ORIGINAL ARTICLE

A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

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ABSTRACT

BACKGROUND

Angioedema induced by treatment with angiotensin-converting–enzyme (ACE) inhibitors accounts for one third of angioedema cases in the emergency room; it is usually manifested in the upper airway and the head and neck region. There is no approved treatment for this potentially life-threatening condition.

METHODS

In this multicenter, double-blind, double-dummy, randomized phase 2 study, we assigned patients who had ACE-inhibitor–induced angioedema of the upper aerodigestive tract to treatment with 30 mg of subcutaneous icatibant, a selective bradykinin B2 receptor antagonist, or to the current off-label standard therapy consisting of intravenous prednisolone (500 mg) plus clemastine (2 mg). The primary efficacy end point was the median time to complete resolution of edema.

RESULTS

All 27 patients in the per-protocol population had complete resolution of edema. The median time to complete resolution was 8.0 hours (interquartile range, 3.0 to 16.0) with icatibant as compared with 27.1 hours (interquartile range, 20.3 to 48.0) with standard therapy (P=0.002). Three patients receiving standard therapy required rescue intervention with icatibant and prednisolone; 1 patient required tracheotomy. Significantly more patients in the icatibant group than in the standard-therapy group had complete resolution of edema within 4 hours after treatment (5 of 13 vs. 0 of 14, P=0.02). The median time to the onset of symptom relief (according to a composite investigator-assessed symptom score) was significantly shorter with icatibant than with standard therapy (2.0 hours vs. 11.7 hours, P=0.03). The results were similar when patient-assessed symptom scores were used.

CONCLUSIONS

Among patients with ACE-inhibitor–induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine. (Funded by Shire and the Federal Ministry of Education and Research of Germany; ClinicalTrials.gov number, NCT01154361.)

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Angioedema induced by treatment with angiotensin-converting–enzyme (ACE) inhibitors is estimated to occur in up to 0.68% of patients who receive ACE inhibitors,[1-5] although the true incidence is difficult to estimate because symptoms can take years to appear.[6] Although the risk of ACE-inhibitor–induced angioedema is low, the increasing use of ACE inhibitors is resulting in a comparatively large number of patients at risk for this condition,[7] which accounts for one third of all cases of angioedema treated in the emergency room.[8] ACE-inhibitor–induced angioedema affects almost exclusively the upper aerodigestive tract but can, in rare cases, affect the gut. Obstruction of the upper airway occurs in 10% of cases and may proceed to acute laryngeal obstruction and death.[8,9]

Standard emergency room treatment of ACE-inhibitor–induced angioedema consists of symptomatic treatment with glucocorticoids and antihistamines. However, because this form of angioedema is not a histamine-mediated reaction, patients generally do not have a response to this therapy.[10] Whether this off-label standard therapy offers any clinical benefit remains subject to debate.

ACE inhibitors exert their therapeutic effects by blocking the conversion of angiotensin I to angiotensin II; they also inhibit the breakdown of bradykinin, thereby increasing its activity. Bradykinin-mediated hereditary angioedema is usually treated with C1 inhibitor concentrates, which inhibit the formation of bradykinin, and with the selective bradykinin B2 receptor antagonist icatibant.[11] In case reports of patients with ACE-inhibitor–induced angioedema who received treatment with icatibant (which is currently not licensed for this indication), the time to a reduction of symptoms was similar to that seen with icatibant in cases of hereditary angioedema.[10,12-16] Here we report the results of a phase 2 study of icatibant, as compared with standard combination therapy consisting of a glucocorticoid and an antihistamine, in patients with ACE-inhibitor–induced angioedema of the upper aerodigestive tract.

Methods

Study Oversight

We performed this multicenter, double-blind, double-dummy, randomized phase 2 study at four sites in Germany. The study was approved by local independent ethics committees and was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and current regulatory requirements.

