



# Management of Patients with Hereditary Angioedema During the COVID-19 Pandemic

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## ABSTRACT

**Objective:** The aim of this study was to determine the clinical course and treatment outcomes of patients with hereditary angioedema (HAE) after infection with coronavirus disease 2019 (COVID-19).

**Materials and Methods:** Thirty-nine patients with HAE were included in this study. These patients were regularly followed up over phone calls since the first COVID-19 case was seen in our country. Patients were asked to visit the hospital if there was a history of contact with a confirmed COVID-19 patient or if the patient developed clinical symptoms of COVID-19.

**Results:** There were 21 (54%) patients with type I HAE, and 18 (46%) with type II HAE. All patients received treatment for angioedema attacks (C1-inhibitor [C1-INH], icatibant), and seven (20%) received long-term prophylaxis (danazol). Treatment for attacks was continued for all patients during the pandemic. Patients taking danazol were switched to long-term prophylaxis using the C1-INH concentrate. Eleven (28%) patients with HAE developed COVID-19 during this study. Only one patient had severe COVID-19. Six patients (54.5%) were diagnosed with type II HAE, and five (45.5%) were diagnosed with type I HAE. The most common COVID-19 symptoms were fever (7/11; 64%) and myalgia (6/11; 55%). Mild angioedema attacks were experienced by 36% (4/11) of the HAE patients diagnosed with COVID-19. Icatibant was used in all patients.

**Conclusion:** Agents used for HAE block the kallikrein-kinin system and may be useful in the treatment of COVID-19. Considering their beneficial effects on COVID-19, it is recommended that HAE patients should continue the use of agents blocking the kallikrein-kinin system.

**Keywords:** COVID-19, hereditary angioedema, kallikrein-kinin system, bradykinin, C1-INH

## INTRODUCTION

Hereditary angioedema (HAE) is an uncommon genetic disease characterized by repeated attacks of subcutaneous or submucosal edema and increased vascular permeability. HAE results from a deficiency (type I) or dysfunction (type II) in C1-inhibitor (C1-INH). Uncontrolled activity of plasma kallikrein causes excessive production of bradykinin (BK) and plays a fundamental role in the pathogenesis of HAE (1,2). BK is converted to des-Arg (9)-bradykinin (DABK) by plasma carboxypeptidase N or endothelial carboxypeptidase M. BK binds to bradykinin receptor B2 (B2R), and DABK binds to both bradykinin receptor B1 and B2R. The binding of BK and DABK to

their receptors causes vasodilatation and increases vascular permeability (3).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a messenger RNA virus that causes coronavirus disease 2019 (COVID-19). SARS-CoV-2 enters the host cells through the angiotensin-converting enzyme 2 (ACE-2) receptor and uses transmembrane protease serine 2 (TMPRSS2) to prepare the spike (S) protein. SARS-CoV-2 reduces the expression of ACE-2 in the plasma membrane of infected cells (4,5). The decrease in ACE-2 receptors results in the accumulation of DABK, which mediates pulmonary edema and inflammation, and potentially BK (6,7).

Due to the overlapping pathophysiological mechanisms, an interaction between HAE and COVID-19 is likely. However, few studies have been conducted on the course of COVID-19 in HAE patients. The aim of this study was to evaluate the course of COVID-19 in patients with HAE and determine changes in the treatment of HAE during the COVID-19 pandemic.

## MATERIALS and METHODS

### Study Design

This study included 39 patients with HAE being managed at the Allergy-Immunology Clinic. These patients were followed up with regular telephone calls from March 11, 2020, when the first COVID-19 case was documented in our country. This study was approved by the local ethics committee of Necmettin Erbakan University Meram Medical Faculty (decision no: 2020/2873).

### Data Collection

We recorded the patients' age, gender, HAE type, frequency of attacks, current treatment, and any changes in treatment. Patients with either a history of contact with a COVID-19 patient or symptoms suggestive of COVID-19 were asked to visit the hospital. COVID-19 was diagnosed using quantitative real-time PCR (RT-PCR) analysis of naso- and oro-pharyngeal swab samples and IgM or IgG SARS-CoV-2 serology.

### Statistical Analysis

The data obtained in this study were analyzed using SPSS version 22.0 (Armonk, NY: IBM Corp). Continuous variables are presented as the means  $\pm$  standard deviations or medians (range: min–max), and categorical variables are presented as numbers with percentages.

