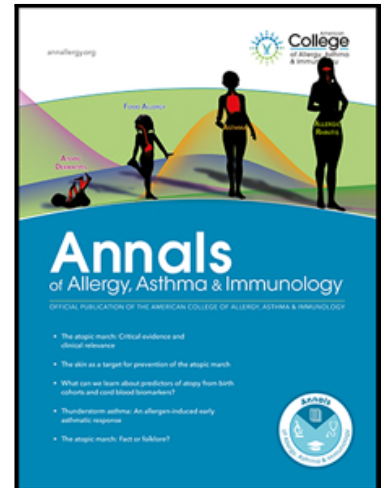


Journal Pre-proof

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PII: S1081-1206(22)00016-3
DOI: <https://doi.org/10.1016/j.anai.2022.01.014>
Reference: ANAI 3815



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 18 November 2021
Revised date: 16 December 2021
Accepted date: 7 January 2022

Please cite this article as: Theodore Kelbel MD , A case of normal C1-esterase inhibitor hereditary angioedema successfully treated with berotralstat, *Annals of Allergy, Asthma Immunology* (2022), doi: <https://doi.org/10.1016/j.anai.2022.01.014>

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A case of normal C1-esterase inhibitor hereditary angioedema successfully treated with berotralstat

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Conflict of interest

Dr. Kelbel has accepted advisory board and consulting fees from Takeda, Pharming, and BioCryst and Speaker Bureau fees from Takeda.

Funding source

Funding for medical writing support and editorial assistance was provided by BioCryst Pharmaceuticals, Inc., Durham, NC, United States. The funder was not involved in patient management, design or writing of this manuscript, or in the decision of where to submit it for publication.

Key words: Berotralstat; Hereditary angioedema; HAE-nl-C1-INH; needle phobia.

Abbreviations: C1-INH, C1-esterase inhibitor gene; C4, component 4; HAE, hereditary angioedema; HAE-C1-INH, type 1 and type 2 HAE; HAE-nl-C1-INH, normal plasma C1-INH levels and functionality; *SERPING1*, serpin family G member 1.

Word count: 903/1000

Figures: none

Tables: none

Hereditary angioedema (HAE) is a rare genetic disorder characterized by unpredictable, recurrent, localized episodes of swelling that often affect the extremities, face, abdomen, and larynx.^{1,2} HAE is most commonly caused by mutations in the C1-esterase inhibitor (C1-INH) gene (serpin family G member 1; *SERPING1*) that result in deficient (type 1) or dysfunctional (type 2) C1-INH protein.³ These mutations lead to dysregulation of the kallikrein–bradykinin cascade and increases in bradykinin production and vascular permeability, which are thought to be the main causes of HAE attacks.⁴ Type 1 and type 2 HAE, which are collectively known as HAE-C1-INH, are associated with lower than normal plasma levels of both complement component 4 (C4) and C1-INH functionality in laboratory tests and represent 95% of HAE cases.^{3,4} However, some patients present with a form of HAE that is typically associated with normal plasma C1-INH levels and functionality (HAE-nl-C1-INH), normal plasma C4 complement levels, and attacks that are predominately facial in nature.³ Diagnosis of HAE-nl-C1-INH represents a significant challenge and is reliant on genetic testing.^{3,5}

Current evidence suggests that, like HAE-C1-INH, HAE-nl-C1-INH is mediated by increased bradykinin production.^{3,6} Consistent with this, mutations in genes involved in bradykinin formation, such as factor XII, plasminogen, angiopoietin-1, kininogen-1, and myoferlin

genes, have been identified in patients with HAE-nl-C1-INH.⁷ However, the genetic basis of HAE-nl-C1-INH is still unknown in many cases,⁷ which, in combination with the absence of an available confirmatory biomarker or diagnostic test,¹ can make it difficult for patients to access insurance coverage for their treatment. Therefore, physicians of patients with suspected HAE-nl-C1-INH may choose to initiate a trial course of an HAE-specific therapy to observe a treatment response,⁸ which can provide a rationale for insurance coverage of long-term treatment costs.