The trial was designed by Klinikum rechts der Isar at Technische Universität München, Germany, and was supported by an educational grant from Shire. The project management, monitoring, data management, and statistical analysis were supervised by Münchner Studienzentrum (Technische Universität München). The statistical analysis was performed by Metronomia Clinical Research. Shire had the opportunity to review and provide comments on the manuscript before submission but had no role in the design of the trial, the collection or analysis of the data, or the decision to submit the manuscript for publication. A medical writer at Prime Healthcare, funded by Technische Universität München, assisted with the writing of the manuscript. The authors vouch for the accuracy and completeness of the data and all the analyses and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

Patients

Patients 18 to 95 years of age who were receiving ACE inhibitors and who presented to the emergency department with ACE-inhibitor–induced angioedema affecting the upper aerodigestive tract (which includes the face, lips, cheeks, tongue, soft palate or uvula, pharynx, and larynx) were eligible for inclusion. Patients with angioedema that was considered, on medical review, to be due to causes other than ACE inhibitors were excluded. Other exclusion criteria were a history of angioedema before the initiation of ACE-inhibitor therapy, acute urticaria, unstable angina, acute myocardial ischemia, acute heart failure with a New York Heart Association class of III or IV, pregnancy, and lactation. All patients provided written informed consent.

Study Design

The study design is shown in Figure S1 in the Supplementary Appendix, available at NEJM.org. Eligible patients were randomly assigned, in a 1:1 ratio, to receive, within 10 hours after symptom onset, subcutaneous icatibant, at a dose of 30 mg injected into the abdominal wall, or standard therapy consisting of intravenous prednisolone (Solu-Decortin H, Merck) at a dose of 500 mg

plus clemastine (Tavegil, Novartis) at a dose of 2 mg. Randomization was performed online with the use of variable block sizes to ensure that the number of study participants in the treatment groups was balanced. Normal saline (0.9%, B. Braun) was administered as an intravenous placebo in patients who were receiving icatibant and as a subcutaneous placebo in those who were receiving standard therapy. The patients and the investigators who were responsible for the assessment of efficacy outcomes were unaware of the study assignments; the investigators who were responsible for randomization, study-drug administration, and assessment of injection-site reactions were aware of the study assignments.

Patients assessed the intensity of six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure) before treatment and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment with the use of a visual-analogue scale that ranged from 0 to 10, with higher scores indicating more severe symptoms. A composite score on the visual-analogue scale was calculated as the average of the measurements for the six symptoms. Investigators who were unaware of the treatment assignments also assessed the severity of the same six symptoms at the same time points, using a scale from 0 (no symptoms) to 3 (severe symptoms); a composite symptom score was calculated from the average of the six symptom scores. In addition, investigators assessed the severity of angioedema at four locations (lips and cheeks, tongue, oropharynx, and hypopharynx or larynx), using a scale from 0 (no angioedema) to 4 (very severe angioedema). Angioedema of the oropharynx and hypopharynx was assessed by an ear, nose, and throat specialist, who performed endoscopy when necessary. A composite angioedema score was calculated as the average of the four symptom scores.

If no reduction in symptoms had occurred by 6 hours after treatment, the investigator could administer rescue medication (30 mg of icatibant with 500 mg of prednisolone), regardless of the group to which the patient had been randomly assigned. In life-threatening situations, appropriate rescue procedures (including intubation or tracheotomy) could be implemented. A final follow-up visit was scheduled 14 days after hospital admission.

END POINTS

The primary end point was the time to the complete resolution of edema after administration of the study treatment, as evaluated on the basis of investigator-assessed and patient-assessed symptom scores, as well as the investigator's assessment of the severity of angioedema on the basis of the physical examination. Secondary end points included the proportion of patients who did not have a response to treatment (i.e., patients who required rescue therapy); the proportion of patients with complete resolution of edema at 4 hours after treatment; the time to the onset of symptom relief, which was defined as the time to the first improvement (i.e., decrease) of at least one point in the composite score of the investigator-assessed symptom score, the angioedema score, or the score on the patient-assessed visual-analogue scale; and the composite and individual investigator-assessed symptom scores, angioedema scores, and scores on the patient-assessed visual-analogue scale, as well as the change in the composite scores from the pretreatment scores, at each protocol-specified time point. Safety was evaluated by assessment of the incidence of and time to rescue intervention, adverse-event reporting, documentation of local (injection-site) reactions, measurement of vital signs, and clinical laboratory testing.

