

Exploratory analysis of genetic variation, clinical activity score, and lanadelumab response in two families with hereditary angioedema due to C1-inhibitor esterase deficiency

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ABSTRACT

Background: Hereditary angioedema due to C1-inhibitor esterase (C1INH) deficiency is caused by mutations in the *SERPING1* gene. The same mutation can cause variable disease severity, highlighting the role of genetic and clinical factors in disease expression. The aim of this study was to evaluate these factors alongside the effectiveness of lanadelumab in two families.

Case presentation: Here, we conducted a comparative analysis of affected members from two families including clinical activity scores, C1INH activity levels at diagnosis and genetic mutations. In lanadelumab treated patients, efficacy was evaluated three and 12 months post-initiation, and the two groups were compared. In family 1, eight affected individuals were identified across five generations. A deletion in exon 4 was detected in three of the six living patients. The clinical activity score was ≥ 5 in all and the C1INH activity level $\leq 40\%$ in five of them. In the three sisters receiving lanadelumab, the uncontrolled disease became a controlled one. In family 2, 16 affected individuals were identified across four generations, with eight patients followed at our center. A missense mutation in exon 8 was detected in five patients. An undetectable C1INH activity level and clinical activity scores ≥ 5 was identified in five patients. In two from the three patients treated with lanadelumab a markedly reduction in attacks frequency was obtained (from 9 to 2 in both of them) and one patient became symptom-free.

Conclusions: The relationship between specific genetic mutations, clinical severity score, and response to prophylactic treatment remains inconclusive.

Keywords: C1-inhibitor esterase, genotype, hereditary angioedema, lanadelumab, quality of life

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INTRODUCTION

Hereditary angioedema (HAE) due to C1-inhibitor esterase (C1INH) deficiency (HAE-C1INH) is a rare, potentially life-threatening disease characterized by recurrent swelling of the skin, gastrointestinal tract, and upper airways [1]. Attacks last 2–7 days and may be fatal if the larynx is involved [2]. Swelling episodes result from increased bradykinin production due to uncontrolled activation of the kallikrein–kinin system and factor XII (FXII) secondary to C1INH deficiency, encoded by the *SERPING1* gene, located on chromosome 11 [3]. This gene exhibits marked allelic heterogeneity, with more than 900 distinct mutations described to date reported in the Human Gene Mutation Database [4] and the Hereditary Angioedema database [5].

Mutations distributed throughout this gene lead to defective synthesis or secretion of C1INH, resulting in HAE-C1INH type 1 (85% of cases). In contrast, HAE-C1INH type 2 is primarily associated with mutations located in the terminal region of exon 8, which encodes the active site of the molecule and represents 15–20% of the cases [6,7]. There are no differences in clinical picture and in treatment strategies between the two types of HAE-C1INH [8].

The disease is inherited in an autosomal dominant manner, with de novo mutations demonstrated in 20–25% of cases [7, 9]. In around 5% of situations, no genetic variants can be identified [10]. It is known that the same genetic mutation may determine a widely different clinical course and severity in different family members [11], with no correlations being demonstrated so far between genotype, C1INH level, and phenotype [6,12].

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In recent years, several first-line preventive drugs have become available for the treatment of HAE-C1INH, regardless of genotype and/or phenotype characteristics.

The aim of our study was to assess genetic variation, clinical activity, C1INH activity level at diagnosis, and response to the plasma kallikrein targeted monoclonal antibody (lanadelumab) treatment in two Romanian HAE-C1INH families. The study was designed as an observational evaluation of the genotype–phenotype relationship, as well as the effectiveness of lanadelumab treatment among affected members of two families with HAE-C1INH.

ETHICS APPROVAL

The study was conducted in compliance with the requirements set forth in the Declaration of Helsinki and was approved in December 2022 by the institutional review board of the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania (Decision no. 1914/02.11.2022). Informed written consent was obtained from all patients.

CASE PRESENTATION

Clinical assessment and diagnostic workup

The investigations were conducted at the Romanian Angioedema Care Excellence and Reference Center (ACARE) between November 2022 and November 2023.

The study included two families with HAE— one with type 1 (family 1) and one with type 2 (family 2) — each comprising at least three affected adult members. Eligible participants were those aged ≥ 18 years with available clinical and diagnostic data required to establish the clinical activity score, including C1INH activity at diagnosis, identified familial genetic mutation, and recent initiation of lanadelumab treatment.

Data (socio-demographic and clinical) were obtained from the Romanian HAE Registry, established in 2006 by the Romanian HAE Network Foundation and hosted by the same institution.

