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Inês C. Farinha[1], Beatriz Tavares[1], Nuno Sousa[2], Eugénia Almeida[3], Carlos Lozoya[4,5], Frederico S. Regateiro[1,6,7], Ana Todo-Bom[1,8], Emília Faria[1]

# COVID-19 infection and vaccination in patients with hereditary angioedema: a multicentric study

[1]Department of Allergy and Clinical Immunology, Coimbra Hospital and University Centre, Coimbra, Portugal
[2]Unit of Allergy and Clinical Immunology, Leiria Hospital Centre, Leiria, Portugal
[3]Unit of Allergy and Clinical Immunology, Tondela-Viseu Hospital Centre, Viseu, Portugal
[4]Department of Allergy and Clinical Immunology, Castelo Branco Local Health Unit, Castelo Branco, Portugal
[5]Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal
[6]Institute of Immunology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[7]ICBR, Coimbra Biomedical and Clinical Research Institute, University of Coimbra, Coimbra, Portugal
[8]Department of Immunoallergology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

**Key words**

*COVID-19; hereditary angioedema; prophylaxis SARS-CoV-2; vaccination.*

**Corresponding author**
Inês Filipa da Costa Farinha
Department of Allergy and Clinical Immunology
Coimbra Hospital and University Centre
Praceta Prof. Mota Pinto
3000-075 Coimbra, Portugal
ORCID: 0000-0002-0427-8814
E-mail: ines_farinha9@hotmail.com

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**Impact statement**

*Patients with HAE can safely receive COVID-19 vaccination. The severity of COVID-19 infection does not appear to be increased in HAE patients.*

***Summary***

***Background.*** *Due to similarities between the pathophysiological mechanisms of hereditary angioedema and COVID-19, it has been hypothesized that SARS-CoV-2 infection may trigger HAE attacks or, alternatively, that HAE patients may experience different of COVID-19 disease severity. Furthermore, the potential for COVID-19 vaccination to trigger angioedema attacks in patients with HAE is still not completely defined.* ***Methods.*** *Retrospective observational, descriptive, non-interventional, multicenter study conducted in four Allergy Units and Departments in Central Portugal between March 2020 and July 2022. HAE patient data were obtained from electronic medical records.* ***Results.*** *The study included 34 patients (67.6% female): 26 with HAE type 1, 5 with HAE type 2, and 3 with HAE with normal C1 inhibitor. Most patients with HAE type 1 and 2 were receiving long-term prophylaxis. Among the 32 patients who received COVID-19 vaccination, 86 doses, were administered with one angioedema attack (1.2%) associated with vaccination. A small increase in the average number of attacks was observed in the year following COVID vaccination (7.1 versus 6.2 in the previous year, p = 0.029), however, this difference is unlikely to be clinically significant, as the context of the COVID-19 pandemic likely introduced numerous confounders. During the study period, 16 HAE patients had COVID-19, all presenting with mild disease. Four out of 16 patients (25%) reported angioedema attacks during COVID-19, and 43.8% during the convalescence period (3 months after infection).* ***Conclusions.*** *Patients with HAE can safely receive COVID-19 vaccination. The severity of COVID-19 infection does not appear to be increased in HAE patients.*

**Introduction**

Hereditary angioedema (HAE) is a rare genetic disease characterized by recurrent, disabling and potentially fatal episodes of mucocutaneous swelling as a consequence of a transient increase in vascular permeability mediated by bradykinin (1, 2). Angioedema episodes are largely unpredictable and generally affect well-defined cutaneous-mucosal areas, predominantly the face, lips, tongue, larynx, abdomen, extremities, and genital areas, but may involve any part of the body. Angioedema attacks are usually self-limited, lasting 1 to 5 days with a very variable duration of inter-critical periods. However, potentially life-threatening attacks may occur. HAE is associated with professional incapacity, decreased quality of life, and with significant physical and emotional burdens for patients and families (1). HAE accounts for only about 2% of all cases of recurrent angioedema. In most cases there are other affected relatives with HAE, but the absence of a family history does not exclude the diagnosis, as about 25 to 30% of the cases are caused by *de novo* mutations (1, 2). Therefore, all patients with recurrent angioedema or unexplained abdominal pain in the absence of urticaria must be assessed for C1 inhibitor deficiency, as mutations of this protease inhibitor account for more than 95% of the HAE cases.

The differential diagnosis of HAE includes other types of angioedema, such as, acquired angioedema, drug-induced angioedema, allergic reactions, chronic urticaria, idiopathic histaminergic angioedema, superior vena cava syndrome or myxedema.