STATISTICAL ANALYSIS

On the basis of previous off-label observations regarding icatibant and standard therapy in ACE-inhibitor–induced angioedema,[10] a skewed distribution was assumed for the time to complete resolution of edema, and the probability of observing a smaller value in one of the two treatment groups was set to 0.9. Given these assumptions, we calculated that with 11 patients in each group, the study would have 90% power to detect the expected between-group difference in distribution with respect to the time to complete resolution of edema, at a two-sided significance level of 5%, with the use of a Wilcoxon rank-sum test. Assuming a maximum dropout rate of 25% (to account for patients requiring rescue intervention for progression of edema), a final sample of 15 patients in each treatment group was planned.

The analysis of the primary end point was performed in the per-protocol population, which included all patients who underwent randomization and received the study medication. For pa-

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Icatibant (N=13)	Standard Therapy (N=14)
Sex — no. (%)		
Male	9 (69)	8 (57)
Female	4 (31)	6 (43)
Age — yr	62.4±9.7	69.4±16.6
ACE inhibitor — no. (%)		
Benazepril	1 (8)	0
Captopril	1 (8)	1 (7)
Captopril–hydrochlorothiazide	1 (8)	0
Enalapril	5 (38)	2 (14)
Lisinopril	0	3 (21)
Ramipril	5 (38)	8 (57)
Previous episode of ACE-inhibitor–induced angioedema — no. (%)	5 (38)	5 (36)
Scores for baseline severity of symptoms		
Composite investigator-assessed symptom score†	1.1±0.2	1.2±0.2
Composite investigator-assessed angioedema score‡	1.1±0.2	1.1±0.2
Composite patient-assessed VAS score§	2.9±0.6	3.5±0.6
Medical history — no. (%)¶		
Cardiac disorder	5 (38)	9 (64)
Endocrine disorder	2 (15)	4 (29)
Metabolism or nutrition disorder	8 (62)	5 (36)
Nervous system disorder	3 (23)	3 (21)
Respiratory, thoracic, or mediastinal disorder	2 (15)	6 (43)
Vascular disorder	13 (100)	13 (93)
Angioedema location — no. (%)		
Lips	3 (23)	4 (29)
Cheeks	3 (23)	2 (14)
Tongue	8 (62)	10 (71)
Pharynx and soft palate	4 (31)	5 (36)
Larynx	6 (46)	7 (50)
Floor of mouth	6 (46)	9 (64)
Face	3 (23)	3 (21)

* Plus–minus values are means ±SD. The baseline characteristics are shown for the per-protocol population, which included all patients who underwent randomization and received the study medication. There were no significant differences between the groups in any of the characteristics listed here. ACE denotes angiotensin-converting enzyme.

† Investigators who were unaware of the treatment assignments assessed the intensity of six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure) before treatment and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment, using a scale from 0 (no symptoms) to 3 (severe symptoms); a composite symptom score was calculated from the average of the six symptom scores.

‡ Investigators assessed the severity of angioedema at four locations (lips and cheeks, tongue, oropharynx, and hypopharynx or larynx), using a scale from 0 (no angioedema) to 4 (very severe angioedema). Angioedema of the oropharynx and hypopharynx was assessed by an ear, nose, and throat specialist, who performed endoscopy when necessary. A composite angioedema score was calculated as the average of the four symptom scores.

§ Patients assessed the intensity of six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure) before treatment and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment, with the use of a visual-analogue scale (VAS) that ranged from 0 to 10, with higher scores indicating more severe symptoms. A composite score on the VAS was calculated as the average of the measurements for the six symptoms.