## RESULTS

### Demographics and Clinical Findings of Study Participants

This study included 39 patients, comprising 26 (67%) females and 13 (33%) males. The mean age of the included patients was  $39.5 \pm 13.1$  years (range: 19–66 years). Type I HAE was seen in 21 (54%) patients, and type II HAE was seen in 18 (46%) patients (Table I). The frequency of attacks increased in 16 (41%) patients during the pandemic (Table II).

Eleven (28%) patients with HAE were infected by COVID-19. The mean age of the HAE patients who were infected with COVID-19 was  $42.3 \pm 13.9$  years (range: 23–60 years); and there were 6 (54.5%) female and 5 (45.5%) male patients with COVID-19. Six patients (54.5%) had type II HAE, and five patients (45.5%) had type I HAE. Nine (82%) patients had COVID-19 as confirmed using RT-PCR, one (9%) had a positive IgM or IgG SARS-CoV-2 serology result, and one (9%) had a high clinical suspicion of COVID-19 based on suggestive symptoms and contact with confirmed COVID-19 cases (Table III).

**Table I: Demographic and clinical characteristics of patients with HAE.**

	n (%)
Age, years (mean $\pm$ SD)	39.5 $\pm$ 13.1
Gender	
Female	26 (67)
Male	13 (33)
HAE type	
Type I	21 (54)
Type II	18 (46)
Attack type	
Cutaneous	20 (51.3)
Cutaneous + gastrointestinal	14 (35.9)
Gastrointestinal	2 (5.1)
Cutaneous + upper airway	2 (5.1)
Cutaneous + gastrointestinal + upper airway	1 (2.6)
Treatment of attacks	
pd C1-INH	39 (100)
Icatibant	29 (74)
Long-term prophylaxis	
Danazol	7 (18)

HAE: Hereditary angioedema, pd C1-INH: Plasma-derived C1 inhibitor.

**Table II: Evaluation of the mental status of patients with HAE during the pandemic.**

	n (%)
Total	39
Increase in the frequency of attacks	16 (41)
Worrying about having a HAE attack	23 (59)
Reluctance to go to the hospital	15 (38.5)

HAE: Hereditary angioedema.

**Table III: Demographic and clinical characteristics of HAE patients infected with COVID-19.**

Case	Age	Gender	Comorbidities	HAE type	Treatment of attacks	LTP	COVID-19 test results	HAE attacks during COVID-19	Treatment of HAE attacks during COVID-19
1	60	F	DM, HT	Type II	pd C1-INH Icatibant	No	RT-PCR	Face Upper airway	Icatibant
2	59	F	No	Type I	pd C1-INH	No	IgM and/or IgG SARS-CoV-2 serology	No	
3	58	M	SLE	Type I	pd C1-INH Icatibant	No	RT-PCR	No	
4	50	M	HT	Type II	pd C1-INH Icatibant	Danazol	RT-PCR	No	
5	46	F	No	Type II	pd C1-INH Icatibant	Danazol	RT-PCR	Extremities Abdominal	Icatibant
6	45	M	No	Type I	pd C1-INH Icatibant	Danazol	RT-PCR	Extremities	Icatibant
7	40	F	No	Type I	pd C1-INH Icatibant	No	RT-PCR	No	
8	30	F	No	Type II	pd C1-INH Icatibant	No	RT-PCR	Extremities Abdominal	Icatibant
9	28	M	No	Type II	pd C1-INH Icatibant	No	RT-PCR	No	
10	26	M	No	Type II	pd C1-INH Icatibant	No	RT-PCR	No	
11	23	F	No	Type I	pd C1-INH	No	High clinical suspicion	No	

**HAE:** Hereditary angioedema, **COVID-19:** Coronavirus 2019 disease, **SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2, **pd C1-INH:** plasma-derived C1 inhibitor, **LTP:** Long-term prophylaxis, **RT-PCR:** Real-time polymerase chain reaction, **DM:** Diabetes mellitus, **HT:** Hypertension, **SLE:** Systemic lupus erythematosus.

The most frequent COVID-19 symptoms were fever (7 of 11; 64%), myalgia (6 of 11; 55%), sore throat (4 of 11; 36%), cough (4 of 11; 36%), dyspnea (1 of 11; 9%), generalized weakness (1 of 11; 9%), anosmia (1 of 11; 9%), and dysgeusia (1 of 11; 9%). One patient was managed in the COVID-19 intensive care unit (case 1) and another was managed in the non-intensive care unit (case 8). All other patients were treated at their homes.

#### Approach to Treatment for HAE During the Pandemic

Acute attacks of HAE were treated using plasma-derived (pd) C1-INH concentrate in all patients and icatibant in 29 (74%) patients. Seven patients (18%) were receiving long-term prophylaxis. The treatment of acute attacks has been unchanged for all patients during the pandemic. Danazol

that has been used for long-term prophylaxis was replaced with pd C1-INH concentrate (Table IV).

