

# Clinical Experience with Berotralstat in Patients with Hereditary Angioedema with Normal C1-Esterase Inhibitor: A Commented Case Series

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**Abstract:** Hereditary angioedema (HAE) is a rare genetic disorder characterized by potentially life-threatening episodes of swelling. Most HAE cases are caused by deficient (type I) or dysfunctional (type II) C1-esterase inhibitor (C1-INH) protein. However, some patients present with a subtype of HAE that is associated with normal plasma levels of functional C1-INH protein and complement component 4 (HAE-nC1INH). Treatment of HAE-nC1INH is driven by clinical experience as robust clinical trial data to inform treatment decisions are lacking in this population. This retrospective case series assessed clinical features and treatment outcomes in 15 patients with HAE-nC1INH who initiated long-term prophylaxis with oral berotralstat 150 mg once daily as part of their disease management pathway. Most patients were female (93%), with a median age of 49 years. All patients experienced abdominal swelling attacks. On average, patients tried a mean of 4 different treatments for their HAE, including berotralstat. Although most patients associated prophylactic and on-demand medications that target the bradykinin pathway with improvements in the frequency and/or severity of attacks, treatment outcomes varied considerably between patients, highlighting the importance of a personalized approach to disease management. In this case series, berotralstat was an effective prophylactic treatment option in most patients with HAE-nC1INH. Further studies are required to demonstrate the potential efficacy, safety, and impact on quality of life of currently approved HAE therapies in patients with HAE-nC1INH.

**Keywords:** hereditary angioedema, normal C1-esterase inhibitor, prophylaxis, berotralstat, lanadelumab, plasma-derived C1-esterase inhibitor, abortive therapy

## Introduction

Patients with hereditary angioedema (HAE) experience unpredictable and potentially life-threatening recurrent episodes of swelling that generally affect the extremities, genitals, abdomen, larynx, and face.<sup>1-3</sup> Some patients present with a form of HAE with normal C1-inhibitor (HAE-nC1INH), which is associated with normal plasma levels of functional C1-inhibitor (C1-INH) protein and complement component 4 (C4).<sup>3</sup> Mutations in genes such as coagulation factor XII (FXII), plasminogen, angiopoietin 1, kininogen 1, heparan sulfate glucosamine 3-O-sulfotransferase-6, and myoferlin have been identified in several patients with HAE-nC1INH. Some of these genes are involved with the production of bradykinin. However, the prevalence and pathophysiology of the disease are less clear than in HAE with low serum level or functional deficiency in C1 inhibitor (HAE-C1INH), and the etiology of the disease remains unknown for many patients.<sup>1,4-9</sup> Additionally, HAE-nC1INH is more challenging to definitively diagnose than HAE-C1INH because diagnosis reliant on genetic testing only identifies a small subset of patients with the disease.<sup>8,10</sup> Additionally, these genetic tests are not readily available in all clinical practices.<sup>1</sup>

Overall, the swelling attacks experienced by patients with HAE-nC1INH and patients with HAE-C1INH are similar, but subtle differences exist between them.<sup>1,7</sup> Patients with HAE-nC1INH typically present with their first symptoms of disease in late adolescence to early adulthood, while the first symptoms of HAE-C1INH typically appear in childhood.<sup>1,5,11</sup>

Furthermore, patients with symptomatic HAE-nC1INH are predominately female, with exposure to estrogens frequently linked to the onset and exacerbation of swelling attacks.<sup>4,5,12–14</sup>

Edema of the face, tongue, and oropharynx have been documented more frequently in patients with HAE-nC1INH than in patients with HAE-C1INH.<sup>1,6,7,15,16</sup> A review of 57 French patients with confirmed *FXII* mutations indicated that 74% of patients experienced HAE attacks affecting the ear, nose, and throat, while 80% experienced abdominal attacks<sup>13</sup> despite some experts suggesting that patients with HAE-nC1INH typically have fewer abdominal symptoms.<sup>1</sup>

