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Icatibant is not helpful for the treatment of ACE inhibitor-induced angioedema

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ABSTRACT A critical appraisal and clinical application of Sinert R, Levy P, Bernstein JA, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. *J Allergy Clin Immunol Pract.* 2017; 5(5): 1402-1409. doi: [10.1016/j.jaip.2017.03.003](https://doi.org/10.1016/j.jaip.2017.03.003).

Keywords: *angiotensin-converting enzyme inhibitor, ACE inhibitor, angioedema, icatibant*

Clinical Context

A 67-year-old African American woman, with a relevant past medical history of chronic obstructive pulmonary disease and hypertension, presented to the general practice unit (GPU) following a one day course in the medical intensive care unit (MICU) for angiotensin inhibitor-induced angioedema (ACE I-induced angioedema). The patient initially presented to the emergency department (ED) with a 3 day history of progressive facial swelling after initiating lisinopril therapy six days prior. Originally periorbital, the swelling gradually increased in severity to include her mouth and throat eliciting vocal changes. Serial arterial blood gases in the ED demonstrated hypercapnic respiratory failure with persistent respiratory acidosis requiring intubation. The patient was transferred to the MICU, stabilized, and was extubated in <24 hours. On admission to the GPU the patient stated, "It scares me that I had to be intubated. Was there any therapy that could have prevented this from happening?"

Clinical Question

Is there a medical therapy targeting ACE-I induced angioedema, manifesting due to elevated levels of bradykinin, that decreases the severity of the disease process and manifestation?

Research Article

Sinert R, Levy P, Bernstein JA, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. *J Allergy Clin Immunol Pract.* 2017; 5(5): 1402-1409. doi: [10.1016/j.jaip.2017.03.003](https://doi.org/10.1016/j.jaip.2017.03.003)

Related Literature

ACE I-induced angioedema occurs in up to 0.68% of patients taking ACE inhibitors with up to a 4.5-fold higher rate of diagnosis in African Americans.¹⁻⁴ It accounts for 30% of all emergency room visits for angioedema and has increasing prevalence due to the widespread administration of ACE inhibitors.^{5,6} The current management of ACE I-induced angioedema includes symptomatic control with glucocorticoids and antihistamines. At this time there is no approved treatment for this potentially life-threatening condition.

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PubMed database was utilized to perform a literature review for articles including the search terms “((Icatibant[Title/Abstract]) AND angioedema[Title/Abstract]) AND ACE inhibitor[Title/Abstract]”, and the results were reviewed. An article by Bas et al. was on topic, and the search results were further explored using the “Similar Articles” feature resulting in 104 titles whose abstracts were reviewed for relevance. Three were selected for further analysis.

A multicenter, double-blind, double-dummy, randomized phase 2 clinical trial published in 2015 in the *New England Journal of Medicine* by Bas et al. found that the use of subcutaneous icatibant for the treatment of ACE I-induced angioedema led to significantly faster onset of symptom relief and complete resolution of symptoms in 70% less time compared to standard treatment.² One concern in regard to this study is the small sample size. Only 27 patients were included, which limits the ability to generalize the conclusions to the public.⁸ In addition one needs to be wary of the possibility of funding bias as the pharmaceutical company Shire, the manufacturer of icatibant, provided funding for the study. Lastly, the study was performed in Germany limiting the applicability to our patient. All study participants were white with only 3 of 27 taking lisinopril.² In addition to the race distribution not being representative of the United States population, African Americans are known to suffer from a more severe form of ACE I-induced angioedema.^{3,4}

Of note, a double-blind placebo-controlled randomized study published in 2017 in the *Journal of Allergy and Clinical Immunology* by Straka et al. was terminated following the publication by Bas et al. with findings discordant to the prior study. Straka et al. provided statistical analysis of data collected prior to study discontinuation. Similarities to the study by Bas et al. include a small sample size of 33 participants and concern for funding bias due to partial funding by Shire Pharmaceuticals.⁹ However, of importance, a greater number of patients identified as black and female and administered lisinopril, versus alternative types of ACE inhibitors, prior to presentation.⁹

The article chosen for the critical appraisal is a phase 3, 2-armed, double-blind randomized clinical trial published in 2017 in the *Journal of Immunology and Clinical Pharmacology* by Sinert et al. with findings that dispute those of Bas et al. This article found that icatibant did not provide a statistically significant benefit in the treatment of ACE I-induced angioedema compared to placebo.¹⁰ The study by Sinert et al. addresses many of the concerns regarding the applicability of the study by Bas et al. including: a larger sample size of 121 subjects, 69.4% of participants identifying as black or African American, and lisinopril as the most frequently taken ACE inhibitor.¹⁰ Our patient met all but one of inclusion criteria of this study.

