Successful use of lanadelumab in a patient with hereditary angioedema with normal C1 inhibitor and negative genetic testing

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We report an approximately 80% reduction in angioedema attacks with lanadelumab, a mAb targeting plasma kallikrein, in a case of hereditary angioedema with normal C1 inhibitor levels. This finding supports a central pathophysiologic role for kallikrein in hereditary angioedema with normal C1 levels and supports the need for prospective studies of lanadelumab use with this condition. (J Allergy Clin Immunol Global 2023;2:100087.)

Key words: *Hereditary angioedema, hereditary angioedema with normal C1 inhibitor, lanadelumab, icatibant, immune deficiency*

Hereditary angioedema (HAE) is a rare genetic condition characterized by recurrent cutaneous and submucosal swelling affecting the oropharynx, face, extremities, genitals, and abdomen.[1] Most cases of HAE are due to monoallelic mutations in *SERPING1* that result in HAE C1 inhibitor (HAE-C1-INH) deficiency. In HAE-C1-INH deficiency, C1 inhibitor deficiency causes excessive activation of the contact pathway, leading to increased generation of bradykinin, activation of the bradykinin 2 receptor, and subsequent fluid extravasation.[1] Patients with HAE-C1-INH deficiency with frequent symptoms have conventionally been treated with plasma-derived C1 inhibitor for long-term prophylaxis. In 2018, lanadelumab, a fully humanized IgG1κ mAb targeting plasma kallikrein (the activated form of prekallikrein), was also approved for use for long-term prophylaxis in HAE-C1-INH deficiency.[2]

Some patients with HAE have normal C1 inhibitor levels and function (HAE-nC1). The pathophysiology of HAE-nC1 is poorly understood, but aberrant activation of the contact pathway is also implicated.[3] Mutations in genes that cause the HAE-nC1 phenotype (eg, factor XII,[4] plasminogen,[5] angiopoietin-1[6]) have recently been reported. These findings have greatly enhanced our understanding of the condition and have facilitated the use of gene sequencing for diagnosis of some patients. However, many patients with HAE-nC1 remain without a genetic diagnosis, and the disease mechanisms in these patients are unclear.

Abbreviations used
HAE: Hereditary angioedema
HAE-C1-INH: Hereditary angioedema due to C1 inhibitor deficiency
HAE-nC1: Hereditary angioedema with normal C1 inhibitor

We report the case of a 62-year-old female with recurrent angioedema affecting her tongue, larynx, extremities, and abdomen since she was an adolescent. Her episodes of swelling develop over several hours and resolve over 2 to 3 days. She has no history of urticaria, and therapies targeting a histaminergic process, including high-dose antihistamines (40 mg of cetirizine per day for 12 weeks) and oral glucocorticosteroids (60 mg of orally administered prednisone daily for 24 weeks), have not been effective. Omalizumab was never trialed in this patient. Her medical history is notable for Behçet disease that was diagnosed when she was 47 years old and presented with posterior uveitis and ulcers of the oral and genital mucosa. She is treated with colchicine and hydroxychloroquine.

Her serum C4 concentration and C1 inhibitor concentration and function were normal on multiple occasions, including during angioedema episodes. Gene sequencing of *FXII, PLG, ANGPT1,* and *SERPING1* did not identify any pathogenic variants; the results of sequencing of *HS3ST6, KNG1,* and *MYOF,* each of which has been described in only 1 proband with HAE-nC1,[2] were not available. The patient has 2 daughters, 1 of whom also has recurrent angioedema with normal complement study results and also did not respond to high-dose cetirizine over 12 weeks or prednisone administered orally in a dose of 40 mg daily for 12 weeks. The patient and her daughter were thus diagnosed with HAE-nC1 based on expert consensus criteria.[7]

For many years the patient was highly symptomatic, with approximately 3 angioedema attacks per week. She used icatibant, 30 mg administered subcutaneously, for acute treatment of most episodes, which led to noticeable symptom relief in approximately 30 minutes and prevented the need for emergency department care, but she still had swelling on most days. The frequency and unpredictability of the swelling episodes continued to significantly impair her quality of life and caused her to greatly reduce her occupational and social activities. She was offered

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Written informed consent was obtained from the patient for publication of this case.

