ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2025.1073
Asthma Allergy Immunol 2025;23:328-334

RESEARCH ARTICLE

Received: 20.10.2025 • Accepted: 28.10.2025
Online Published: 01.12.2025

Evaluation of Disease Control in Patients with HAE-nC1INH Receiving Tranexamic Acid

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This abstract was presented at the 29th National Congress of Allergy and Clinical Immunology, held on November 29 – December 3, 2023, Antalya, Türkiye

ABSTRACT

Objective: Hereditary angioedema (HAE) is a rare disease with recurrent angioedema (AE) attacks as a result of accumulation of excess bradykinin in the tissues. Both the level and function of C1 inhibitor protein (C1INH) are within the normal range in HAE with normal C1INH (HAE-nC1INH). This study aimed to evaluate the disease control of HAE-nC1INH patients receiving tranexamic acid (TXA) for long-term prophylaxis (LTP).

Materials and Methods: The study was conducted as a retrospective, single-center pilot cohort survey. A total of six patients with HAE-nC1INH receiving TXA were enrolled. The angioedema control test (AECT) and quality of life (AE-QoL) scale, which are used to evaluate disease control, were administered before and after TXA.

Results: The median age at diagnosis of HAE-nC1INH was 45 (IQR, 28-52) years. The median age at onset of the patients' first AE episodes was 31 (IQR, 18-45) years. The median time to diagnosis was 78 (IQR, 28-240) months. FXII mutation was detected in two cases, and the others were HAE-nC1INH with unknown genetic etiology. All patients were receiving 1000-1500 mg/d TXA for LTP, while two patients had received TXA for acute AE attacks. The median duration of TXA LTP therapy was 48 (IQR, 28-72) months. The median number of annual attacks before and after TXA was 36 and 1, respectively. The median AECT score before TXA was 6 (IQR, 3-6), while the median AECT score after TXA was 13 (IQR,11-15). At least a two-fold improvement in terms of minimal clinically important difference was detected in all four sub-headings (function, fatigue, fear, and nutrition) of the AE-QoL scale.

Conclusion: TXA was highly effective in reducing attack frequency and significantly improving disease control in patients with HAE-nC1INH. Moreover, substantial improvements were observed across all AE-QoL domains, indicating a marked positive impact on the patients' quality of life.

Keywords: HAE-nC1INH, hereditary angioedema, F12 mutation, tranexamic acid, angioedema control

INTRODUCTION

Hereditary angioedema (HAE) is characterized by random and often unpredictable attacks of painful swelling typically affecting the extremities, genitals, bowel mucosa, face, and upper airway (1). Attacks can lead to loss of function, decrease in the quality of life, and even death as a result of laryngeal attacks (2,3). The prevalence of HAE in the literature ranges from 1:10,000 to 1:150,000, and it is inherited as an autosomal dominant disorder, but 25% of patients have no family history (4-6). HAE is divided into

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three types. Type 1 and 2 HAE with C1 inhibitor deficiency (HAE-C1INH) is the most prevalent, representing approximately 95% of cases, and results from low concentration and functional levels of C1 inhibitor (C1INH) (7,8). HAE with normal C1INH (HAE-nC1INH), previously referred to as type III HAE, was initially described and remains poorly understood (9). HAE-nC1INH is characterized by normal plasma levels of C1INH, and normal C1 inhibitor function and complement levels (6). Up to date, nine subgroups of HAE-nC1INH types have been defined. Eight of them were based on mutant genes; FXII mutation (HAE-FXII), plasminogen mutation (HAE-PLG), angiopoietin 1 mutation (HAE-ANGPT1), kininogen1 mutation (HAE-KNG1), myoferlin mutation (HAE-MYOF), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HAE-HS3ST6), carboxypeptidase N (HAE-CPN) disabled homolog 2 interacting protein mutation (HAE-DAB2IP), and the other group (HAE-UNK) that meets HAE-nC1INH criteria, but whose mutation has not yet been detected (10,11). FXII mutations are detected in approximately 25% of patients with HAE-nC1INH (12). The first mutation in HAE-nC1INH was two missense mutations located in the ninth exon of the Factor XII gene, which was identified in six members of a German family in 2006 and is the best understood subtype (11,13,14). However, there is limited data about the disease characteristics of HAE-nC1INH patients with FXII mutation (1,15,16).