The occurrence of non-specific presenting symptoms in patients with HAE-nC1INH often results in misdiagnosis, ongoing treatment with inappropriate therapy (ie, antihistamines, corticosteroids, adrenaline) and/or unnecessary procedures (ie, surgical intervention).<sup>5,17–19</sup> Furthermore, the absence of robust data from clinical trials evaluating HAE therapies in patients with HAE-nC1INH means that, once diagnosis is suspected, the treatment of this patient population is based on clinical experience in patients with HAE-C1INH. These treatments include a combination of on-demand (ie, injectable ecallantide, injectable icatibant, and infusions of C1-INH concentrate) and prophylactic agents (ie, intravenous or subcutaneous C1-INH concentrate, injectable lanadelumab, and oral berotralstat) that either directly or indirectly target bradykinin metabolism.<sup>1,8,14,20–22</sup> In response to these challenges, it is common for physicians of patients with suspected HAE-nC1INH to initiate a trial course of HAE therapies as part of the diagnostic process.<sup>23,24</sup> The purpose of this manuscript is to help raise awareness of HAE-nC1INH by exploring the clinical features that trigger a suspected diagnosis, and provide insights into the observed treatment outcomes in a retrospective case series of 15 patients.

## Materials and Methods

This report follows CARE reporting guidelines<sup>25</sup> and describes a retrospective patient case series using anonymized data. All patients provided written informed consent for their de-identified case information to be retrospectively collected and published.

The medical records of patients from one treatment center in the USA (Kanarek Allergy, Asthma & Immunology) were reviewed to identify patients with HAE-nC1INH who received oral berotralstat 150 mg once daily for long-term prophylaxis as part of their treatment plan. Information was extracted from each patient's medical record by the author or a designated member of staff at the medical center using a template that included patient age, patient gender, date and description of assessments, areas of the body affected by attacks, details of any major attacks and their outcomes, medical procedures undertaken because of attacks, and details of any treatments given and their associated outcomes.

Given the lack of standardized, validated biochemical diagnostic tests for HAE-nC1INH, physicians often rely on strategies for differential diagnosis. At this practice (Kanarek Allergy, Asthma & Immunology), HAE-nC1INH diagnosis is based on the following clinical criteria: the patient has a history of recurrent angioedema with no signs of concomitant urticaria and no use of medication that is known to cause angioedema, such as angiotensin-converting enzyme inhibitors; laboratory testing indicates that the patient has normal, or close to normal, plasma levels of C4 and C1-INH antigens and normal C1-INH functionality; the patient either has a genetic mutation in one of the genes known to be associated with HAE-nC1INH or has a personal or family history of recurrent angioedema episodes that were non-responsive to high-dose antihistamine therapy for at least 12 weeks. Assessing treatment response to four times daily (QID) antihistamines, multiple courses of steroids, and epinephrine generally takes place over a period of several months. Careful consideration is made to exclude other diagnoses such as chronic spontaneous urticaria (CSU) without wheals. An understanding of attack features like location and duration can help to differentiate CSU from HAE-nC1INH; CSU is less likely to affect the larynx or abdomen and generally attack durations are shorter versus HAE-nC1INH.<sup>26</sup> Beyond non-responsiveness to mast-cell targeted therapies (such as omalizumab),<sup>1,23–25,27</sup> responsiveness to available HAE abortive medications (ie icatibant or formulations of C1-INH) is a useful and commonly utilized strategy for differential diagnosis.<sup>28</sup> Rapid and durable response to HAE medications provides additional evidence for an HAE-nC1INH diagnosis. As noted in a recent survey of physicians who treat HAE, response to HAE-specific medication was used to inform diagnosis by 74% of survey respondents, while only 43% utilized Factor XII genetic testing.<sup>28</sup> Patients often have a challenging journey to obtain an accurate diagnosis of HAE-nC1INH and frequently consult several healthcare providers across multiple specialties. As such, some patients in this case series may have trialed and failed high-dose antihistamines or other therapies prior to becoming a patient at Kanarek Allergy, Asthma & Immunology, and such details may not have been included in the chart notes from this practice.

## Patient Demographics

A total of 15 patients with HAE-nC1INH treated with oral berotralstat 150 mg once daily for long-term HAE prophylaxis as part of their disease management pathway were included in this case series. All patients indicated they had experienced swelling attacks, with many of them affecting the face, tongue, throat, and/or abdomen prior to starting berotralstat treatment (see [Table 1](#)). Only one patient within the group was male, which is consistent with typical preponderance of female patients with HAE-nC1INH. Due to the low likelihood of identifying specific genetic mutations and the availability of other differential diagnostic strategies like response to HAE medications, none of the patients were screened for known mutations associated with the condition.

## Results

### HAE-nC1INH Diagnosis

Many patients in this case series noted that they had received prior misdiagnoses, which included menstrual cramps, food allergies, gastrointestinal (GI) disorders (including irritable bowel syndrome), and anaphylaxis. One patient (Patient 2) was also tested for lupus and Lyme disease because of the non-specific presenting symptoms she had experienced before receiving a diagnosis of HAE-nC1INH.