¶ Disorders are included if they were noted in the medical history of more than three patients in either treatment group.

Table 2. Clinical Outcomes.*

Outcome	Icatibant (N=13)	Standard Therapy (N=14)	P Value
Median (IQR) time to complete resolution of edema: primary end point — hr	8.0 (3.0–16.0)	27.1 (20.3–48.0)	0.002†
Patients with complete resolution of edema at 4 hr after treatment — no. (%)	5 (38)	0	0.02‡
Median (95% CI) time to onset of symptom relief — hr§			
According to composite investigator-assessed symptom score	2.0 (1.0–8.1)	11.7 (8.0–18.0)	0.03¶
According to composite patient-assessed VAS score	2.0 (2.0–6.3)	7.9 (1.2–11.8)	0.36¶
According to composite investigator-assessed angioedema score	2.0 (2.0–12.0)	12.0 (11.3–NE)	0.003¶

* Clinical outcomes were assessed in the per-protocol population. CI denotes confidence interval, IQR interquartile range, and NE not estimable.
† The P value was calculated with the use of the Wilcoxon rank-sum test.
‡ The P value was calculated with the use of Fisher's exact test.
§ The time to the onset of symptom relief was defined as the time to the first improvement (i.e., decrease) of at least 1 point in the composite score.
¶ The P value was calculated with the use of the Peto–Peto–Prentice test.

tients who did not have a response to treatment (i.e., patients who required administration of rescue intervention), the time to the complete resolution of edema was set to the longest observed resolution time in the per-protocol study population. The superiority of icatibant over standard therapy was assessed by a between-group comparison of the median time to the complete resolution of edema, with the use of the Wilcoxon rank-sum test at a two-sided significance level of 5%. Various sensitivity analyses were performed to assess the robustness of the primary efficacy analysis (see the Supplementary Appendix).

Secondary efficacy analyses were performed in the per-protocol population, whereas secondary safety analyses were performed in the as-treated population, which included all patients who received at least one dose of either study medication, with results attributed to the treatment they actually received. (Patients in the standard-therapy group who had no reduction in symptoms by 6 hours after treatment and were administered icatibant and prednisolone as rescue medication were included in the standard-therapy group.) The number and percentage of patients who required rescue intervention and the number and extent of adverse events were compared between the groups with the use of Fisher's exact test. All statistical tests of the secondary end points were two-sided with a significance level of 5% and were not adjusted for multiple testing.

RESULTS

PATIENTS

Of the 32 patients screened, 30 were enrolled in the study during the period from July 2010 through December 2011 — 15 patients in each group. The median time from the onset of angioedema to treatment was 6.1 hours (range, 3.0 to 10.0) in the icatibant group and 5.1 hours (range, 2.0 to 9.3) in the standard-therapy group.

In the case of 3 patients, the decision to administer treatment was made by the investigator before randomization (icatibant therapy in the case of 2 patients and standard therapy in the case of 1 patient). These patients were excluded from the per-protocol analyses, leaving 27 patients in the per-protocol population. No patients discontinued the study owing to adverse events; however, 4 patients were lost to follow-up (Fig. S2 in the Supplementary Appendix).

The baseline characteristics of the per-protocol population are shown in Table 1. Data on all 30 patients according to the treatment they received are provided in Table S1 in the Supplementary Appendix. All the patients were white. Five patients in each group had had a previous episode

of ACE-inhibitor–induced angioedema. Patients in the standard-therapy group were older than those in the icatibant group; otherwise, the two treatment groups were similar.

EFFICACY END POINTS

All the patients in the per-protocol population had complete resolution of edema; however, three patients in the standard-therapy group required rescue therapy (icatibant and prednisolone) and were classified as having had treatment failure. One of these patients also required a tracheotomy for dyspnea that was classified as a serious adverse event (see below). The maximum recorded time to the complete resolution of edema (61.2 hours) was used to replace the data for these three patients in the primary efficacy analysis.