Management of HAE-nC1INH

The therapeutic approach to HAE-nC1INH is largely guided by international consensus recommendations, given the limited availability of randomized controlled trials in this subgroup. The principles of management are parallel those for HAE-C1INH, encompassing on-demand treatment of acute attacks, short-term prophylaxis (STP), and long-term prophylaxis (LTP) (17). It is unresponsive to corticosteroid and antihistamine therapy, even when administered at high doses (18). For acute attacks, first-line therapies include bradykinin B2 receptor antagonists (icatibant) and plasma-derived human C1INH concentrate (pdC1INH) or recombinant C1INH concentrate. Ecallantide, where available, is also considered an effective option. Supportive care, including airway protection, remains critical in laryngeal edema (19-21). STP is recommended prior to procedures known to trigger attacks, such as dental interventions or surgeries, with pdC1INH as the preferred agent (22). There is no approved treatment yet for LTP in HAE-nC1INH. LTP in HAE-nC1INH should be individualized, considering attack frequency, severity, and impact on quality of life. Current guidelines support the use of tranexamic acid (TXA) or progestin (in women) as first-line options in suitable patients, given their favorable safety profile and cost-effectiveness (23-26). Lanadelumab, Garadacimab, and plasma-derived C1-INH may be considered in refractory cases, although evidence in HAE-nC1INH is limited (27,28).

TXA, progestin, attenuated androgens, pdC1-INH concentrate are available in Türkiye and used in LTP (12). TXA and attenuated androgens provided complete disease control or partial improvement in some patients with the FXII mutation (29).

The aim of this study was to evaluate the disease control and to characterize the demographic and clinical features of patients with HAE-nC1INH receiving TXA.

MATERIALS and METHODS

The study was designed as a retrospective, single-center, cohort survey. This study included a total of 12 HAE-nC1INH patients from January 1, 2001, to December 31, 2023 at a tertiary care allergy clinic. Six of them were receiving TXA. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, revised in 2013, and was approved by Hacettepe University Ethics Committee (2023/03-04). Inclusion criteria were age ≥18 years, and diagnosis with HAE-nC1INH.

The clinical and laboratory data of the patients were obtained from the hospital database. Parameters to be assessed include year of initial symptom onset, age at symptom onset, year of HAE-nC1INH diagnosis, genetic mutations associated with HAE, localizations of angioedema (AE), attack frequency and duration, precipitating factors, comorbidities, medications administered during attacks, number of life-threatening episodes, LTP therapies, duration and dosage of TXA therapy, frequency and distribution of attacks during treatment, and pre- and post-treatment quality of life (QoL). Disease control and QoL were assessed using the Angioedema Control Test for the last four weeks (AECT), and AE-QoL (12, 30). The AECT consists of four questions assessing the frequency of symptoms, the impact on QoL, the unpredictability of attacks, and the level of disease control achieved with current treatment. Each question is scored from 0 to 4, yielding a total score ranging from 0 to 16. Previous studies have demonstrated that a score of 10 serves as a threshold for distinguishing

between poorly controlled and well-controlled patients. The AECT is completed retrospectively, and in this study the 4-week retrospective version was used (31-33). The AE-QoL Questionnaire is used for patients with recurrent AE, such as HAE, consists of 17 items, and is used to analyze the four dimensions of functioning, fatigue/mood, fear/shame, and nutrition. The total AE-QoL Questionnaire score and each dimension are scored between 0 (best) and 100 (worst). The AE-QoL Questionnaire dimension scores were calculated by using the following formula: ([R items – minimum R items]/[maximum R items – minimum R items]) x 100 (34).

In the mutation analysis at our centre, FXII, plasminogen, and angiopoietin 1 mutations were examined.

Data were analyzed using SPSS ver. 25.0 software. Descriptive data were presented as numbers (n) and percentages (%). Numerical variables showing normal distribution were stated as mean± standard deviation values, and otherwise as median and interquartile range (IQR) values.

RESULTS

A total of six patients with HAE-nC1INH were enrolled. The mean age was 42 ± 14 years, and the median BMI was 25.6 kg/m² (IQR, 22–33). The median age at diagnosis of HAE-nC1INH was 45 (IQR, 28-52) years. The median age at onset of patients' first AE episodes was 31 (IQR, 18-45) years. The median time to diagnosis was 78 (IQR, 28-240) months. A mutation in the FXII gene was identified in two patients (33%), while the remaining cases were classified as HAE-nC1INH with an unknown genetic etiology. The baseline clinical characteristics of the cohort were summarized in Table I. AE attack in the form of recurrent abdominal pain was experienced in two (33%) patients, while AE in the face and extremities was observed in five (83%) patients. Three (50%) of the patients had at least one episode of laryngeal edema during their life. A family history of AE was present in three patients (50%), two (66%) of whom tested positive for the FXII mutation. Chronic urticaria (CU) was present in two (33%) patients, whereas familial Mediterranean fever (FMF), asthma, gastroesophageal reflux disease (GERD), and hypothyroidism were each observed in one (17%) patient. pdC1INH was administered to three (50%) patients during acute AE episodes. One patient (17%) required STP and received pdC1INH prior to surgery. All patients were receiving 1000-1500 mg/d TXA for LTP, while two (33%) patients had also received 500-1500 mg TXA for acute AE attacks. The median time to TXA therapy was 48 (IQR, 28-72) months. None of the patients had side effects related to TXA. The median number of annual attacks before and after TXA was 36 (IQR, 16-48) and 1 (IQR, 0-8), respectively. Moreover, in patients with laryngeal edema, the annual reduction in AE attacks reached ≥85%, which exceeded the overall mean reduction of 75%. The median AECT score before TXA was 6 (IQR, 3-6), while the median AECT score after TXA was 13 (IQR, 11-15). Disease control (AECT>10) was achieved in all patients. At least a two-fold improvement in terms of minimal clinically important difference (MCID) was detected in all four sub-headings (function, fatigue, fear, and nutrition) of the AE-QoL scale after TXA therapy (Figure 1). None of the patients experienced any adverse effect related with TXA treatment.