Two patients in the case series indicated they had previously endured medical procedures because of HAE attacks. Patient 5 experienced multiple intubations as a direct consequence of throat swelling, and Patient 6 reported undergoing a hysterectomy and a cholecystectomy as a direct result of abdominal swelling.

The location, severity, and duration of angioedema symptoms were inconsistent with other conditions such as CSU without wheals. Some of the patients in this series experienced severe abdominal swelling that resulted in dehiscence post-Caesarian section or resembled a 4- to 9-month pregnancy which lasted for weeks. With CSU, swelling is less likely to affect the abdomen and, generally, attacks are shorter in duration than with HAE.<sup>26</sup>

### HAE-nC1INH Treatment

In this case series, treatment trialed for the management of HAE-nC1INH varied by patient. Patient-reported treatment outcomes with previous HAE medication have been denoted on [Table 1](#) with a simple legend of + (effective) or – (ineffective). Prophylactic therapies used immediately prior to switching to berotralstat are indicated with footnote “d”, and those agents used concurrently with berotralstat are indicated with footnote “e”. Overall, nine patients in this case series switched directly from lanadelumab to berotralstat prophylaxis, two patients switched from plasma-derived C1-INH (pdC1-INH) concentrate to berotralstat prophylaxis, and four patients initiated berotralstat for prophylaxis after use of abortive therapy only. All patients had access to on-demand abortive therapies while on berotralstat. At the time of manuscript preparation, 13 patients reported that berotralstat improved the frequency and/or severity of their HAE attacks, with several reporting that berotralstat had improved their day-to-day life, reduced or eliminated symptoms of abdominal swelling, and made known triggers less likely to contribute to HAE attacks (see [Table 1](#)).

Two of the 15 patients reported that berotralstat did not improve the severity or frequency of HAE attacks. Patient 13 discontinued prophylactic treatment with berotralstat after 6 weeks due to perceived lack of efficacy. Patient 5 continued with berotralstat despite no perceived improvement beyond what she had achieved with lanadelumab as she had become hypersensitive to needles following a dental procedure, rendering her unable to continue with injectable therapies. Berotralstat, an oral medication, provided her with the ability to continue with HAE prophylactic treatment.

GI side effects (described as GI upset) were reported by two patients; both continued treatment with berotralstat as these effects abated over time.

## Discussion

Significant unmet needs persist in the diagnosis and treatment of patients with HAE-nC1INH. Here, in this retrospective case series, we explore the clinical features that trigger a suspected diagnosis of HAE-nC1INH and provide insights into the observed treatment.

**Table 1** Patient Demographics with Prior HAE Medication History and Treatment Response with Berotralstat

Patient	Demographics		Laboratory Assessments <sup>5,29</sup>			Additional Diagnostic Cues <sup>4,5,13</sup>			Prior HAE Medication History	Treatment Response with Berotralstat? (Patient-Reported Improvement in Frequency and/or Severity of HAE Attacks) Y/N	Additional Changes After Berotralstat Initiation
	Age (Years)	Gender	C1-INH Plasma Level (mg/dL) <sup>a</sup>	C4 Plasma Level (mg/dL) <sup>b</sup>	C1-INH Function (%) <sup>c</sup>	Age at Symptom Onset	Family History of HAE	Location of Swelling with HAE Attacks			
1	41	Female	31	25	>100	Childhood	–	Abdomen Hands Lips Tongue	°Icatibant 30 mg as required (abortive agent) + °Ecallantide 30 mg as required (abortive agent) + rhC1-INH concentrate 4200 IU IV as required (abortive agent) + pdC1-INH concentrate SC 2000 IU (abortive agent) – Lanadelumab 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	<ul style="list-style-type: none"> <li>Improved day-to-day life</li> <li>Known triggers no longer associated with HAE attacks</li> <li>Spontaneous resolution of attacks to face and extremities without any other pharmacological intervention</li> </ul>
2	42	Female	30	42	>100	~40 years	–	Abdomen Face Extremities Genitals	°rhC1-INH concentrate 4200 IU IV as required (abortive agent) + °Icatibant 30 mg as required (abortive agent) + Lanadelumab 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	<ul style="list-style-type: none"> <li>Improved day-to-day life (feels less exhausted)</li> <li>Patient reports that HAE attacks are restricted to face, neck, and legs (no longer experiencing abdominal swelling)</li> </ul>
3	54	Female	31	26	>100	~40 years	–	Hands Face Feet Throat Abdomen	°Icatibant 30 mg as required (abortive agent) + °Ecallantide 30 mg as required (abortive agent) + °rhC1-INH concentrate 4200 IU IV as required (abortive agent) + Lanadelumab 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	<ul style="list-style-type: none"> <li>Berotralstat initially caused significant gastrointestinal upset (improved over time)</li> </ul>
4	27	Female	26	24	93	~20 years	Mother has HAE-nC1INH (Patient 14) Aunt has HAE-nC1INH	Throat Abdomen Extremities	°pdC1-INH concentrate 1500 mg IV every 2–3 days (abortive agent) + °Ecallantide 30 mg as required (abortive agent) + °rhC1-INH concentrate 4200 IU IV as required (abortive agent) + Lanadelumab 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	–