#### DISCUSSION

This is one of the few studies evaluating the approach toward the treatment of patients with HAE during the COVID-19 pandemic. Agents used in the treatment of HAE block the kallikrein-kinin system (C1-INH replacement therapy, icatibant, ecallantide, and lanadelumab), which may be a potential treatment target for COVID-19.

HAE is characterized by recurrent episodes of angioedema that can be potentially life-threatening. Mechanical trauma, physical stress, and mental stress are the most common triggers for HAE attacks (8). We found an increase in the number of attacks experienced by HAE patients during the pandemic. In addition, these patients

**Table IV: Comparison of the pre- and post-pandemic treatment of patients with HAE**

Treatment agent	The previous treatment, n (%)	The subsequent treatment, n (%)	Changes of treatment
<b>Treatment of attacks</b>			
pd C1-INH	39 (100)	39 (100)	Treatment continued
Icatibant	29 (74)	29 (74)	Treatment continued
<b>Long-term prophylaxis</b>			
Danazol	7 (100)	-	Danazol prophylaxis, replaced with C1-INH prophylaxis
pd C1-INH	-	7 (100)	

**HAE:** Hereditary angioedema, **pd C1-INH:** Plasma-derived C1 inhibitor.

had excessive fear of having an attack and avoided visiting the hospital. Our results suggest that even HAE patients who are not infected by COVID-19 may suffer from mental stress that can worsen their disease control.

In the 2019 update of the International Union of Immunological Societies phenotype classification system, HAE is classified as an inborn error of immunity and grouped with other complement deficiencies (9). There is no evidence that HAE patients have a higher risk of COVID-19 infection. However, due to their overlapping pathogenic mechanisms, COVID-19 may increase the frequency and severity of attacks in patients with HAE, and HAE may accelerate the progression of COVID-19 and be associated with more severe pulmonary involvement (10). Only one patient (case 1) met the National Institute of Health criteria for severe COVID-19 (11). This was an elderly patient who had multiple comorbidities and was not on any prophylactic treatment. He experienced a mild HAE attack during COVID-19. Contrary to previous reports, our patients did not experience severe HAE attacks or severe COVID-19. However, most of our patients were females and had an average age of less than 50 years.

Overactivation of the kallikrein-kinin system is correlated with severe COVID-19. Therefore, drugs targeting the kallikrein-kinin system, which are already in use by patients with HAE, may prevent or treat severe COVID-19 (12,13) (Figure 1). The mild course of COVID-19 in our HAE patients supports the use of these drugs for COVID-19.

Drugs used for HAE prevent the excessive production of BK. C1-INH blocks the production, replacement, and function of BK (14). The aim of treating HAE attacks is to reduce the severity and duration of angioedema, thereby preventing the morbidity and mortality of patients. Four first-line treatments are approved for HAE attacks:

intravenous pd C1-INH, intravenous recombinant human C1-INH, subcutaneous kallikrein inhibitor ecallantide, and subcutaneous B2R antagonist icatibant. Fresh frozen plasma contains C1-INH and can be used to treat HAE attacks if the first-line treatments are not available. In contrast to the treatment of HAE attacks, short-term prophylaxis aims to prevent attacks under conditions of expected stress, and long-term prophylaxis aims to reduce the number, severity, and burden of angioedema attacks (15,16).

By inhibiting both kallikrein and factor XIIa, C1-INH regulates the contact activation system and reduces BK formation (3). Some studies have suggested that blocking the kallikrein-kinin system with C1-INH in COVID-19 patients may prevent acute respiratory distress syndrome (17,18). The inhibitory effects of C1-INH on the contact activation, complement, fibrinolytic, and coagulation systems may be useful in the management of COVID-19 patients (19). C1-INH replacement in patients with COVID-19 may reduce coagulopathy by inhibiting factor XIIa, factor XIa, thrombin, tissue plasminogen activator, and plasmin. C1-INH replacement also regulates the coagulation and fibrinolytic systems (20). Therefore, C1-INH replacement in HAE patients with COVID-19 may reduce pulmonary complications by preventing the excessive production of BK. In addition, starting C1-INH replacement therapy early in the disease may prevent acute respiratory distress syndrome and reduce the need for intensive care and mechanical ventilation. Because of the potential beneficial effects of pd C1-INH replacement, we suggested all our patients to continue using it. Pd C1-INH can also be used as short-term prophylaxis for patients before invasive procedures and stressful events. In one of our patients, we administered pd C1-INH before a dental procedure, and the patient tolerated the procedure well with no adverse effects.





