CJEM Journal Club

Icatibant Compared to Steroids and Antihistamines for ACE-Inhibitor-Induced Angioedema

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Article chosen
Bas M, Greve J, Stelter K, et al. A Randomized Trial of Icatibant in ACE-Inhibitor-Induced Angioedema. *N Engl J Med* 2015;372:418-25. doi:10.1056/NEJMoa1312524.

Keywords: angioedema, icatibant, corticosteroids, ACE-inhibitor, antihistamines

BACKGROUND

Angiotensin-converting-enzyme-inhibitor (ACEI) induced angioedema occurs in 0.68% of those taking the medication[1] and accounts for one-third of angioedema cases treated in the emergency department. Upper airway compromise, potentially leading to acute laryngeal obstruction and death, may occur in up to 10% of cases.[1,2] Standard therapy consists of glucocorticoids and antihistamines. Case reports of off-label use of icatibant, a bradykinin receptor blocker, in patients with ACEI-induced angioedema showed a reduction in symptom duration similar to what is observed in hereditary angioedema patients.[3-9] This study compared the effectiveness and safety of icatibant to current standard therapy in ACEI-induced angioedema.

POPULATION STUDIED

Patients between the ages of 18 to 95 taking an ACEI who presented to the emergency department with ACEI-induced angioedema were included. Patients with other causes of angioedema, a history of angioedema before ACEI use, acute urticaria, acute coronary syndromes, and acute heart failure NYHA class III or IV, as well as those pregnant and lactating, were excluded.

STUDY DESIGN

This was an industry and government funded, multi-centre, double-blind, double-dummy randomized phase 2 study. Block randomization was performed online. Patients were randomly assigned in a 1:1 ratio. Primary investigators and patients were blinded to the treatment. Investigators who were responsible for the randomization, study-drug administration, and assessment of injection site reactions were aware of study assignments. Patients in the treatment group received icatibant 30 mg subcutaneously and those in the control group (standard therapy group) received prednisolone 500 mg and clemastine 2 mg (an antihistamine) intravenously. Patients assessed the intensity of symptoms at several intervals within 48 hours. Blinded investigators further assessed the signs and symptoms. If there was no symptom improvement at six hours after treatment administration, a rescue therapy of icatibant and prednisolone was administered irrespective of the study group. A final follow-up was performed at day 14 after discharge.

OUTCOMES

The primary endpoint was the median time to the complete resolution of edema after administration of the treatment. A per-protocol analysis was performed. Secondary endpoints included: 1) the proportion of patients who did not have a response to treatment and required rescue therapy; 2) the proportion of patients with complete resolution of edema at four hours;

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3) time to onset of symptom relief; and 4) the measures of safety.

RESULTS

Between July 2010 and December 2011, out of 32 patients screened, 30 were enrolled. All patients were white. For three patients, treatment was administered before randomization occurred. The remaining 27 patients were treated as per protocol. All 27 patients had complete resolution of edema. The icatibant group required a median time of 8.0 hours (interquartile range 3.0 to 16.0) for resolution of symptom compared to 27.1 hours (interquartile range 20.3 to 48.0) for the control treatment group ($p = 0.002$). Three patients in the control treatment group required rescue therapy. There were five patients in the icatibant group who had complete resolution of edema at four hours after treatment, compared to none in the standard therapy ($p = 0.02$). The median time to onset of symptom relief was shorter in the icatibant group as per the investigator-assessed symptom score (2.0 hours, 95% CI [1.0-8.1]) compared to standard therapy (11.7 hours, 95% CI [8.0-18.0]) ($p = 0.03$). The patient-assessed symptom score trended towards faster relief with icatibant, although the difference was not statistically significant. Pain at the injection site was the only adverse effect reported in the icatibant group. There were seven patients affected by pain at the site in the icatibant group, compared to two in the standard therapy group. Other adverse events were reported only in the standard therapy group and included mild chronic obstructive pulmonary disease exacerbation, high blood glucose level, fatigue, and influenza-like illness.

STUDY CONCLUSION

The authors concluded that the median time to complete resolution of angioedema was shorter with icatibant than with the combination of steroids and antihistamines.