5	52	Female	Not recorded	16	100	~40 years	–	Face Throat Abdomen Neck Genitals	pdCI-INH concentrate 2000 units IV every 3 days (prophylaxis) – °Icatibant 30 mg as required (abortive agent) + °Ecallantide 30 mg as required (abortive agent) + °rhCI-INH concentrate 2100 IU IV as required (abortive agent) + pdCI-INH concentrate 400 IU SC every 3 days (prophylaxis) – Lanadelumab 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> +	N	<ul style="list-style-type: none"> <li>● Patient continued to report 2–3 moderate HAE attacks per week, each lasting 1–2 days</li> <li>● Patient continued with berotralstat prophylaxis due to hypersensitivity to needles</li> <li>● Experienced some gastrointestinal symptoms with berotralstat</li> <li>● Stated similar frequency and severity of attacks as experienced with lanadelumab</li> </ul>
6	39	Female	27	29	94	~25 years	Daughter has HAE-nCIINH	Throat Face Abdomen	°Icatibant 30 mg as required (abortive agent) + Lanadelumab-flyo 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	<ul style="list-style-type: none"> <li>● Patient is now able to eat any foods she wants without vomiting and/or swelling</li> <li>● Reported decrease in abdominal attacks</li> </ul>
7	26	Female	32	29	>100	~16 years	Mother has HAE-nCIINH	Abdomen Laryngeal	°rhCI-INH concentrate 4200 IU IV as required (abortive agent) + Lanadelumab-flyo 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	–
8	53	Female	31	32	>100	~50 years	–	Lips Face Extremities Abdomen	°Ecallantide 30 mg as required (abortive agent) + °Icatibant 30 mg as required (abortive agent) + Lanadelumab 300 mg SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	–
9	61	Female	21	33	>90	~50 years	–	Abdomen Laryngeal Leg	°Icatibant 30 mg as required (abortive agent) + °Ecallantide 30 mg as required (abortive agent) + °rhCI-INH concentrate 4200 IU IV as required (abortive agent) + Lanadelumab 300 mg SC every 2 weeks (prophylaxis) – pdCI-INH concentrate 500 IU SC every 3 days (prophylaxis) <sup>d</sup> –	Y	–
10	49	Female	43	29	94	~48 years	–	Tongue Abdomen Laryngeal Genitals	°rhCI-INH concentrate 4200 IU IV as required (abortive agent) + °Ecallantide 30 mg as required (abortive agent) + °Icatibant 30 mg as required (abortive agent) + °pdCI-INH concentrate 2000 IU SC as required (abortive agent) +	Y	–

(Continued)