DISCUSSION

In our cohort, LTP with TXA was associated with a substantial reduction in the frequency of attacks and a marked improvement in disease control among patients

Table I: The baseline clinical characteristics of the cohort.

Patients No.	Age	Sex	HAE-Mutation	Age at first AE attack, years	Family history	Comorbidities	Localizations of the attacks	Frequency of the attacks/years before TXA	The baseline AECT score
1	31	Female	FXII	27	yes	FMF, CU	Face, extremities	4.00	6.00
2	40	Female	-	35	no	Hypothyroidism	Face, extremities	36.00	4.00
3	50	Male	-	46	yes	Asthma	Abdomen	48.00	6.00
4	20	Female	-	19	no	-	Face, extremities	20.00	2.00
5	50	Male	-	45	no	CU	Face, extremities	48.00	6.00
6	58	Female	FXII	16	yes	GERD	Face, extremities, abdomen	36.00	6.00

FMF: Familial Mediterranean fever, **CU:** Chronic urticaria, **GERD:** Gastroesophageal reflux disease.

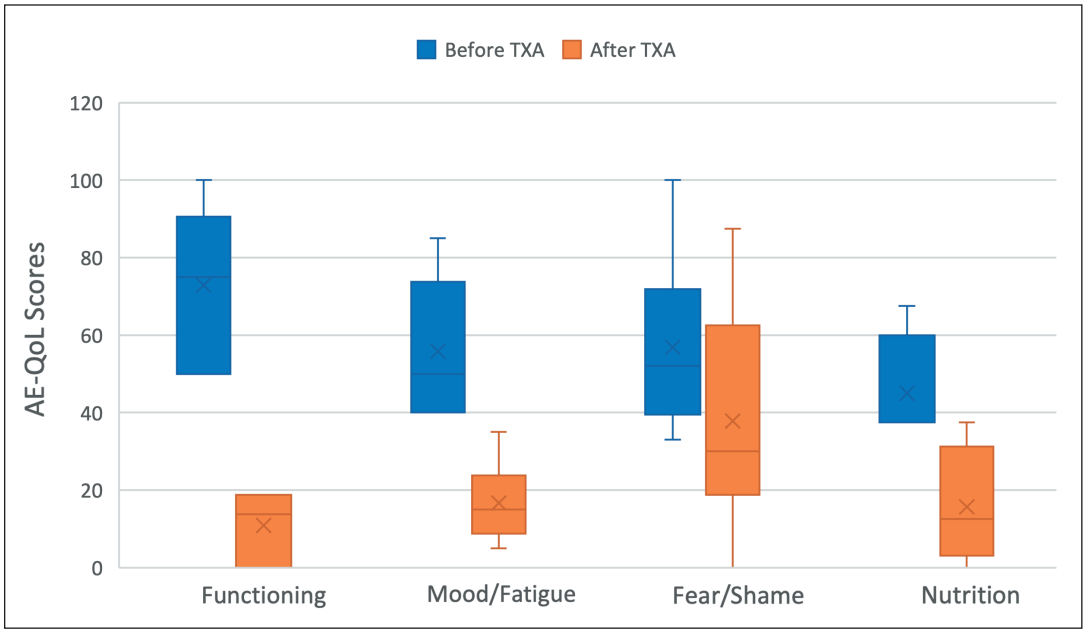

Figure 1: Results of AE-QoL Results of AE-QoL Questionnaire scores. Box and whisker plots demonstrate the distribution of the AE-QoL Questionnaire scores in the study before and after TXA therapy (The band around the middle of the box shows the median, and the ends of the whiskers show the minimum and maximum values). Higher values indicate higher impairment. At least a two-fold improvement in terms of minimal clinically important difference (MCID) was detected in all four sub-headings (function, fatigue, fear, and nutrition) of the AE-QoL scale after TXA therapy. AE-QoL = Angioedema Quality of Life, TXA=Tranexamic acid.

with HAE-nC1INH. The annual attack rate declined from a median of 36 to 1 episode after initiation of TXA, while AECT scores improved substantially, reflecting better disease control and disease control was achieved in all patients. Importantly, all domains of the AE-QoL instrument demonstrated at least a two-fold improvement, emphasizing the broad positive impact of TXA on physical, psychological, and functional outcomes. Also, CU was most common comorbidity in the study population.

