Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema

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Background: The B_2 receptor antagonist icatibant is approved for treatment of attacks of hereditary angioedema. Icatibant has been reported to decrease time-to-resolution of angiotensin-converting enzyme (ACE) inhibitor-associated angioedema in 1 study of European patients.

Objective: We sought to test the hypothesis that a bradykinin B_2 receptor antagonist would shorten time-to-resolution from ACE inhibitor-associated angioedema.

Methods: Patients with ACE inhibitor–associated angioedema (defined as swelling of lips, tongue, pharynx, or face during ACE inhibitor use and no swelling in the absence of ACE inhibitor use) were enrolled at Vanderbilt University Medical Center from October 2007 through September 2015 and at Massachusetts General Hospital in 2012. C1 inhibitor deficiency and patients with bowel edema only were excluded. Patients were randomized within 6 hours of presentation to subcutaneous icatibant 30 mg or placebo at 0 and 6 hours later. Patients assessed severity of swelling using a visual analog scale serially following study drug administration or until discharge.

Results: Thirty-three patients were randomized and 31 received treatment, with 13 receiving icatibant and 18 receiving placebo. One patient randomized to icatibant did not complete the visual analog scale and was excluded from analyses. Two-thirds of patients were black and two-thirds were women. Time-to-resolution of symptoms was similar in placebo and icatibant treatment groups ($P = .19$ for the primary symptom and $P > .16$ for individual symptoms of face, lip, tongue, or eyelid swelling). Frequency of administration of H1 and H2 blockers, corticosteroids, and epinephrine was similar in the 2 treatment groups. Time-to-resolution of symptoms was similar in black and white patients.

Conclusions: This study does not support clinical efficacy of a bradykinin B_2 receptor antagonist in ACE inhibitor-associated angioedema. (J Allergy Clin Immunol 2017;140:242-8.)

Key words: *Angioedema, angiotensin-converting enzyme, bradykinin, icatibant, substance P*

Angioedema is a potentially life-threatening side effect sometimes seen in patients taking angiotensin-converting enzyme (ACE) inhibitors and is characterized by well-demarcated edema of the lips; tongue; mucous membranes of the throat, nose, or other parts of the face; and occasionally the hands or gastrointestinal mucosa.[1] The incidence of angioedema among ACE inhibitor users ranges from 0.7 to 1.3 episodes per thousand person-years of exposure in whites and 3.3 to 4.6 person-years of exposure in blacks.[2]

The mechanism of angioedema is not fully understood but is presumed to involve bradykinin. Activation of the kallikrein-kinin system contributes to the pathogenesis of hereditary angioedema.[3] ACE or kininase II catalyzes the formation of angiotensin II from angiotensin I but is also involved in the breakdown of bradykinin to inactive metabolites. ACE inhibitors potentiate the effects of bradykinin through its action at the B_2 receptor.[4,5] Stimulation of B_2 receptors induces vasodilation and vascular permeability and also stimulates the release of substance P from sensory fibers.[6] Substance P increases vascular permeability and contributes to ACE inhibitor–associated angioedema in rodent models.[7,8]

The standard-of-care for ACE inhibitor-associated angioedema has been nonspecific and consists of discontinuation of the ACE inhibitor, observation, and airway management. Antihistamines, corticosteroids, and epinephrine are often administered but ineffective in this nonallergic form of angioedema.[1] Icatibant or HOE 140 (D-Arg-[Hyp3, Thi5, D-Tic7, Oic8]) bradykinin (Shire, Lexington, Mass) is a selective bradykinin B_2 receptor antagonist, which has been used in human studies to delineate the contribution of bradykinin to the beneficial effects of ACE inhibitors.[4,5,9] Icatibant reduces the time-to-resolution of symptoms in patients with hereditary angioedema[10,11] and has been approved by the US Food and Drug Administration for this indication. Recently Bas et al[12] reported that icatibant significantly decreases time-to-complete resolution of ACE inhibitor–associated angioedema in patients of European descent. Whether these findings can be applied to a more heterogeneous patient population remains to be determined. The purpose of this study was to test the hypothesis that administration of icatibant decreases the duration and severity of ACE inhibitor–associated angioedema.

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Abbreviations used
ACE: Angiotensin-converting enzyme
VAS: Visual analog scale

METHODS

Subjects

Patients age 18 to 65 years with ACE inhibitor–associated angioedema were enrolled at Vanderbilt University Medical Center between October 2007 and August 2011 (NCT00517582) and at Massachusetts General Hospital (a single case enrolled in 2012) and Vanderbilt University Medical Center between August 2011 and September 2015 (NCT01574248). Two other sites initiated the study but did not enroll any patients. Patients were defined as having ACE inhibitor–associated angioedema if they had swelling of the lips, pharynx, or face while taking an ACE inhibitor and had never had swelling in the absence of ACE inhibitor use. Patients with hereditary angioedema were excluded. Cases of ACE inhibitor–associated bowel edema were excluded because it would be difficult to define time of onset and time-to-resolution accurately. Patients who presented with features of hypersensitivity, such as pruritus or urticaria, were not considered as having ACE inhibitor–associated angioedema. Patients who had presented to medical care >6 hours prior to screening and randomization were excluded. Pregnant women were excluded by measurement of urine beta-human chorionic gonadotropin on enrollment; initiation of oral contraceptive therapy within 6 months of presentation was also a criterion for exclusion.