The clinical activity score was determined based on parameters defined by Bygum et al. [12], including time of onset of symptoms, number of organs involved, and need for long-term prophylaxis (LTP). The score ranges from 0 to 10 points, cumulatively, as follows: age at onset (0-5 years- 3 points; 6-10 years- 2 points; 11-20 years - 1 point; and >20 years- 0 points), oedema (skin, at least once- 1 point; painful abdominal, at least once - 2 points; laryngeal, at least once- 2 points), other clinical manifestations (1 point), and LTP (1 point).

In addition, the level of C1INH activity at the time of diagnosis, determined by the ELISA method, was compared between affected family members.

Genetic mutations were identified on the DNA extracted from EDTA-containing whole blood samples based on a standard desalting process followed by the analysis of variants in the *SERPING1* gene, using the Sanger sequencing method.

In the case of the large deletion (family1), confirmation was performed using Multiplex Ligation-dependent Probe Amplification (MLPA), which is used to detect mutations that are missed by standard sequencing. It covers exons 1 through 8.

In lanadelumab-treated patients [13], disease control, quality of life, and attack frequency were assessed using the 3-month recall Angioedema Control Test (AECT), the Angioedema Quality of Life questionnaire (AE-QoL), and patient attack diaries. These parameters were assessed at baseline (pre-treatment), 3, and 12 months respectively.

The AECT (4 items) evaluates attack frequency, impact, unpredictability, and treatment effectiveness (score 0–16; ≥ 10 = well-controlled; the minimal clinically important difference, MCID: 3) [14]. The AE-QoL (17 items, 4-week recall) measures quality-of-life impairment across four domains (score 0–100; higher scores indicate greater impairment; MCID: 6) [15]. MCID is the lowest score change between two consecutive evaluations that reflects a meaningful improvement of the parameter evaluated [14,15]. Both instruments are validated in Romanian.

Descriptive statistics were used to summarize demographic characteristics and therapeutic management of patients. The three-month AECT score, AE-QoL score and the clinical activity score were calculated according to the authors' instructions.

Diagnostic findings

Family 1

In family 1, eight affected members were identified across a five-generation pedigree (Figure 1). Among the six living patients (five female and one male), a deletion in exon 4 was detected in three (Figure 1). In all cases, the mutation was also confirmed by MLPA. Symptoms began during childhood (≤ 5 years) in five patients (four female and one male); all of whom had a clinical activity score above six. In the sixth patient, the symptoms started at the age of 19, and she had a clinical activity score of seven (Table 1).

Three sisters received LTP with lanadelumab (Figure1), at a dose of 300 mg every two weeks during the study. In two of them (patients 2 and 3), LTP was switched from intravenous plasma-derived C1-INH (pdC1INH). All three patients were under treatment for hypertension and two of them (patients 1 and 3) had a positive personal history of breast cancer.

Data on AECT, AE-QoL, and attack frequency pre- and post-treatment with lanadelumab are summarized in Figure 2.

Table 1. Demographic, clinical, and laboratory characteristics of the two families

Patient	Sex	Age at onset (years)/points	Skin oedema/points	Abdominal oedema/points	Laryngeal oedema/points	Other/points	Long-term prophylaxis/points	Clinical activity score	C1INH % at diagnosis	Lanadelumab treatment
Family 1										
1	F	5/3	Y/1	Y/2	Y/2	Y/1	N/0	9	16	L
2	F	5/3	Y/1	Y/2	Y/2	Y/1	Y/1	10	30	L
3	F	3/3	Y/1	Y/2	Y/2	Y/1	Y/1	10	45	L
4	F	19/1	Y/1	Y/2	Y/2	Y/1	N/0	7	6	-
5	M	3/3	Y/1	Y/2	N/0	Y/1	N/0	7	24	-
6	F	2/3	Y/1	Y/2	N/0	N/0	N/0	6	26	-
Family 2										
1	F	7/2	Y/1	Y/2	Y/2	Y/1	Y/1	9	0	-
2	M	10/2	Y/1	Y/2	Y/2	N/0	N/0	7	0	L
3	M	33/0	Y/1	Y/2	N/0	Y/1	N/0	4	0	-
4	F	2/3	Y/1	Y/2	N/0	Y/1	Y/1	9	12	L
5	M	2/3	Y/1	Y/2	Y/2	Y/1	Y/1	10	0	L
6	M	4/3	Y/1	Y/2	Y/2	Y/1	N/0	9	0	-
7	M	44/0	Y/1	Y/2	N/0	N/0	N/0	3	43	-
8	F	14/1	Y/1	Y/2	N/0	N/0	N/0	4	18	-

The Arabic numbers of patients correspond with the patient numbers from figures 1 and 2. Abbreviations: F- female, L- lanadelumab, M- male, N- No, Y- Yes.