An early diagnosis is fundamental to prevent fatal outcomes. The diagnosis of HAE is typically made by measuring serum levels of C4 complement, C1 inhibitor, and functional C1 inhibitor (1, 2). HAE is classified into three types based on the results of serum complement fraction assays: type I or quantitative HAE, type II or qualitative HAE, and HAE with normal complement. Studies report widely varying prevalence rates of type I and II HAE, ranging from 1:50,000 to 1:100,000 (3). The prevalence of HAE with normal complement is unknown, but it is presumed to be much lower (3). In Portugal, there are an estimated 200 to 300 people with HAE (1). Among a cohort of 138 Portuguese patients with HAE, 94 single mutations were observed, corresponding to 22 different pathogenic mutations, of which 64% were not yet described in the HAE database (4).

Angioedema flares may occur spontaneously, but they are often triggered by various factors, including emotional stress, medical or surgical procedures, infections, pain, physical trauma or certain drugs (such as oral contraceptives, hormone replacement therapy and angiotensin-converting enzyme inhibitors) (2). In some cases, flares may be preceded by prodromal signs or symptoms, such as extreme fatigue, mood swings, pain, and *erythema marginatum*, among others.

The management of HAE involves regular reassessments and individualization of therapy based on the frequency, severity and location of attacks, as well as the patient's clinical profile (*e.g.*, age, sex, comorbidities and preferences). Treatment should include: 1) general measures to minimize trigger, 2) on-demand treatment, 3) short-term prophylactic therapy, and 4) long-term prophylactic therapy, when needed to control symptoms, reduce risk of future attacks and minimize adverse drug effects (1, 2).

According to existing consensus, HAE patients must receive short-term prophylaxis before dental, surgical, endoscopic and other minimally invasive procedures involving the head and/or neck (1, 2). This has been shown to effectively prevent HAE exacerbations and related complications. However, current guidelines do not provide guidance on some other potential situations for prophylaxis, *e.g.*, prior to administration of COVID-19 vaccines (5).

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which was declared a global pandemic on 11 March 2020 (6). While most infected individuals exhibit mild to moderate symptoms, a subset of patients develop severe symptoms that require medical assistance. The discovery that SARS-CoV-2 interacts with the angiotensin-converting enzyme 2 receptor in the context of the COVID-19 has led to the hypothesis that this infection may provoke angioedema attacks or result in more severe symptoms in HAE patients (6-8).

There are only some studies examining the frequency of angioedema attacks in HAE patients during COVID-19. Most published literature contradicts the hypothesis that HAE patients experience more severe clinical symptoms of COVID-19 or have worse outcomes than the general population without HAE (7, 9). Vaccination has emerged as a crucial strategy in the fight against COVID-19, with several vaccines approved by the European Medicines Agency (EMA) and administered to the general population in Portugal and globally. INFARMED, the Portuguese regulatory agency, has approved five vaccines to date for COVID-19: two modified nucleoside mRNA vaccines (Comirnaty/Pfizer and Spikevax/Moderna); one recombinant Chimpanzee adenovirus vector vaccine (Vaxzevria/AstraZeneca); one with recombinant adenovirus vector type 26 (Johnson & Johnson/Janssen); and, more recently, a vaccine with a laboratory-created version of the SARS-CoV-2 spike protein and adjuvant (Nuvaxovid/Novavax) (10).

The necessity for short-term prophylaxis before administering COVID-19 vaccines to patients with hereditary angioedema (HAE) has been debated. Some of these vaccines have been associated with a higher frequency of adverse effects than other vaccines (5). Additionally, mRNA vaccines might have an associated risk of HAE attacks as RNA is known to serve as a potent stimulator of the contact activation system (5).

The objective of this study was twofold: 1) to investigate the clinical features associated with COVID-19 in HAE patients under the care of Allergy and Clinical Immunology Depart-

ments and Units in the Central region of Portugal, and 2) describe the adverse effects of COVID-19 vaccination in these patients, such as the potential onset of angioedema attacks.

## Materials and methods

### *Study type and study population*

This was a multicenter, observational, retrospective, descriptive, and non-intervention study conducted in four Allergy and Clinical Immunology Departments and Units of four Hospital Centers in the Central region of Portugal.

Data were retrieved from electronic medical records of patients diagnosed with hereditary angioedema, based on the latest guidelines of the World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) (2). The patients were under follow-up in the Immunoallergology (Allergy and Clinical Immunology) consultations between March 2020 and July 2022. Patients with differential diagnoses of hereditary angioedema were excluded.

