ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.439
Asthma Allergy Immunol 2019;17:47-52

RESEARCH ARTICLE

Received: 07/06/2018 • Accepted: 20/06/2018

Opinions of Turkish Hereditary Angioedema Patients Regarding the Use of C1 Inhibitor Concentrate in the Treatment of Acute Attacks

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ABSTRACT

Objective: No data exists about the perceptions of Turkish hereditary angioedema patients regarding the use of C1 inhibitor concentrate that has been used in the treatment of acute attacks for the last 7 years. Our aim was to evaluate patient opinions about the C1 inhibitor (C1-inh) concentrate and determine the level of satisfaction with this drug.

Materials and Methods: Fifty-seven hereditary angioedema (HAE) patients who used C1-inh concentrate for their angioedema attacks were asked to complete a questionnaire which contained various questions related to demographic information, clinical features, and experiences with C1-inh concentrate use.

Results: Sixty-five % of the patients were female and 94.7% of the patients had type 1 HAE. The mean curent age and age of diagnosis were 38.11±12.6 and 29.95±13.85 years, respectively. Thirteen patients did not have a family history. Forty patients were under prophylaxis (danazol n=39, tranexamic acid= 1). The mean duration of the C1-inh concentrate usage was 4.07±1.76 years. The patients had taken this drug 6 times over the past year on average. All patients stated that they experienced difficulties during injections with this medication in the emergency units due to a lack of awareness by health care professionals regarding both HAE and C1-inh concentrate. While 61.4% of the patients reported overall satisfaction about the efficacy of drug, 43.8% stated that this medication should have a more practical application; 52.6% proposed that the drug should be more accessible in hospital emergency rooms.

Conclusion: Patients with HAE generally considered that C1-inh concentrate was effective in their attacks. However, this group of patients expressed concerns related to the medical personnel's awareness about HAE as well as access to the medication.

Key words: Hereditary angioedema, C1 inhibitor concentrate, opinion of patients

ABBREVIATIONS: AE: Angioedema, **C1-inh:** C1 inhibitor, **HAE:** Hereditay angioedema, **LTP:** Long-term prophylaxis, **pdC1inh:** Plasma-derived C1-inh concentrate

INTRODUCTION

Hereditary angioedema (HAE) is a serious and potentially life-threatening rare genetic disorder with an autosomal dominant inheritance. HAE develops due to the deficiency or dysfunction of the plasma levels of C1- inhibitor (C1-inh) (1). These defects lead to a kind of bradykinin-mediated angioedema presenting as non-pruritic and non-pitting, well-demarcated swelling episodes of mucocutaneous tissues involving any part of the body such as the skin, face, larynx, extremities, gastrointestinal tract, genitalia or respiratory tract (2). The episodes are unpredictable and vary depending on the involvement site, severity, and frequency (3). Unfortunately, a delay in diagnosis is common because of the lack of awareness of the physicians about this rare disease. Edema of the gastrointestinal tract can present with severe abdominal pain, leading to unnecessary surgical interventions and,

furthermore, edema of the larynx can cause asphyxia and eventually death, making early accurate diagnosis crucial (2). Additionally, HAE as a debilitating disease negatively affects the quality of life and often leads to patient anxiety and depression (4,5).

The management of the disease comprises the prevention of attack development and the treatment of acute episodes with plasma derived C1-inh concentrate (pdC1inh), the bradykinin-2 reseptor antagonist (icatibant), and kallikrein inhibitor (ecallantide) (1,6,7). For long-term prophylaxis (LTP) attenuated androgens, anti-fibrinolytics and pdC1-inh are used and they are significantly effective in decreasing duration and severity of attacks (1,8). Despite these preventive measures for HAE patients (9), an unexpected acute attack requiring emergency care is always possible. Furthermore, because of the lack of awareness for both the disease as well as the recommended drugs to treat an acute attack, appropriate treatment can be delayed, and mortality and morbidity can thus increase. Clearly, considerations of the HEA patients about their treatments may facilitate support mechanisms, decrease the burden of the disease attacks, and improve the quality of life. In our country, Turkey, C1-inh concentrate became available in 2011; since that date, HAE management has significantly improved. However, we do not have sufficient knowledge about our patients' experiences with this medication. The Adult Allergy and Immunology Department of the Istanbul Faculty of Medicine, where this study was conducted, is one of the several main centers providing services for the management of HAE patients in Turkey. Istanbul is a megacity with a population of nearly 20 million, which is spread out over surrounding areas. We currently have 150 patients, including those from neighboring towns.