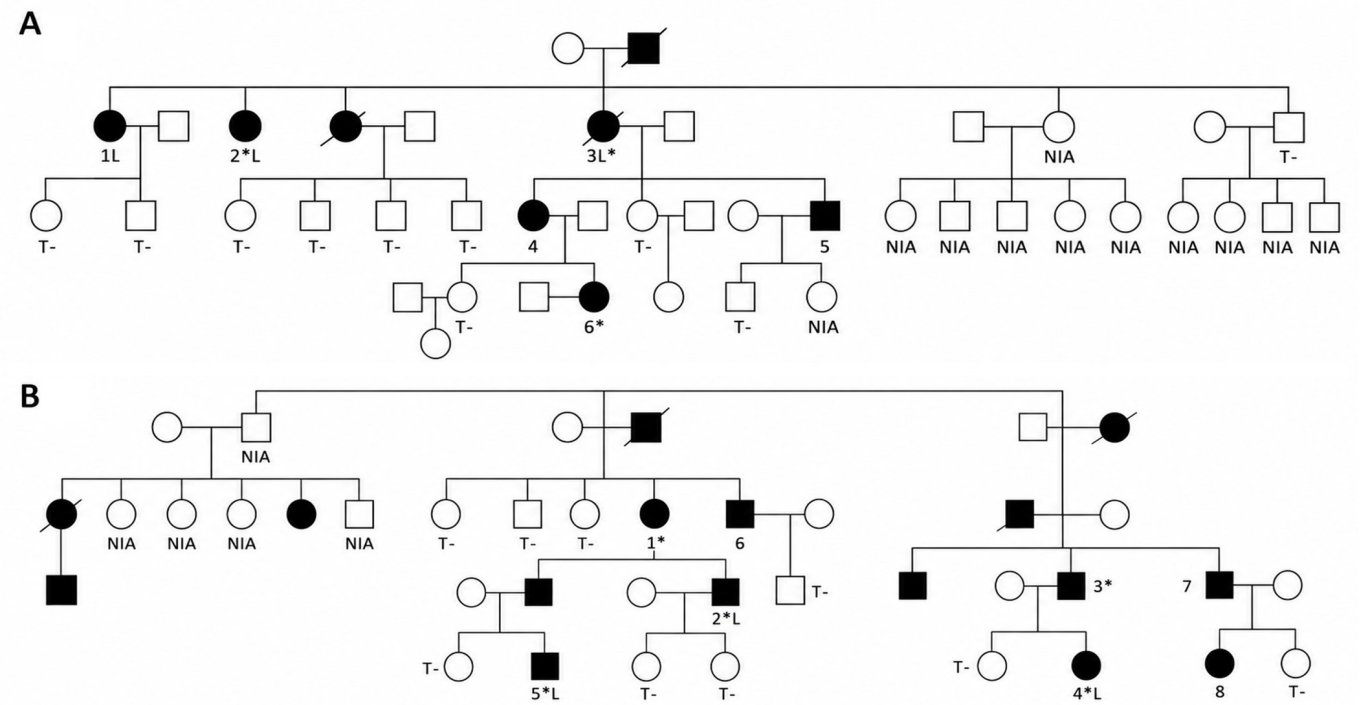


Figure 1. Pedigrees of the two families: (A) Family 1 – HAE-C1INH type 1 and (B) Family 2 – HAE-C1INH type 2. Affected individuals are indicated by filled (black) symbols and numbered (Family 1: n=6; Family 2: n=8). Individuals who underwent genetic testing are marked with an asterisk (*), and those receiving lanadelumab treatment are indicated by “L”.

Family 2

In family 2, 16 affected members were identified across four generations (Figure 1). Eight patients (out of 10 members alive) were followed at our center during the study. A missense mutation in exon 8 was detected in five of these patients (Figure 1). At diagnosis, five patients had undetectable C1INH activity, symptom onset before the age of 10 years, and a clinical activity score above six (Table 1). During the study, three patients received two doses of lanadelumab treatment per month. In patient 5, this was

switched from pdC1-INH LTP. Patient 4 became attack-free after the first dose of lanadelumab, so after 6 months, the dose was decreased to 300 mg at four weeks. No comorbidities were identified in these three patients. Figure 2 presents data on AECT, AE-QoL, and attack frequency before and after lanadelumab treatment. In both families, the first two doses of lanadelumab were administered by health-care personnel, and then by self-administration as home-treatment. Adverse effects were evaluated at each visit.