Study protocol

The double-blind, placebo-controlled study protocol was approved by the institutional review boards of the participating institutions in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

After consent was obtained, patients underwent a baseline history and assessment of their angioedema. Patients were randomized 1:1 to receive icatibant 30 mg (Firazyr; Jerini AG/Shire Human Genetic Therapies, Lexington, Mass) or matching placebo (normal saline) at 0 and 6 hours using a permuted-block randomization algorithm. Randomization was stratified by race. The Vanderbilt Investigational Drug Service was responsible for the storage, preparation, and labeling of the study drug. Study medication was delivered in 2 1.5-mL syringes and was administered subcutaneously in the abdominal region by the nurse caring for the patient, so that investigators would remain blinded if there was any local irritation. Patients were not questioned about irritation at the injection site and nurses were instructed not to tell research personal if a patient commented on irritation so as to maintain blinding. Blood pressure and heart rate were measured prior to and every 15 minutes following study drug administration for 1 hour and then with each assessment of angioedema severity.

In addition to study drug, patients received standard-of-care medical therapy at the discretion of the treatment team and administration of antihistamines, steroids, or epinephrine was recorded as a secondary end point. In all cases, the patient's ACE inhibitor was stopped and the patient was given a list of ACE inhibitors so that he or she could avoid re-exposure. Disposition was also determined by the treatment team. Patients who were discharged home were offered the option of being admitted to the Vanderbilt Clinical Research Center to complete study procedures up to 48 hours after study drug administration. Patient's electronic medical records were also reviewed for recurrence of angioedema after discontinuation of ACE inhibitor use and study medication until completion of the study; 1 patient in the placebo group and 1 patient in the icatibant group were lost to follow-up.

Angioedema severity assessment

Patients were given a 10-cm nonhatched visual analog scale (VAS) that had been developed for trials of icatibant in hereditary angioedema to assess severity of face, lip, tongue, and eyelid swelling, as well as shortness of breath, difficulty speaking, difficulty swallowing, and voice change.[10-12] Patients completed the VAS at baseline and 1, 2, 4, 6, 8, 16, 24, and 48 hours following study drug administration or until discharge. Patients were provided with a mirror to view their swelling if desired prior to using the VAS and graded symptom score. At the same times, patients were also asked to contrast the current severity of their signs and symptoms to the previous time point with a graded symptom score using the following verbal descriptors: "none," "much less," "a little less," "about the same," "a little more," and "much more."

The investigator or research nurse independently assessed the severity of angioedema using a graded sign and symptom score, assigning a score equal to 0 for "absence of symptoms," 1 for "mild," 2 for "moderate," and 4 for "severe" symptom or signs. The study personnel completed this scale at baseline and 1, 2, 4, 6, 8, 16, 24, and 48 hours after study drug administration or at discharge.

Laboratory analysis

Blood for complete blood count, metabolic panel, prothrombin, and partial thromboplastin time were collected at enrollment and at discharge and measured in the clinical laboratory. Blood for measurement of C1 esterase inhibitor and complement levels was collected at baseline. C1 esterase inhibitor protein was determined by quantitative nephelometry at a third-party laboratory (ARUP Laboratories, Salt Lake City, Utah), and C1 esterase inhibitor activity was determined using a commercially available chromogenic assay (Technoclone, Vienna, Austria). C3 and C4 levels were assessed by immunoturbidimetric method at the Vanderbilt Pathology Laboratory. Blood samples for future research assays were collected at baseline and 6, 24, and 48 hours (or at discharge) after study drug administration and were immediately centrifuged at 5°C for 20 minutes. Serum and plasma were then separated and stored at −80°C until the time of assay.

Statistical analysis

The calculated sample size for the study was 16 patients per study arm. This sample size had a 0.8 power to detect a difference in the median times to resolution of 8.5 hours versus 23.3 hours between treatment based on a log-rank test with 2-sided type I error rate of 0.05. The expected median times were based on time-to-resolution following treatment with icatibant versus placebo in hereditary angioedema.[10]

In February 2015, the principal investigator convened the Data and Safety Committee of the study to seek input regarding continuation of the study after Bas et al[12] published the report of a randomized trial comparing the effect of icatibant to prednisolone/clemastine comparator on time-to-resolution of ACE inhibitor–induced angioedema. The Data and Safety Monitoring Committee concluded that equipoise still existed and that the study should continue, based on important differences in outcomes and participant demographics between the published study and the current study. After the publication of the Bas et al[12] trial, however, enrollment declined and, in September 2015, it was decided to discontinue the study after consultation with the Data and Safety Monitoring Committee.

An intention-to-treat analysis was completed in all patients who received any study drug. The primary analyses were (1) survival analysis using a log-rank test to assess the time-to-resolution of symptoms and (2) generalized least squares linear regression analysis of the VAS measurement of the primary (most severe) sign or symptom over time. In the log-rank test, signs or symptoms with a VAS measurement ≤1 cm were defined as resolved. Data were also analyzed using a Cox proportional hazards model that controlled for severity at baseline (VAS score at time 0) and race.

Secondary outcomes included the frequency of concomitant medications, the incidence of admission to the intensive care unit, the incidence of intubation, the effect of treatment on blood pressure, and the frequency of adverse events.

A 2-sided P value of <.05 was considered statistically significant. All the analyses were performed using R 3.1.2 (R Foundation, Vienna, Austria).