**Table 1** (Continued).

Patient	Demographics		Laboratory Assessments <sup>5,29</sup>			Additional Diagnostic Cues <sup>4,5,13</sup>			Prior HAE Medication History	Treatment Response with Berotralstat? (Patient-Reported Improvement in Frequency and/or Severity of HAE Attacks) Y/N	Additional Changes After Berotralstat Initiation
	Age (Years)	Gender	CI-INH Plasma Level (mg/dL) <sup>a</sup>	C4 Plasma Level (mg/dL) <sup>b</sup>	CI-INH Function (%) <sup>c</sup>	Age at Symptom Onset	Family History of HAE	Location of Swelling with HAE Attacks			
11	23	Female	24	39	80	~20 years	–	Abdomen Lips Face	<sup>e</sup> Ecallantide 30 mg as required (abortive agent) + pdCI-INH concentrate 700 IU SC every 2 weeks (prophylaxis) <sup>d</sup> –	Y	–
12	18	Female	25	18	93	~18 years	Mother has HAE-nCIINH (Patient 13)	Abdomen	<sup>e</sup> Icatibant 30 mg as required (abortive agent) +	Y	● Patient attributes breakthrough HAE attacks with missed doses of berotralstat
13	51	Female	34	36	>100	~20 years	Daughter has HAE-nCIINH (Patient 12)	Abdomen	<sup>e</sup> Icatibant 30 mg as required (abortive agent) +	N	● Berotralstat discontinued after 6 weeks because patient stated it did not have a significant impact on her life
14	59	Female	29	32	>90	Unknown	Daughter has HAE-nCIINH (Patient 4) Sister has HAE-nCIINH	Abdomen Extremities Face Throat	<sup>e</sup> Ecallantide 30 mg as required (abortive agent) + <sup>e</sup> Icatibant 30 mg as required (abortive agent) + pdCI-INH concentrate 5000 IU IV twice daily (prophylaxis) – <sup>e</sup> pdCI-INH concentrate 6000 IU SC three times daily (prophylaxis) + Lanadelumab-flyo 300 mg SC once every 2 weeks (prophylaxis) <sup>d</sup> –	Y	–
15	49	Male	26	22	89	Childhood	–	Abdomen	Icatibant 30 mg as required (abortive agent) – <sup>e</sup> Ecallantide 30 mg as required (abortive agent) +	Y	–

**Notes:** <sup>a</sup>The normal range for CI-INH in adults is 16–33 mg/dL. <sup>29</sup> <sup>b</sup>The normal range for C4 in adults is usually 10 or 14 mg/dL to 40 or 44 mg/dL. <sup>5</sup> <sup>c</sup>The normal level for CI-INH function in adults is >67%. <sup>5</sup> <sup>d</sup>Prophylactic therapy used immediately prior to berotralstat initiation. <sup>e</sup>Medications used concurrently with berotralstat. + Patient reported as effective. – Patient reported as ineffective.

**Abbreviations:** CI-INH, CI-esterase inhibitor; C4, complement component 4; HAE, hereditary angioedema; IU, international units; IV, intravenous; pdCI-INH, plasma-derived CI-esterase inhibitor; rhCI-INH, recombinant CI-esterase inhibitor; SC, subcutaneous.

Although a positive family history of HAE-nC1INH could aid in its diagnosis, it cannot be relied upon as the sole means of identifying patients because HAE-nC1INH appears to have a low penetrance, ultimately leading to some patients having undiagnosed, asymptomatic family members.<sup>27</sup> In an Italian study of 32 females with HAE-nC1INH caused by mutations in the coagulation factor XII gene, 44.4% were asymptomatic.<sup>14</sup> Accordingly, in our case series, a family history of symptomatic HAE was identified in six patients (Patients 4, 6, 7, 12, 13, and 14. Patients 4 and 14, and Patients 12 and 13 are respective daughter-mother pairs).

While patients with HAE-C1INH usually experience their first symptoms in childhood, patients with HAE-nC1INH often do not present with symptoms until late adolescence or early adulthood.<sup>1,5,11,30</sup> In a study of 138 patients with a confirmed diagnosis of HAE-nC1INH, the mean age of symptom onset was 26.8 years, and only 8% of these patients experienced their first swelling attack before the age of 10 years.<sup>15,27</sup> Our findings generally support this point, with only 3 of the 15 patients specifically indicating that they may have experienced their first swelling episode during childhood or adolescence. More specifically, Patient 1 reported a severe swelling episode during the fifth grade that affected her feet, and Patient 15 had a history of irritable bowel syndrome with diarrhea and abdominal cramping that occurred throughout childhood. Patient 7 began experiencing swelling episodes in her mid-teens.

Although some experts have suggested that patients with HAE-nC1INH typically have fewer abdominal symptoms than patients with HAE-C1INH,<sup>1</sup> case studies indicate that abdominal symptoms may be more common than previously thought.<sup>13</sup> Similarly, all 15 patients in this case series reported experiencing at least one attack that affected the abdominal region, suggesting that abdominal pain and/or swelling may be a useful indicator of all forms of HAE. Furthermore, multiple patients in this case series were initially referred from physicians who specialize in GI disorders.

The effects of estrogen on HAE attacks in the HAE-nC1INH population have been well described in the literature.<sup>4,5</sup> In our predominantly female case series, 2 of the 14 female patients described HAE attacks that fluctuate according to their menstrual cycle.