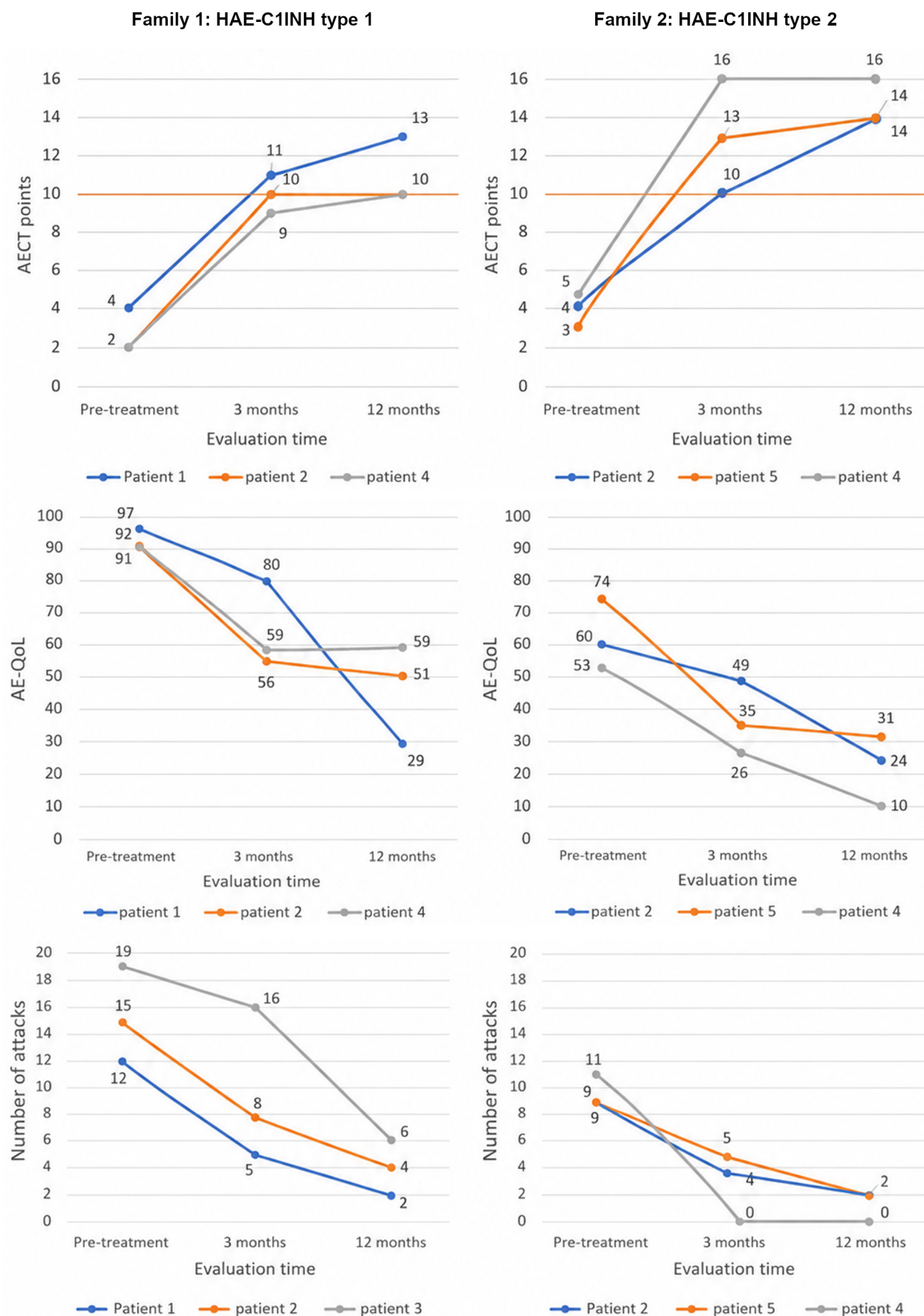


Figure 2. Patient-reported outcomes - AECT, AE-QoL, and attack frequency - before and after lanadelumab treatment

DISCUSSION

The present study describes the genetic mutation, clinical severity and the response to lanadelumab treatment according to genotype in two Romanian families, one with type 1 and one with type 2 HAE-C1INH. As genetic testing is not mandatory for the diagnosis of HAE-C1INH, correlations between genotype, phenotype and specific treatment response remain limited; therefore, our findings may provide complementary data to those published so far.

Fourteen HAE-C1INH patients (eight females and six males), from two unrelated families were evaluated: six patients (five women and one man) from the family type 1 HAE-C1INH and eight (three women and five men) from the HAE-C1INH type 2 family.