The aim of this study was to assess the patients' opinions about the C1-inh concentrate treatment for their HAE attacks.

MATERIALS and METHODS

This cross-sectional study was conducted at the Istanbul Faculty of Medicine, Adult Allergy and Immunology Department. HAE patients older than 17 years who had previously used C1-inh concentrate for the treatment of angioedema attacks were asked to complete a questionnaire which included various questions on demographic data, clinical features, and the usage of C1-inh concentrate during their routine visits.

Most of the survey questions were multiple choice but two of them were open-ended. The patients answered one multiple-choice question, 'Do you have any problems when receiving treatment with C1-inh concentrate in emergency rooms during an acute attack?' If the answer was 'yes', then they were then asked an open-ended question, 'In your opinion, what are the problems leading to difficulties in getting proper treatment in the emergency rooms?'

The other open-ended question concerned the patients' opinions about the C1-inh concentrate. First, the patients were asked to rank their satisfaction level of C1-inh concentrate as 'I am very satisfied',' I am satisfied', 'I have no idea', 'I am somewhat satisfied' and 'I am not satisfied'. In the following open-ended question, patients were asked 'What kind of enhancements can be realized for better and trouble-free treatment with the drug?'.

The study was approved by the Ethics Committee of the Istanbul Faculty of Medicine and written informed consent was obtained from all patients.

Statistical Analysis

The results were demonstrated as percentages and mean ± standard deviation or median according to the distribution.

RESULTS

Fifty-seven HAE patients who had previously used C1-inh concentrate for the treatment of angioedema attacks were included in the study.

Sixty-four % of the patients were female and 94.7% of them had type 1 HAE. The mean age and age of diagnosis were 38.11±12.6 and 29.95±13.85 years, respectively. The mean duration between onset of symptoms and diagnosis was 17.02±12.95 years. Thirteen patients did not have a family history. Forty patients were under prophylaxis (mostly danazol, n=39). The patients' clinical features are illustrated in Table I.

In the last year, the median numbers of angioedema attacks occurring in the patients were 7.4, 5 and 9.1 for abdominal pain, angioedema of the face and/or larynx, and extremity swelling, respectively. The patients had used C1-inh concentrate 6 times over the past year on average. The mean duration of C1-inh concentrate usage was 4.07±1.76 years.

Sixty-one point four % of the patients reported overall satisfaction about the effects of the drug (Figure 1). On the other hand, 43.8% of the patients stated that the drug should have more practical application while 52.6% reported that the drug should be more easily accessible. Thirty-nine patients (68.4%) stated that they experienced difficulties in the injection of this drug in emergency units due to the lack of awareness of the healthcare professionals about HAE and the C1-inh concentrate. Twenty-six patients (66.6%) who experienced difficulties in emergency rooms pointed out that the drug was unavailable in the emergency rooms that they had attended.

Patient answers for multiple-choice questions about C1-inh concentrate are shown in Table II. Almost half of the patients used the C1-inh concentrate within 30 minutes after the initiation of symptoms. Ten patients waited for 2 hours before using the drug. Twenty-nine patients stated that their symptoms started to resolve within one hour after using the drug. Most of the patients (n=38) stated that their attacks totally resolved in 2-4 hours. No patients reported rebound symptoms as well as adverse events after the use of C1-inh concentrate.