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intravenous plasma-derived C1 inhibitor for acute attacks and for long-term prophylaxis, but she was not able to obtain intravenous access on her own because of vision impairment from uveitis at the time.

In 2018, she began taking lanadelumab, 300 mg subcutaneously every 2 weeks, in an attempt to reduce her symptom burden. In 2 months, her average attack frequency was reduced from approximately 12 to 2 per month, and the attacks became sufficiently mild that she did not require icatibant in most cases. She continues to take lanadelumab with ongoing benefit, and at her last visit her angioedema control test score was 14 (of a possible 16 points, with scores >10 indicating well-controlled disease).[8]

Here, we have presented a patient with HAE-nC1 with a high symptom burden who responded to the antikallikrein biologic lanadelumab with an approximately 80% reduction in attack frequency and reduced attack severity. There have been no randomized controlled trials in patients with HAE-nC1; hence, there are no approved therapies for this condition.[3] Typically, patients with HAE-nC1 are treated similarly to those with HAE-C1-INH deficiency based on case reports or observational studies; hence, we believe that it is reasonable to trial lanadelumab in highly symptomatic patients with HAE-nC1. Jones et al reported 10 patients with HAE-nC1 who were treated with lanadelumab.[9] Of these patients, 2 stopped therapy on account of a lack of efficacy, 7 had a reduction in attack frequency, and 1 required weekly lanadelumab dosing and acute therapy every 2 to 3 days. However, the criteria used to diagnosis HAE-nC1 were not detailed, and whether the patients were genotyped is unclear.[9] Future prospective studies evaluating the efficacy of lanadelumab in patients with HAE-nC1 are needed.

The successful use of lanadelumab in this case suggests that kallikrein plays a central role in the pathophysiology in at least a subset of patients with HAE-nC1, which is likely a genetically and physiologically heterogenous condition. This finding supports further investigation of the contact pathway in the search for additional monogenic causes of the HAE-nC1 phenotype. Patients with HAE-nC1 who do not respond to lanadelumab may conversely have novel disease mechanisms that do not involve the contact pathway. Future studies of lanadelumab and other novel targeted therapeutics in HAE-nC1 may therefore help to identify patient subgroups in whom alternate mechanisms should be investigated.

REFERENCES

1. Busse PJ, Christiansen SC. Hereditary angioedema. N Engl J Med 2020;382:1136-48.
2. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygoren-Pursun E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2021 revision and update. Allergy 2022;77:1961-90.
3. Magerl M, Germenis AE, Maas C, Maurer M. Hereditary angioedema with normal C1 inhibitor: update on evaluation and treatment. Immunol Allergy Clin North Am 2017;37:571-84.
4. Bork K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. Clin Immunol 2011;141:31-5.
5. Bork K, Wulff K, Steinmuller-Magin L, Braenne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. Allergy 2018;73:442-50.
6. Baffert F, Le T, Thurston G, McDonald DM. Angiopoietin-1 decreases plasma leakage by reducing number and size of endothelial gaps in venules. Am J Physiol Heart Circ Physiol 2006;290:H107-18.
7. Zuraw BL, Bork K, Binkley KE, Banerji A, Christiansen SC, Castaldo A, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc 2012;33(suppl 1):S145-56.
8. Weller K, Donoso T, Magerl M, Aygoren-Pursun E, Staubach P, Martinez-Saguer I, et al. Validation of the Angioedema Control Test (AECT)-a patient-reported outcome instrument for assessing angioedema control. J Allergy Clin Immunol Pract 2020;8:2050-7.e4.
9. Jones DH, Bansal P, Bernstein JA, Fatteh S, Harper J, Hsu FI, et al. Clinical profile and treatment outcomes in patients with hereditary angioedema with normal C1 esterase inhibitor. World Allergy Organ J 2022;15:100621.