**Figure 2.** Case 1, thorax CT at diagnosis.

females (24). Therefore, androgen sensitivity may be a marker of the severity of COVID-19 (25). Androgens have an immunosuppressive effect and increase the expression of TMPRSS2, a co-receptor necessary for SARS-CoV-2 invasion (26). Because danazol has the potential to exacerbate the COVID-19 severity, patients are recommended to switch to other prophylactic treatments. However, danazol is unavailable in many countries. If there is no alternative available, danazol can be used with extreme caution and should be withheld if the patient comes in contact with a COVID-19 patient. Because pd C1-INH is available in our country, we switched danazol to pd C1-INH prophylaxis in all patients using danazol for long term prophylaxis.

Tranexemic acid (TA) is an antifibrinolytic agent, and it is the preferred long-term prophylaxis for HAE patients. TA reduces plasmin production and increases the risk of thrombosis, especially in patients with COVID-19 (27-29). None of our patients were using TA prophylaxis, and it is not recommended for use in HAE patients with COVID-19 infection. However, if it is necessary to use TA in patients with HAE infected with COVID-19, TA should be given with anticoagulant therapy.

Lanadelumab is a monoclonal antibody against plasma kallikrein. Although plasma kallikrein is necessary for the breakdown of high-molecular-weight kininogen into BK, plasminogen activates plasmin and affects the fibrinolytic pathway, leading to fibrin destruction (30,



**Figure 3.** Case 1, thorax CT after treatment.

31). It is not available in our country. However, similar to other therapeutic agents targeting the kallikrein-kinin system, lanadelumab may be useful for the prevention of acute respiratory distress syndrome. The results of an ongoing study on the use of lanadelumab for the treatment of COVID-19 (COVID-LAN) will provide further information on its use in patients with COVID-19 (32).

Because of the low prevalence of the disease, uncontrolled observational studies will be useful for determining the best management approach for COVID-19 in patients with HAE. Although clinical practices change rapidly and frequently, our study summarizes the treatments undertaken by our HAE patients during the pandemic (Table V). The main weakness of this study is the small sample size.

## CONCLUSION

During the pandemic, it is recommended to continue to use the drugs that block the kallikrein-kinin system in HAE patients. Future research should focus on evaluating the effectiveness of these drugs in patients with both HAE and COVID-19. When selecting a treatment option for HAE patients during the pandemic, drugs that can be administered at home without hospital visits are preferred. There are inadequate data on the risk and disease course of COVID-19 in HAE patients. More studies are needed to lower the risk of severe COVID-19 and reduce the frequency of angioedema attacks in patients with HAE and COVID-19.

**Table V: Treatment recommendations for HAE during the pandemic.**

		Treatment recommendations
<b>C1-INH</b>	Replacement therapy Prevents excessive BK production Used for attack, short-term and long-term prophylaxis	We recommend to continue It may be useful in preventing pulmonary complications in COVID-19
<b>Icatibant</b>	Bradykinin B2 receptor antagonist It is administered SC by the patient Used for treatment of attacks	We recommend to continue It may be useful in preventing pulmonary complications in COVID-19
<b>Ecallantide</b>	Recombinant plasma kallikrein inhibitor By binding to kallikrein, it prevents kininogen converting to bradykinin Ecallantide has been approved for the treatment of HAE acute attacks in patients aged $\geq 12$ years Care should be taken due to the risk of anaphylaxis	We recommend to continue It may be useful in preventing pulmonary complications in COVID-19
<b>FFP</b>	Contains C1-INH Can paradoxically worsen the attack	It can be used for attack treatment when first-line treatments are not available
<b>Lanadelumab</b>	Plasma kallikrein monoclonal antibody Used for long-term prophylaxis in HAE patients aged $\geq 12$ years	We recommend to continue It may be useful in preventing pulmonary complications in COVID-19
<b>Danazol</b>	Attenuated androgen Increases C1-INH level Accelerates BK breakdown Used for short-term and long-term prophylaxis	We recommend switching to other prophylaxis treatments When there is no alternative treatment, it should be used with care or only terminated in patients who have been in contact with COVID-19
<b>TA</b>	Antifibrinolytic Prevents BK formation Used for long-term prophylaxis Risk of thrombosis	We do not recommended its use; if used, it should be used with concomitant anticoagulants

**HAE:** Hereditary angioedema, **COVID-19:** Coronavirus 2019 disease, **BK:** Bradykinin, **C1-INH:** C1 inhibitor, **FFP:** Fresh frozen plasma, **TA:** Tranexamic acid.

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