DISCUSSION

This is the first study to evaluate patients' opinions about C1-inh concentrate, a drug prescribed since 2011 to treat acute attacks of HAE in our country. The results indicate that although their satisfaction level with C1-inh concentrate was high, patients still had concerns related to access to medication as well as its application, and the lack of awareness of health professionals about the

Table I. Clinical features of the patients.

	n	%
Symptoms		
Abdominal pain	57	100
Angioedema of the face	48	84.2
Laryngeal angioedema	41	71.9
Angioedema of the extremities	57	100
Prodromal symptoms	44	77.2
Lassitude/Fatigue	20	35.08
Nausea	14	24.56
Tingling	12	21.05
Pain	6	10.5
Irritability	3	5.26
Other	46	80.7
Triggering factor	56	98.24
Stress	49	85.96
Fatigue	23	40.35
Trauma	42	73.68
Hormonal	16	28.07
Infections	14	24.56
Minor/major surgical interventions	10	17.54
Drug	9	15.78
Attack treatment		
To increase the dose of danazol	7	12.38
C1 inhibitor concentrate	57	100
Icatibant	17	29.8
Fresh frozen plasma	2	3.5

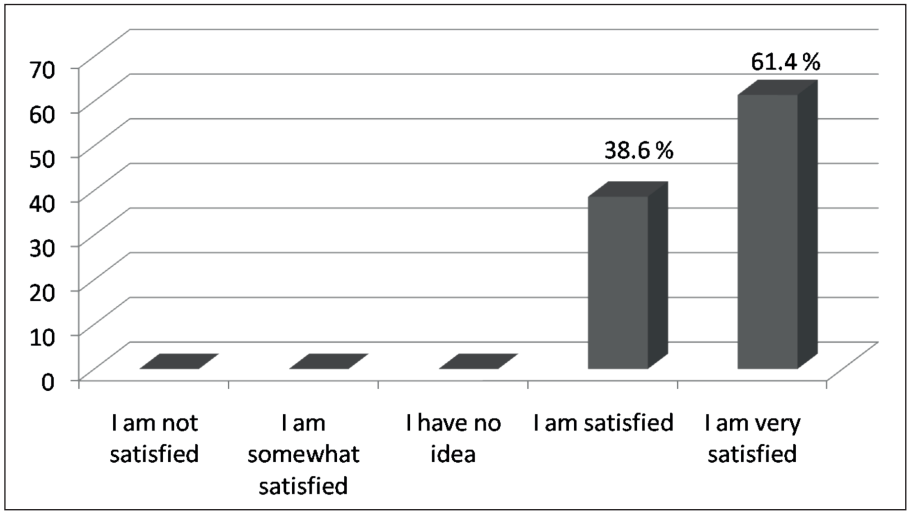

Figure 1. The satisfaction levels of the HAE patients with C1-inh concentrate.

disease and its treatment. C1-inh concentrate has not yet been licenced for long-term prophylaxis and also for self administration at home in Turkey. C1-inh concentrate can be prescribed only in case of an acute laryngeal or severe abdominal attack and administered in the emergency unit or immunology and allergy clinics that the patient has attended. Consequently, difficulties related to HAE management are expected to arise and require solutions in the form of new regulations.

In a previous study from Turkey that assessed HAE patients' experiences in emergency departments, the difficulties which HAE patients encountered were as follows: lack of awareness about HAE among physicians and nurses; lack of experience with the administration of the drug; inappropriate treatment for their attacks despite accurate diagnosis; and finally, insufficient supplies of C1-inh concentrate in the units (10).

The current study indicated the presence of similarly major problems in the management of the disease. The HAE patients in this survey were generally satisfied with the efficacy of C1-inh concentrate for acute attack treatment. However, most of their concerns pointed to

Table II. Patient responses to the questions about C1-inh concentrate.

