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Icatibant for ACE-inhibitor angioedema, an opportunity to treat the patients?



To the Editor:

Icatibant was no more effective than placebo in treating at least moderately severe ACE-inhibitor (ACE-I)-induced angioedema in a phase III trial as reported by Sinert et al.¹ However, in this study, more than 90% of the subjects received corticosteroids, antihistamines, or epinephrine before the study drug, and the time to onset of symptom relief was 2 hours in the placebo group. This rapidly favorable outcome of patients in the placebo group (who received antihistamines and/or corticosteroids in a large majority of cases), contrary to all descriptions of bradykinin angioedema, may lead to the mistaken inclusion of histamine-mediated angioedema and explain the absence of a difference. Moreover, the expertise in the diagnosis of ACE-I angioedema of the investigators in this trial was limited. Indeed, 31 centers were needed to include 121 patients, whereas in our study, 4 centers were sufficient to include 62 patients.² Our prospective, multicentric, observational study reported the severity of ACE-induced angioedema and the feasibility of centralization of advices requested by emergency physicians for patients presenting with ACE-induced angioedema, to optimize diagnosis and follow-up.² The call center has already been set up for hereditary patients and has featured in a publication, which indicates feasibility.³ Despite the severity of the cases in our study of ACE-I angioedema, response to treatment with the specific agents plasma-derived C1-inhibitor and icatibant was favorable. We think that a therapeutic trial is possible to demonstrate the efficacy, on morbidity, of icatibant treatment for severe ACE-induced angioedema attacks, the diagnosis of which will be confirmed prospectively and jointly by an angioedema expert, compared with the placebo.

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Reply



To the Editor:

We thank Javaud et al¹ for their insightful comments on our phase III study² and appreciate the opportunity to respond.

Javaud et al describe positive findings from their group's observational study published in 2015,³ in which 62 patients with angiotensin-converting enzyme (ACE) inhibitor-induced angioedema attacks visiting 1 of 4 emergency departments in Paris were diagnosed with the aid of a centralized call center linking emergency physicians with experts in diagnosing bradykinin-mediated angioedema. They reported a significantly shorter median time from drug administration to onset of symptom relief in patients receiving icatibant or plasma-derived C1 inhibitor versus no specific treatment (0.5 vs 3.9 hours, respectively; $P < .0001$).³ These findings are encouraging but should be interpreted within the context of clear study design limitations, including the absence of a control group and the likelihood of multiple confounders between patients receiving treatment and those not receiving treatment. Moreover, and in direct contrast to our study, Javaud et al did not include a standardized measure for patient reassessment and there is likely to have been inherent variability in subjective determination of symptom relief. The fact that more than half of the 27 patients admitted to the hospital were discharged within 24 hours, only 2 were admitted to the intensive care unit, and just 1 was intubated also raises questions about the purported severity of cases included in their cohort.

With regard to Dr. Javaud's suggestion of a lack of diagnostic expertise in our phase III study, we appreciate the potential benefits of a centralized call center providing expert assistance with diagnosing ACE inhibitor-induced angioedema, particularly in a country like France where emergency medicine is not a recognized specialty and dedicated residency training does not exist. However, nearly all patients in our study were enrolled at academic medical centers in the United States, United Kingdom, and Canada, where a rigorous board certification process for emergency physicians exists, ensuring that clinicians involved in our study were adequately qualified to recognize the presence of this condition without such support. It is, of course, possible that our study population inadvertently included some patients with histamine-induced angioedema (as may have occurred in Dr.

Javaud's observational study). However, this is an underlying limitation of a pragmatic study design, evaluating the efficacy of icatibant in a real-world practice setting in which the use of traditional antiallergy medications is commonplace. Given that our trial had strict inclusion and exclusion criteria, required senior medical review before patient enrollment, and used a validated clinical rating scale for assessing symptom severity, we feel that possible misclassification had limited impact on our outcomes. We do acknowledge that our stringent inclusion and exclusion criteria may have impacted enrollment but, as Javaud et al surely know, it is unrealistic to compare recruitment rates in a phase III prospective, randomized, controlled trial that required written informed consent within 12 hours of symptom onset before administration of study drug with an observational study, where all comers were eligible.

In summary, our phase III study did not demonstrate the efficacy of icatibant in the treatment of ACE inhibitor–induced angioedema. Future research efforts (such as the type of clinical study suggested by Dr. Javaud) may shed further light on the possible utility of icatibant for this condition.

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Throat-derived eosinophil peroxidase is not a reliable biomarker of pediatric eosinophilic esophagitis



To the Editor:

We read with interest the article from Saffari et al¹ demonstrating that eosinophil peroxidase (EPX) levels from pharyngeal mucosal samples do not correlate with eosinophilic inflammation in patients with eosinophilic esophagitis (EoE). This was in contrast to their previous analysis of esophageal mucosal brushings that suggested that esophageal EPX levels accurately reflect EoE disease activity with high sensitivity and specificity.²

We have performed a similar study of pharyngeal and nasal swabs obtained from pediatric subjects with EoE (n = 21) at Phoenix Children's Hospital using our novel EPX ELISA.³ This study was approved by the Phoenix Children's Hospital's institutional review board (16-098). Methods for collection and processing of the swabs have been described previously.⁴ Active EoE cases (n = 12) were defined by consensus criteria and controls consisted of nonatopic subjects or atopic subjects without EoE or inactive EoE (eos/hpf < 15). Clinical data including demographic characteristics and comorbid atopic disorders are described in Table I. EPX was quantified by ELISA and normalized for protein content. We compared throat-derived EPX levels in cases and controls and correlated throat-derived EPX with eosinophil counts from esophageal biopsy specimens. We also quantified EPX levels in nasal swabs from the same subjects. Throat-derived EPX was undetectable in all EoE cases and did not distinguish cases from controls. Consequently, EPX levels from the throat swabs did not correlate with esophageal eosinophil counts. Nasal EPX levels were higher in subjects with allergic rhinitis; however, this difference did not reach statistical significance.

The method of EPX detection used by Saffari et al has notable shortcomings. First, this assay is an indirect measurement dependent on peroxidase activity that requires sodium cyanide to block myeloperoxidase activity; therefore, there remains potential for confounding due to incomplete myeloperoxidase inhibition. This limitation could have been addressed by including controls treated with resorcinol, an EPX-specific inhibitor. Second, the authors did not incorporate bromide into their protocol, which preferentially increases EPX activity 7-fold, thereby enhancing sensitivity.⁵ In contrast, our sandwich ELISA technique increases the specificity of detection by requiring 2 recognition events by mAbs specific for EPX. This allows us to quantify EPX independent of enzyme activity. Finally, the EPX ELISA is more sensitive than the activity assay with lower limits of detection of 0.17 ng/mL versus 0.01 µg/mL, respectively. The utility of this assay has been shown in validation studies of the esophageal string test.⁶

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