The treatment response to HAE therapy is a critical part of the diagnostic process for many patients with suspected HAE-nC1INH.<sup>23,24</sup> The number of HAE treatments trialed by patients in our case series ranged from a minimum of two to a maximum of eight. This variability likely reflects the difficulty in achieving a HAE-nC1INH diagnosis, since several therapeutics are often trialed before identifying the correct one for each individual.<sup>5,27</sup>

To our knowledge, this case series represents one of the first published studies exploring the use of oral berotralstat as a long-term prophylactic treatment option in patients with HAE-nC1INH. Here, most patients indicated that treatment with berotralstat either stabilized their condition or reduced the frequency and/or severity of their HAE attacks. Notably, berotralstat was found to be effective in most patients with HAE-nC1INH who switched from prior prophylaxis with either lanadelumab or pdC1-INH concentrate as well as in patients who used it as their first prophylactic treatment option.

Our findings support those of a case report describing a 60-year-old female with HAE-nC1INH who had a severe needle phobia and benefited from long-term prophylaxis with berotralstat.<sup>23</sup> In this case report, berotralstat treatment was initially associated with mild to moderate GI symptoms, including upset stomach and diarrhea, which were self-limiting and managed by ingesting the medication with food.<sup>23</sup> In our case series, two patients (Patient 3 and Patient 5) reported that berotralstat treatment was initially associated with some adverse GI symptoms, but the symptoms resolved over time and did not detract from the overall benefits gained from this prophylactic option.

Overall, similar to what was reported in a case series of 23 patients with HAE-nC1INH, our findings indicate that treatment options and disease management strategies recommended for patients with HAE-C1INH may also benefit patients with HAE-nC1INH.<sup>5</sup> However, given the heterogeneity in treatment outcomes described in those 23 patients<sup>5</sup> and in our case series, it is advisable to adopt a personalized approach to HAE-nC1INH management.

Limitations of our case series include the relatively small sample size, which hampers generalization of the findings to all patients with HAE-nC1INH. Additionally, the retrospective nature of the study means the diagnosis of HAE-nC1INH and the reporting of patient outcomes were not standardized. Patient outcomes were also not quantified in a standardized manner using validated tools such as the angioedema control test (AECT), HAE activity score (HAE-AS), or angioedema quality of life questionnaire (AE-QoL). This made it more difficult to compare the impact of different treatment options on HAE attack frequency and severity.



## Conclusions

In summary, the experiences of the patients in our case series indicate that episodes of otherwise unexplained abdominal bloating, pain, and swelling of the hands, extremities, and larynx should raise suspicion of HAE-nC1INH, even if laboratory values rule out a diagnosis of HAE-C1INH. Our findings also support the suggestion that FDA-approved HAE treatments may also benefit patients with suspected or diagnosed HAE-nC1INH and that adoption of a personalized approach to disease management is critical to optimize treatment outcomes. Oral berotralstat 150 mg once daily was an effective prophylactic treatment option in most of the patients in this case series. Further studies in patients with HAE-nC1INH are required to demonstrate the efficacy, safety, and impact on quality of life of HAE therapies, including berotralstat, that may benefit this patient population.

## Abbreviations

HAE, hereditary angioedema; C1-INH, C1-esterase inhibitor; C4, complement component 4; CSU, chronic spontaneous urticaria; HAE-C1INH, HAE due to deficiency/defect in C1-INH; HAE-nC1INH, HAE with normal C1-esterase inhibitor and complement component 4; FDA, Food and Drug Administration; pdC1-INH, plasma-derived C1-esterase inhibitor; rhC1-INH, recombinant C1-esterase inhibitor; QID, four times daily.

## Data Sharing Statement

The data supporting the conclusions of this manuscript are included within.

## Ethics Approval and Informed Consent

This report describes a retrospective patient case series using anonymized data. Patients provided written informed consent for their de-identified case details to be collected, and all data was maintained with confidentiality. IRB review and approval was not sought for this research. This research was exempt from IRB review as it was a retrospective, longitudinal case review and involved an FDA approved medication for standard of care practice and these patients were treated as such.

## Consent for Publication

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

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

HJK is a speaker for AstraZeneca plc, BioCryst Pharmaceuticals, Inc., Pharming Group N.V., and Teva Pharmaceuticals Industries Ltd., and has contracted research with ADMA Biologics, Inc., BioCryst Pharmaceuticals, Inc., BioMarin Pharmaceutical, Inc., Kedrion Biopharma, Inc., Novartis AG, Octapharma AG, Regeneron Pharmaceuticals, Inc., and Takeda Pharmaceutical Company Ltd. DASM has contract research with ADMA Biologics, Inc., BioCryst



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