The median time to the complete resolution of edema was 8.0 hours (interquartile range, 3.0 to 16.0) with icatibant as compared with 27.1 hours (interquartile range, 20.3 to 48.0) with standard therapy (P=0.002) (Table 2 and Fig. 1). The respective mean (±SD) times to complete resolution of edema were 15.4±18.8 hours and 33.2±18.0 hours. Kaplan–Meier sensitivity analyses in which the data for the three patients who received rescue intervention were censored at the time of the first rescue event resulted in similar estimates of the median time to complete resolution of edema — 8.0 hours (95% confidence interval [CI], 3.0 to 16.0) with icatibant versus 23.7 hours (95% CI, 17.8 to 35.9) with standard therapy (P=0.008) (Table S2 in the Supplementary Appendix). All other sensitivity analyses of the primary efficacy end point confirmed these results (Table S2 in the Supplementary Appendix).

Five patients (38%) who received icatibant, as compared with none who received standard therapy, had complete resolution of edema within 4 hours after treatment (P=0.02). On the basis of Kaplan–Meier analyses, the median time to the onset of symptom relief was shorter with icatibant than with standard therapy — 2.0 hours (95% CI, 1.0 to 8.1) versus 11.7 hours (95% CI, 8.0 to 18.0) (P=0.03) (Fig. S4 in the Supplementary Appendix). Similar results were observed with respect to the composite investigator-assessed angioedema score; the area under the curve at 12 hours was 6.6 (range, 3.0 to 18.7) in the icatibant group as compared with 8.9 (range, 2.8 to 24.0) in the standard-therapy group. Patient-assessed scores followed the same pattern. Mean changes in the intensity of symptoms (as assessed by investigators and by patients) and in the severity of angioedema (as assessed by investigators) were greater with icatibant than with standard therapy from 1 hour after treatment to 8 hours after treatment (Fig. S6 in the Supplementary Appendix). Photographic examples of angioedema at baseline and at 12 hours after treatment in patients assigned to each regimen are shown in Figure S3 in the Supplementary Appendix.

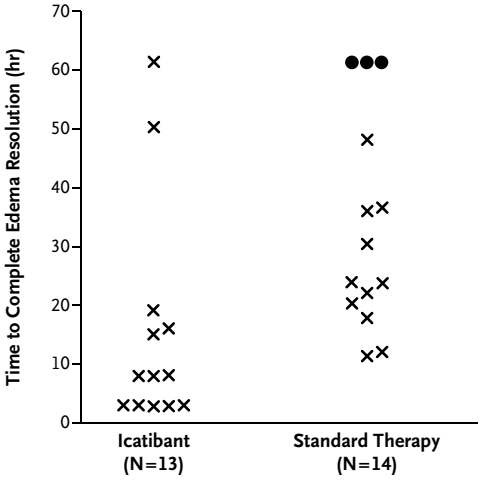

Figure 1. Time to Complete Resolution of Edema, According to Study Treatment.

The per-protocol population, which included all patients who underwent randomization and received the study medication, comprised 27 patients — 13 in the icatibant group and 14 in the standard-therapy group. For 3 patients in the standard-therapy group who required rescue intervention (circles), the time to complete resolution of edema was set at 61.2 hours, which was the longest observed resolution time in the per-protocol study population.

SAFETY AND SIDE-EFFECT END POINTS

Seven patients in the icatibant group and two in the standard-therapy group had pain on administration of treatment, as reported by the investigators (Table 3). In addition, six patient-reported adverse events occurred in five patients. In the icatibant group, the only patient-reported adverse event was pain at the injection site. In the standard-therapy group, mild exacerbation of chronic obstructive pulmonary disease was reported in one patient, an increase in the blood glucose level in

Table 3. Adverse Events and Injection-Site Reactions.*

Outcome	Icatibant (N=15)	Standard Therapy (N=15)
	no. of patients (%)	
Any adverse event	1 (7)†	4 (27)
Drug-related adverse event	1 (7)	1 (7)
Serious adverse event	0	1 (7)
Injection-site reaction‡		
Redness	12 (80)	4 (27)
Swelling	8 (53)	3 (20)
Pain	7 (47)	2 (13)
Itching	4 (27)	1 (7)
Sensation of warmth	4 (27)	0

