

Correspondence and Replies

RE: Successful management of hereditary angioedema with normal C1-INH (type III HAE) when using on-demand ecallantide

TO THE EDITOR:

Riedl¹ recently reviewed clinical characteristics of hereditary angioedema with normal C1 inhibitor (HAE-nmlC1-INH), also known as type III hereditary angioedema. In his review, the potential role of bradykinin in the pathogenesis of HAE-nmlC1-INH is discussed in light of several case series that demonstrated successful on-demand treatment of acute attacks with the bradykinin B2 receptor antagonist icatibant and one case report that demonstrated successful on-demand treatment of an acute attack of HAE-nmlC1-INH in an adolescent boy with ecallantide.²⁻⁴

Since the time of the initial case report, this young boy has been successfully treated for acute attacks of HAE-nmlC1-INH with ecallantide 17 times, including 7 inpatient and 10 outpatient treatments. As mentioned previously, treatment failed with high-dose antihistamines, corticosteroids, fresh frozen plasma, and plasma-derived C1-INH. Prophylaxis with attenuated androgens and high-dose antihistamines also failed. Before bradykinin-targeted therapy was available to him, his recurrent and unpredictable episodes of laryngeal edema resulted in 21 intubations and numerous pediatric intensive care unit admissions. His acute attacks are now successfully treated at home, and he has not been intubated since initiation of on-demand treatment with ecallantide. Despite multiple administrations, he has not experienced any adverse reactions. Numerous successful treatments with a kallikrein inhibitor have dramatically improved this patient's quality of life and provide supportive diagnostic evidence that his HAE-nmlC1-INH is bradykinin mediated.

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REPLY:

I read with interest the descriptive follow-up¹ to the clinical case originally published by Cronin and Maples.² This commentary adds to the accumulating clinical literature that supports underlying dysregulation of the kallikrein-bradykinin pathway as a cause of angioedema symptoms in hereditary angioedema (HAE) with normal C1INH (HAE-nmlC1INH). As summarized in my recent review, current evidence that supports the use of kallikrein-bradykinin targeted interventions for HAE-nmlC1INH is largely composed of uncontrolled case series and anecdotal reports.³ It seems clear, based on such reports, including Cronin and Maples,² that some patients diagnosed with HAE-nmlC1INH benefit significantly from ecallantide, icatibant, or C1INH concentrates, as evidenced by dramatic reductions in emergency care, hospitalization, and intubation. However, it is difficult to confidently ascertain the true efficacy of these therapies in treating HAE-nmlC1INH for a number of reasons, including reporting bias, subjective symptom measures in the absence of controlled comparators, and uncertainty surrounding the appropriate diagnosis of HAE-nmlC1INH.

Rigorous controlled studies would more firmly establish the efficacy of treatments for HAE-nmlC1INH. At present such studies are hampered by the lack of any reliable diagnostic test to identify the condition. Although published clinical criteria for HAE-nmlC1INH based on current evidence⁴ are useful, designing meaningful clinical studies in a yet poorly defined patient population remains challenging. Efforts are ongoing to develop laboratory assays that can clearly identify individuals with bradykinin-mediated angioedema, including hereditary forms. Until such diagnostics become available, allergist/immunologists and other specialists will be challenged with difficult-to-manage angioedema for which comprehensive evaluation fails to identify a clear underlying cause. The task of developing individual management plans in such patients, some of whom are critically ill, for now rests largely on carefully gauging and documenting clinical response to empiric targeted therapies. It is important to recognize the potential dramatic clinical benefit of newer HAE-specific therapies in a subset of patients as reported in published cases, while remaining cognizant of the uncontrolled descriptive nature of such data. In addition, given the cost of newer angioedema therapies, objective measurements of clinical response, and outcomes should be documented to support the appropriate and rational use of medications in HAE-nmlC1INH.

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