Critical Appraisal

Sinert et al. conducted a phase 3, 2-armed, double-blind randomized clinical trial at 31 of 59 centers in the United States, United Kingdom, Israel, and Canada from December 2013 through August 2015.¹⁰ The purpose of the study was to determine the efficacy of icatibant as a treatment for ACE I-induced angioedema of at least moderate severity. As a multicenter randomized control trial, the strength of the study is level 1 based on SORT criteria.¹¹

Study participants were enrolled if they met the following criteria: aged 18 years or older, presenting with at least moderate severity ACE-I angioedema that manifested in the last 12 hours, and did not have a diagnosis, personal history, or family history of other types of angioedema. A blinded physician assessing 4 clinical domains determined the episode severity. These domains were difficulty breathing, difficulty swallowing, voice changes, and tongue swelling and were measured with a severity rating of 0 to 4. Once enrolled, study participants were randomly assigned to the icatibant group or the placebo group in a 1:1 ratio. All subjects received a single 3 mL subcutaneous injection of 30 mg icatibant or an isotonic acetate-buffered solution. A physician measured the severity of the 4 symptoms at baseline, 30 minutes, 1 hour, and hourly up to 8 hours following drug administration. Severity continued to be measured every 2 hours until 24 hours and every 3 hours from that point on if the primary end point of the study was not met.

The primary efficacy end point of the study was time to meeting discharge criteria. Discharge criteria was defined as the earliest time following study drug administration that difficulty breathing and swallowing were absent and voice changes and tongue swelling were mild or absent. Secondary outcomes included time to onset of symptom relief, occurrence of airway intervention, and admission to the hospital.

The analysis was performed using an intention-to-treat analysis, which led to a total of 121 patients. Sinert et al. demonstrated that there were no statistically significant differences in the primary efficacy end point and the secondary end points of the study. In both study groups, median time to meet discharge criteria was 4.0 hours ($p = 0.68$). The median time to onset of symptom relief was 2.0 hours in the icatibant group and 1.6 in the placebo group ($p = 0.57$). The results of this study are not consistent with the study performed by Bas et al.

Strengths of the study include a large sample size. The study investigators determined that a sample size of at least 100 would result in a 95% power to detect a difference in the primary efficacy end point using Kaplan-Meier estimates. In addition, evidence was provided demonstrating that both the care team and subjects were blinded to the study treatment administered.

There are several limitations to the study as well. Potential confounding factors are present as participant treatment was not confined to study drug administration. 90% of subjects were administered corticosteroids, antihistamines, and epinephrine prior to study drug administration. 45% of subjects were administered antihistamines following study drug administration. Therefore, study participants were receiving the current standard of care with concurrent study drug administration. In addition, the median time for administration of the study drug was 7.8 hours. The delay in administration may have led to the exclusion of eligible study candidates who were rapidly decompensating. A limitation of the exclusion criteria exists as it was not specified if patients had previous episodes of ACE I-induced angioedema. Successive exacerbations are known to increase in both frequency and severity.¹²

Of critical importance, the patient of interest did not align with all aspects of the study by Sinert et al. She met all of the inclusion criteria with the exception of experiencing symptoms for greater than 12 hours. Her age, race, and use of lisinopril correlated with baseline characteristics. However, other factors in regard to her care were not appropriately addressed including her history of pulmonary disease, use of multiple hypertension medications, and the small sample size of subjects requiring a MICU stay.

Of additional concern is the possibility of funding bias as Shire, the manufacturer of icatibant, funded the study. However, the results of the study do not support the use of Shire's product. In addition, employees of Shire were not involved in the interpretation of data or the decision to publish the results.

Clinical Application

Current clinical practice utilizes the administration of glucocorticoids and antihistamines for symptomatic relief of ACE I-induced angioedema. The treatment protocol does not endorse the use of icatibant at this time. Bas et al. and Sinert et al. provide conflicting recommendations that complicate the overall picture and understanding of the impact of icatibant on patient care. Based on the findings of the larger, more comprehensive Sinert trial, which showed no improvement in time to discharge or symptom relief over placebo, it is unlikely that treatment with icatibant would have improved this patient's outcome or prevented her from being intubated.

Learning points:

1. Although rare, ACE I-induced angioedema accounts for 30% of all emergency room visits for angioedema.
2. Icatibant offers no reduction in time to discharge or resolution of symptoms of angioedema compared to placebo.
3. Currently there is no appropriate treatment regimen to address the mechanism of ACE I-induced angioedema. Management provides symptomatic relief with glucocorticoids and antihistamines.

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