* These analyses were performed in the as-treated population, which included all patients who received at least one dose of either study medication, with results attributed to the treatment they actually received.
† The only patient-reported adverse event in the icatibant group was "pain at the administration site (local pain)."
‡ Injection-site reactions were assessed by the investigators.

one patient, fatigue in one patient, and an influenza-like illness in one patient. The influenza-like illness was accompanied by a serious adverse event (dyspnea). The patient received rescue treatment with icatibant and prednisolone and underwent tracheotomy, with complete recovery after 20 days. All the adverse events resolved and none led to study discontinuation.

Investigator-assessed injection-site reactions were more common in the icatibant group than in the standard-therapy group (Table 3). The results were similar when patients assessed local injection-site reactions (Table S3 in the Supplementary Appendix). According to investigator assessments, all injection-site reactions resolved completely within 4 hours after treatment. Two patients in the icatibant group, however, still reported injection-site reactions at 4 hours.

DISCUSSION

In this randomized trial involving patients with ACE-inhibitor–induced angioedema, complete resolution of edema occurred significantly more quickly after treatment with 30 mg of subcutaneous icatibant than after standard therapy with glucocorticoids and antihistamines. This finding is consistent with observations in earlier case reports.[10,13-16] We previously reported that the mean time to complete relief of symptoms was 4.4 hours among 8 patients with ACE-inhibitor–induced angioedema who received icatibant, as compared with 33 hours in a historical group of 47 patients receiving standard therapy.[10] In the current study, the median time to the complete resolution of edema was 70% shorter with icatibant than with standard therapy (8.0 hours vs. 27.1 hours, P=0.002). In phase 3 studies of icatibant in patients with hereditary angioedema, the median time to almost-complete symptom relief was similar (8.5 to 10 hours).[11]

We also observed a significantly faster time to the onset of symptom relief with icatibant than with standard therapy (P=0.03). The time to the onset of symptom relief was consistent whether assessed by patients or by investigators (2.0 hours according to each type of assessment) and was similar to the time reported in previous studies involving patients with ACE-inhibitor–induced angioedema (0.9 hours)[10] and patients with hereditary angioedema (0.8 to 1.5 hours).[11]

Although the sample size in this trial was too small to allow for a robust evaluation of safety, no patient discontinued participation in the study owing to adverse events. As expected,[11] local injection-site reactions were seen more often in the icatibant group than in the standard-therapy group. These events were transient and resolved in 87% of the patients (13 of 15) within 4 hours after administration of the study drug.

Experimental evidence suggests that ACE-inhibitor–induced angioedema is mediated by bradykinin and would therefore not be expected to respond to standard therapy with antihistamines. Glucocorticoids have been shown to induce the expression of ACE and thereby could possibly accelerate bradykinin metabolism[17,18]; however, their use as a treatment for nonallergic angioedema has not previously been investigated systematically. Although the causal role of bradykinin in ACE-inhibitor–induced angioedema is not yet completely understood, ACE is the most important enzyme regulating the breakdown of bradykinin in plasma and tissues. Studies in animals as well as studies involving humans have shown that blocking bradykinin B2 receptors attenuates the efficacy of ACE inhibitors.[19,20] Icatibant is therefore a logical treatment choice for ACE-inhibitor–induced angioedema. Indeed, the French National Center for Angioedema recently recommended first-line off-label use of bradykinin antagonists

and second-line use of C1-inhibitor concentrates in patients with ACE-inhibitor–induced angioedema.[21] However, icatibant is not currently licensed for this indication.

In conclusion, in this randomized trial involving patients with ACE-inhibitor–induced angioedema, complete resolution of edema was achieved significantly more quickly with subcutaneous icatibant than with standard therapy consisting of glucocorticoids and antihistamines.

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