COMMENTARY

The positive findings of Bas and colleagues are potentially practice-changing. However, the small sample size, the slight differences in baseline patient characteristics appearing to favor the icatibant group, the exclusion of enrolled patients secondary to investigator deviation from protocol, the unclear effect of the icatibant rescue therapy in the standard treatment patients, the absence of several important clinical outcomes, the homogenous sample population, and the absence of comparison with likely more effective treatments such as fresh frozen plasma (FFP) constitute trial limitations. Furthermore, this study was partially sponsored by Shire, which implies theoretical risks of bias, as with any industry-funded trials.

To start, although this study was powered to detect statistical difference in symptom duration, it remains a small study with only 27 patients. This potentially limits its generalizability and measurement of true effect size. In addition, there are slight differences, but ones of potential significance, in terms of baseline patient characteristics. The icatibant group had overall less angioedema of the lips, tongue, pharynx, larynx, and floor of the mouth compared to the standard therapy group. The baseline severity of symptoms as determined by the composite investigator-assessed symptom score and the composite patient-assessed VAS (visual analogue scale) score were slightly lower in the icatibant group. One can wonder whether less symptomatic patients experienced a faster clinical improvement because they were less sick to start with. In addition, the authors did not discuss inter-rater reliability of the investigator scores, which may have impacted these results. To continue, three patients were lost before randomization because of investigator deviation from protocol. This constitutes a possible source of selection bias.

Furthermore, it is unclear how quickly another three patients who received the rescue therapy had an actual improvement in their angioedema symptoms after receiving icatibant. The efficacy of icatibant when used as a rescue therapy was not described in these most symptomatic patients. The maximal recorded time to the complete resolution of edema was set at over 61 hours, and was used to replace the data for these three patients. As described in the study appendix, a more conservative sensitivity analysis that recorded time to complete edema resolution, including these three patients in the control group, confirmed that the original icatibant group had a quicker time to resolution of symptoms.

It further appears that most of the patients in this study had mild to moderate symptoms, which may improve without clinically significant complications and without the need of pharmacological intervention. It would have been important to study if patients with more severe symptoms would improve, as well.

https://doi.org/10.1017/cem.2016.21 Published online by Cambridge University Press

The cost of icatibant in Canada is reported to be between $2,000 to $3000 per treatment.[10] Although the time to complete resolution of symptoms met statistical significance, other important clinically significant outcomes were not evaluated. The authors did not address rates of intubation, surgical airway, ICU admission, or duration of stay. It would be desirable to evaluate the cost effectiveness of icatibant compared to standard therapy with respect to other clinically significant outcomes.

In terms of concerns regarding external validity, it is noteworthy to mention that all the included patients were white. Black patients are known to develop more severe ACEI-induced angioedema symptoms.[11,12] It will be critical to have data from a more heterogeneous population pool representative of the typical North American practice to properly evaluate clinical effectiveness.

Finally, the standard treatment used for ACEI-induced angioedema is one known to be minimally effective. Antihistamines, steroids, and epinephrine are effective in histamine-mediated angioedema but not in bradykinin-mediated types (which includes ACEI-induced, acquired C1 esterase inhibitor deficiency, and hereditary angioedema).[3] FFP has been suggested as an effective treatment option for ACEI-induced angioedema[13-16] through enhanced kininase II activity leading to increased breakdown of bradykinin[13]. Comparing icatibant to FFP, an agent that makes physiological sense in the treatment of ACEI-induced angioedema, would have been of greater interest.

CONCLUSION

Cessation of the medication along with supportive care remain first-line therapy in the treatment of ACEI-induced angioedema. This small study has introduced a potentially new treatment for ACEI-induced angioedema. In this study, Bas et al. have shown that icatibant did reduce the time required for complete resolution of edema compared to standard therapy in a specific population subset. This comes at a high monetary cost, however. Furthermore, this study did not allow a robust evaluation of safety nor many other important clinically significant outcomes. Icatibant was approved by the FDA in 2011 for hereditary angioedema[17] and by Health Canada in 2014 for C1 esterase inhibitor deficiency–related angioedema.[18] Icatibant may be of value in selected patients, but we believe that further studies are necessary to assess the cost-efficacy, safety, and clinical utility of icatibant for the treatment of ACEI-induced angioedema.

Competing Interests: None declared.

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