP, et al. A variant in XPNPEP2 is associated with angioedema induced by angiotensin I-converting enzyme inhibitors. *Am J Hum Genet*. 2005;77:617–626.
- [21] Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am*. 2006;26:725–737.
- [22] Bernstein JA, Biedenkapp J. Ecallantide for the treatment of acute attacks of hereditary angioedema due to C1-inhibitor deficiency. *Clin Invest*. 2013;3:859–873.
- [23] Ishoo E, Shah UK, Grillone GA, Stram JR, Fuleihan NS. Predicting airway risk in angioedema: staging system based on presentation. *Otolaryngol Head Neck Surg*. 1999;121:263–268.
- [24] Benson BC, Smith C, Laczek JT. Angiotensin converting enzyme inhibitor-induced gastrointestinal angioedema: a case series and literature review. *J Clin Gastroenterol*. 2013;47:844–849.
- [25] Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. *JAMA*. 1997;278:232–233.
- [26] Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J*. 2007;97:244–245.
- [27] Dean DE, Schultz DL, Powers RH. Asphyxia due to angiotensin converting enzyme (ACE) inhibitor mediated angioedema of the tongue during the treatment of hypertensive heart disease. *J Forensic Sci*. 2001;46:1239–1243.
- [28] Slater EE, Merrill DD, Guess HA, et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA*. 1988;260:967–970.
- [29] Bluestein HM, Hoover TA, Banerji AS, Camargo CA Jr, Reshef A, Herscu P. Angiotensin-converting enzyme inhibitor-induced angioedema in a community hospital emergency department. *Ann Allergy Asthma Immunol*. 2009;103:502–507.
- [30] Moellman JJ, Bernstein JA, Lindsell C. A consensus parameter for the evaluation and management of angioedema in the emergency department. *Acad Emerg Med*. 2014;21:469–484.
- [31] Malde B, Regalado J, Greenberger PA. Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Ann Allergy Asthma Immunol*. 2007;98:57–63.
- [32] Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161:1153–1158.
- [33] Gang C, Lindsell CJ, Moellman J, et al. Factors associated with hospitalization of patients with angiotensin-converting enzyme inhibitor-induced angioedema. *Allergy Asthma Proc*. 2013;34:267–273.
- [34] Lewis LM, Graffeo C, Crosley P, et al. Ecallantide for the acute treatment of angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter, randomized, controlled trial [published ahead of print August 30, 2014]. *Ann Emerg Med*. <http://dx.doi.org/10.1016/j.annemergmed.2014.07.014>.