Our findings are consistent with previous reports that have demonstrated the efficacy of TXA in HAE-nC1INH, particularly in reducing attack frequency and improving patient-reported outcomes (23,35,36). Moreover, AE attacks were effectively controlled in patients who experienced AE episodes as abdominal pain or laryngeal edema, resulting in at least an 85% reduction in the annual attack frequency. The magnitude of benefit observed in our cohort, despite genetic heterogeneity—including FXII mutations, and cases with unknown etiology—suggests that TXA may be an effective prophylactic option across different genetic subtypes of HAE-nC1INH, although larger studies are needed to confirm whether mutation status predicts treatment response. Notably, the absence of TXA-related adverse events over a median treatment duration of 48 months further supports its safety profile, particularly in the context of LTP. In our series, TXA was not only used for LTP but was also administered for acute AE episodes in two (33%) patients, aligning with its role as an adjunctive therapy in acute settings (37,38). While the small sample size limits generalizability, the observed benefit in both genetically confirmed and idiopathic cases reinforces the therapeutic potential of TXA in diverse clinical contexts.

In our cohort, disease control improved markedly with TXA, as reflected by a rise in median AECT from 6 (IQR, 3–6) to 13 (IQR, 11–15), with all patients achieving controlled disease (AECT > 10). This exceeds the established MCID of 3 AECT points and aligns with validation studies supporting AECT as a sensitive, responsive measure of control in recurrent AE (33,39). The parallel, clinically meaningful gains across all AE-QoL subdomains (function, fatigue/mood, fear/shame, nutrition/food)—with at least a two-fold improvement—are consistent with AE-QoL interpretability work, which identifies a total-score MCID of approximately ≥6 points and demonstrates good sensitivity to change (40). The magnitude of control we

observed (including ≥85% annual attack reduction in high-risk subgroups such as those with laryngeal edema) approaches the attack-rate reductions reported with modern targeted prophylaxis (e.g., lanadelumab), which achieved ~87% mean reductions and sustained health related-QoL benefits in HAE-C1INH, albeit in different populations and study designs (41). Taken together, these data suggest that, for carefully selected HAE-nC1INH patients, TXA can translate into not only fewer attacks but also meaningful improvements in day-to-day functioning and well-being, while underscoring the need for prospective, subtype-resolved trials that benchmark TXA against kallikrein-pathway inhibitors using standardized outcomes (AECT, AE-QoL).

In our cohort, CU was present in two patients (33%), while FMF, asthma, GERD, and hypothyroidism were each observed in one patient (17%). The coexistence of CU and HAE has been occasionally reported (42,43). While these conditions are pathogenically distinct, their overlap may complicate diagnostic evaluation and delay appropriate treatment initiation. Given that patients with HAE-nC1INH often experience significant diagnostic delays—as reflected by the median time to diagnosis of 78 months in our cohort—effective and well-tolerated prophylactic strategies are critical to improving long-term outcomes.

The limitations of our study include the relatively small sample size, its retrospective design, and the restricted availability of treatment options for HAE-nC1INH in Türkiye.

Our data suggest that TXA may serve as a viable alternative for patients who are unsuitable for or have limited access to newer targeted therapies, especially in resource-limited settings. The consistent clinical benefit observed regardless of underlying genetic findings further reinforces the potential role of TXA in the management of this rare and heterogeneous disease. Nevertheless, prospective studies with larger cohorts are required to validate these findings and to define optimal patient selection criteria, dosing strategies, and the comparative effectiveness of TXA against newer therapies in HAE-nC1INH.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

None.

Author Contributions

Concept: **Gulseren Tuncay, Ebru Damadoglu, Gul Karakaya, A. Fuat Kalyoncu,** Design: **Gulseren Tuncay, A. Fuat Kalyoncu,** Data collection or processing: **Gulseren Tuncay, Ozge Uysal Soyer, Esra Birben, Ebru Damadoglu, Gul Karakaya, A.Fuat Kalyoncu,** Analysis or Interpretation: **Gulseren Tuncay, Ebru Damadoglu, Gul Karakaya, A.Fuat Kalyoncu,** Literature search: **Gulseren Tuncay,** Writing: **Gulseren Tuncay,** Approval: **Gulseren Tuncay, Ebru Damadoglu, Gul Karakaya, A. Fuat Kalyoncu.**

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