In family 1, the large deletion was identified in three members over two generations, and in family 2, a missense mutation (c.1396C>T, with p. Arg466Cys) was detected in five members over three generations.

The mean age at onset was 6.2 years (range: 2-19) in family 1 and 14.5 years (range: 2- 44) in family 2. The mean clinical activity score was higher in family 1 (8.1; range: 6-10) compared with family 2 (6.8; range: 3-10). In contrast, the mean functional C1INH level at diagnosis was lower in family 2 (9.1%; 0-43) compared with family 1 (24.5%; 6- 45) (Table 1). These findings suggest that individuals in family 1 tend to have a younger age of onset and greater clinical severity of disease compared with those in family 2, although functional C1INH levels at diagnosis were lower in the latter group. Our results are consistent with those reported by Speletas et al. [16], indicating that onset before the age of 10 years is less common in cases with missense mutations, but do not support the data published by Kelemen et al. [17], according to which functional C1INH levels at baseline are correlated with disease severity. Bors et al. [18] also reported a less severe disease, reflected by a lower annual attack rate, in patients identified with missense mutations.

In our cohort, an empirical comparison of the mean attack frequency in the three-month period preceding lanadelumab treatment between three members of each family showed higher values in family 1 (15.3 vs. 9.7), despite the fact that two patients were on LTP with pdC1-INH, compared to only one patient in family 2.

Following initiation of lanadelumab, attack frequency decreased markedly in all treated patients; however, it remained higher in family 1 than in family 2 at both the 3-month (mean 9.7 vs. 3 attacks) and 12-month (mean 4 vs. 1.3 attacks) evaluations. In family 2 one patient became symptom-free after the first dose of lanadelumab, and this status was maintained at the 12-month evaluation. This rate was lower than that reported in the HELP-OLE study (NCT02741596), in which nearly 70% of patients remained attack-free for at least one year of treatment [19]. Despite the persistence of some attacks on the lanadelumab treatment, disease control was achieved in all patients except one at 3 months, and in all patients at 12 months (Figure 2).

Regarding the QoL, its improvement followed a less pronounced trajectory in family 1, where it remained in the same impairment category at both follow-up assessments (mean 65 at 3 months and 46.3 at 12 months). However, the MCID was reached by all three patients at 3 months and in two of them at 12 months.

In family 2, the QoL improved from a “large effect” at baseline (mean 93.3) to a “small effect” at 3 months (mean 36.7) and to “no effect” at 12 months (mean 21.7). These findings are consistent with the results of the HELP study (NCT02586805), in which 81% of patients receiving lanadelumab experienced improvements in QoL [20].

Taken together, the results on attack frequency, disease control, and quality-of-life improvement suggest that lanadelumab led to greater improvements in these parameters for family members with HAE-C1INH type 2. This observation is noteworthy, given that two patients had 0% functional C1INH activity at diagnosis, and one had maximal disease severity.

The main strength of our study is the inclusion of well-characterized patients from two families and the use of validated Romanian-adapted instruments, ensuring reliable patient-reported outcomes. However, the small sample size and family-based design limit generalizability and preclude robust statistical analyses. Another limitation of our study is the lack of a comparison group and the lack of knowledge of the potential effect of comorbidities on quality of life. The observational nature also prevents causal inferences. Additionally, the lack of assessment of other gene mutations and non-genetic modifiers is a limitation. Therefore, the findings should be interpreted with caution and confirmed in larger, multicentre studies.

CONCLUSIONS

In summary, our results suggest that LTP with lanadelumab markedly reduced attack frequency, leading to better disease control and improved quality of life in all treated patients. Although the relationship between specific genetic mutations, clinical activity scores, and response to lanadelumab remains inconclusive, an integrated evaluation of these parameters in larger patient cohorts may improve understanding of the disease’s natural history and its potential influence on treatment response.

ABBREVIATIONS

ACARE – Angioedema Care Reference and Excellence Center
 AECT – Angioedema Control Test
 AE-QoL – Angioedema Quality of life Questionnaire
 C1INH – C1 inhibitor esterase
 HAE – hereditary angioedema
 HAE-C1INH – hereditary angioedema due to C1INH deficiency
 LTP – long-term prophylaxis
 MCID – minimal clinically important difference
 MLPA – Multiplex Ligation-dependent Probe Amplification
 pdC1INH – plasma derived C1inhibitor

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AUTHORS' CONTRIBUTION

NAB – conceptualization, investigation, project administration, data curation, resources, writing (original draft).

VN – formal analysis, data curation, visualization, supervision, writing (review & editing).

DD – validation, supervision, writing (review & editing).

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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