Herein we report a case of HAE-nl-C1-INH occurring in the context of a family history of HAE-C1-INH (type 1) disease, which was difficult to treat because of the patient's needle phobia but ultimately responded well to oral berotralstat therapy.

The patient was a 60-year-old woman who reported several previous episodes of swelling that came on over the course of a day and were atypically limited mostly to her hands, feet, breasts, or abdomen. The patient reported that these painful swelling episodes occurred at a frequency of 2-3 times a month and typically lasted 2-4 days, during which she struggled to go about her usual daily activities. Before undergoing a total hysterectomy in her 40s, the patient had also experienced severe abdominal pain and swelling during her menstrual cycle occasionally including genital involvement. The patient's mother, sister, cousin, and daughter experienced similar symptoms, and her daughter had received a diagnosis of laboratory-supported HAE-C1-INH (type 1). Therefore, the patient's family history and presenting symptoms led to a suspicion of undiagnosed HAE.

During laboratory assessments for HAE in August 2020, the patient had normal serum levels of C1-INH antigen (21 mg/dL), C1-INH functionality that was 90% of normal, and normal serum levels of C4 complement (30 mg/dL). These values remained at normal levels when measured during 2 swelling attacks and the patient also had normal tryptase levels during

attack episodes. These clinical findings indicated that the patient likely had HAE-nl-C1-INH despite having a family history of HAE-C1-INH (type 1). Analysis of the patient's *SERPING1* gene using the GeneDx HAE-C1-INH (type 1 and type 2) panel did not identify any reportable variants, consistent with HAE-nl-C1-INH. The patient declined additional genetic testing because of cost.

A review of the patient's medical history indicated that previous use of antihistamines (cetirizine and diphenhydramine), hydroxychloroquine for rheumatoid arthritis, and steroids for asthma did not noticeably affect her swelling attacks. However, the patient reported (and documented with photographs) that the use of recombinant C1-INH replacement therapy (conestat alfa) had resolved swelling attacks within an hour of administration on 2 separate occasions before our involvement. Her positive response to recombinant C1-INH replacement therapy was supportive of an HAE diagnosis and consistent with the successful treatment of HAE-nl-C1-INH attacks with C1-INH concentrate and icatibant reported in the literature.⁷ At the time of the patient's presentation, commonly prescribed HAE-specific prophylactics included intravenous and subcutaneous treatments.² Therefore, we initially prescribed the patient lanadelumab prophylaxis (300 mg) every 2 weeks and icatibant (30 mg) on demand. However, due to severe needle phobia, the patient declined treatment with lanadelumab or icatibant. Therefore, documentation of a treatment response to standard HAE therapeutics could not initially be obtained for this patient, causing significant challenges in acquiring long-term insurance coverage for treatment.

From the fall of 2020 through February 2021, the patient continued to have 2-3 swelling attacks per month. During this time, we were able to offer the patient oral treatment with berotralstat, a plasma kallikrein inhibitor that was approved as a once-daily prophylactic therapy to prevent HAE attacks in patients 12 years and older by the Food and Drug Administration in December 2020.⁹ During the first 2-3 weeks of berotralstat therapy, the

patient reported experiencing mild to moderate upset stomach and diarrhea, which were self-resolving and managed by taking the medication with food. Follow-up of the patient after 6 months of berotralstat treatment indicated that her HAE was well-controlled with no breakthrough swelling attacks since starting berotralstat. The patient also reported a noticeable improvement in her anxiety levels because berotralstat prophylaxis reassured her that she would be much less likely to need to use injectable medication for on-demand/abortive HAE therapy. Based on our findings, berotralstat may benefit other patients with HAE-nl-C1-INH and needle phobia.

Acknowledgment

Medical writing support was provided by Jennifer Shepherd, PhD, of Porterhouse Medical Group and funded by BioCryst Pharmaceuticals, Inc., Durham, NC, United States, in accordance with Good Publication Practice (GPP3) guidelines.

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