	N	%
For which attacks did you receive C1-inh concentrate		
AE of the face/larynx	12	21.1
Abdominal pain	11	19.3
AE of the face/larynx/extremities and abdominal pain	3	5.3
AE of the face/larynx and abdominal pain	31	54.4
Do you have problems when receiving C1-inh concentrate in emergency rooms during your acute attack?		
No	18	31.6
Yes	13	22.8
Sometimes	26	45.6
How long did it take to receive the C1-inh concentrate after the onset of the attack?		
In 30 minutes	30	52.6
30-60 minutes	17	29.8
2 hours	5	8.8
2-4 hours	5	8.8
How many vials of C1-inh concentrate did you receive in an attack?		
One	24	42.1
Two	20	35.1
One or two depending on the severity of the attack	13	22.8
When did your symptoms start to resolve after the C1-inh concentrate usage?		
Within 30 minutes	11	19.3
30-60 minutes	18	31.6
1-2 hours	16	28.1
2-4 hours	8	14.0
More than 4 hours	4	7.0
When did your symptoms completely resolve after the C1-inh concentrate usage?		
Within 30 minutes	2	3.5
30-60 minutes	4	7.0
1-2 hours	6	10.5
2-4 hours	38	66.7
More than 4 hours	7	12.3

AE: Angioedema.

inefficient administration of the medication as well as its inaccessibility. The latter problem can only be solved by health authorities changing the regulations so as to give permission to prescribe patients a sufficient amount of C1-inh concentrate for severe attacks. In 2012, the Hereditary Angioedema International Working Group suggested that in order for HAE patients to obtain proper treatment, patients should be given their drugs to treat HAE attacks as well as be educated on self-administering their drugs at home as early as possible (11). Another consensus encouraged similar recommendations: patients should always carry two doses of the drug for use as soon as an attack is recognized (12). The reports point out that the introduction of the home treatment has improved the quality of life of HAE patients in the United States and Denmark (13). Furthermore, the reports indicate that home treatment reduced the costs of HAE management (14).

Our study patients did not report any adverse events or rebound effects in the use of the drug. This finding can explain high satisfaction levels in patient responses. The safety and tolerability studies find that C1-inh concentrate was well tolerated (15,16). The adverse events rate was lower than 5% and the most frequent adverse events including respiratory infections, headache, sinusitis, and rash were characterized as mild (17). Most patients indicated that their symptoms began to resolve within a short time and were almost totally resolved in 4 hours, in accordance with the previously published report (18). The efficacy of a medication certainly enhances the level of patient satisfaction. In the United States, Riedl et al. assessed the satisfaction level of 50 patients; these researchers concluded that patients were fairly satisfied with the drug and the most important reasons for dissatisfaction centered around the administration of the drug, including its intraveous route and the time spent for infusion, in accordance with our research (19).

HAE is a debilitating chronic disease and misdiagnosis can lead to morbidity and mortality as well as deterioration in the patient's quality of life, depression, and anxiety (4,5). One of the major recommendations/findings is to increase the awareness of the disease among physicians for assuring the correct diagnosis. In the current study, the mean duration between the onset of the symptoms and diagnosis was 17.02±12.9 years, a period in accordance with the findings of a study from another big city of our country which reported approximately a 17-year delay in diagnosis (10). However, a previous study conducted in Turkey reported the mean diagnostic delay time as 26 years (20). These findings suggest a significant, although still insufficient, improvement in awareness of the disease, thus recommending the continuation of efforts to decrease diagnostic delay.

Although this is the first study assessing the Turkish HAE patients' perception about C1-inh concentrate (which is the major agent for treating acute HAE attacks), one limitation of this research is in the recall bias of HAE patients. To address this limitation, patients were asked to provide answers based on attacks occurring in the last year.

In conclusion, our HAE patients were generally satisfied with C1-inh concentrate in their attack treatments. They considered the drug sufficiently effective. However, their concerns relating to the low level of awareness of health care professionals about HAE and the difficulties for access to the medication need to be addressed.

ACKNOWLEDGMENTS

We thank the HAE patients who kindly replied to our survey.

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