This study protocol was reviewed and approved by the competent Ethical Committees and was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

### *Study variables*

The study analyzed the following variables based on the patients' clinical records: gender, current age, angioedema classification, as per international and national consensus (1, 2), age of symptom onset, age at diagnosis, location of angioedema attacks and their frequency (number of episodes per year based on medical records of each appointment and episodes of Emergency Department), laboratory data (C4 and C1 inhibitor dosing, C1 inhibitor function), comorbidities, long-term and short-term pre-COVID-19 vaccination prophylactic treatment, doses and which vaccine was administered, attacks in the context of vaccination (considered if occurred in 2 days after vaccination), their severity (mild, moderate or severe according interference with daily activities) and therapy, hypersensitivity reaction to vaccine, adverse effects to vaccine, frequency of attacks in the year before the 1st dose of vaccine and in the year after (number of episodes based in medical records of each appointment and episodes of emergency department), occurrence of SARS-CoV-2 infection (based in a positive viral test either a reverse-transcription polymerase chain reaction (RT-PCR) assay or an antigen test), its severity and symptomatology (based in classification in Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (11)), attacks during and after infection, and need for treatment.

The severity of disease was classified using the criteria published by Agostoni *et al.* and translated by Cadinha *et al*. (12), based on a score defined by the duration of angioedema attacks and their severity (mild − discomfort, no interference with daily activities; moderate − sufficient discomfort to limit daily activities; severe − inability to work or carry out daily activities), need for conservative emergency or replacement treatment, need for invasive emergency treatment such as intubation or tracheostomy, long-term prophylaxis for more than 6 months or for a period of 3 to 6 months. The total score allows classified patients from class 5 (asymptomatic) to class 1 (severe).

### *Statistical analysis*

The statistical analysis was carried out using IBM SPSS Statistics®, version 27.0. All data were analyzed in an anonymized form. The frequencies of nominal variables were calculated, while medians and ranges were determined for continuous variables. Normality of continuous variables' distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using the non-parametric Wilcoxon test. Statistical significance was defined as $p < 0.05$.

## Results

Thirty-four patients were enrolled in the study (67.6% female). The median current age of the patients was 40 years (IQR 26-51 years), and the median age at diagnosis was 26 years (IQR 15-32). On average, there was a 10-year delay between the onset of symptoms and the time of diagnosis. **Table I** provides a summary of the demographic, clinical characteristics and therapeutic approach of HAE patients.

The study population comprised 26 patients with HAE type I, 5 patients with HAE type II, and 3 patients with HAE with normal complement, one of whom with a pathogenic mutation of *SERPING1* gene.

Among patients with HAE type I and II, the majority (n = 19, 61.3%) were receiving long-term prophylaxis with attenuated androgens (danazol), while 5 were treated tranexamic acid. Seven patients were not receiving any long-term prophylactic therapy.

Regarding the severity of the disease, three patients presented with class 5 criteria (asymptomatic), four with class 4 (minimal), one with class 3 (mild), twenty-three with class 2 (moderate) and three with class 1 (severe). Twelve patients reported at least one episode of laryngeal edema during their lifetime. Nineteen patients had comorbidities, including twelve with rhinitis/rhinosinusitis, five with autoimmune disease, three with cardiovascular disease, two with asthma, one with obesity, and one with psychiatric disease.

As rare cardiovascular events have been reported as an adverse effect of androgen therapy, it is noteworthy that in our sample, several patients had significant cardiovascular past history: one patient had cerebrovascular thrombosis and myocardial infarction, another patient had myocardial infarction, and a third

***Table I*** *- Demographic and clinical characteristics and therapeutic approach of HAE patients.*

| Characteristics | |
|---|---|
| Total, n (%) | 34 (100) |
| Female, n (%) | 23 (67.6) |
| Age (years), median (IQR) | 40 (26-51) |
| Comorbidities, n (%) | 19 (55.9) |
| Classification | - |
| Type I, n (%) | 26 (76.5) |
| Type II, n (%) | 5 (14.7) |
| Type III, n (%) | 3 (8.8) |
| Age at onset of symptoms (years), median (IQR) | 14 (9-19) |
| Age at diagnosis (years), median (IQR) | 26 (15-32) |
| Time between symptom onset and diagnosis (years), median (IQR) | 5 (1-17) |
| Preferred locations of angioedema attacks | - |
| Face, n (%) | 11 (32.4) |
| Extremities, n (%) | 23 (67.6) |
| Abdomen, n (%) | 15 (44.1) |
| At least one episode of laryngeal edema, n (%) | 12 (35.3) |
| Severity of disease | - |
| Class 1 (severe), n (%) | 3 (8.8) |
| Class 2 (moderate), n (%) | 23 (67.6) |
| Class 3 (mild), n (%) | 1 (2.9) |
| Class 4 (minimal), n (%) | 4 (11.8) |
| Class 5 (asymptomatic), n (%) | 3 (8.8) |
| Long-term prophylactic therapy, n (%) | 27 (79.4) |
| Danazol, n (%) | 20 (58.8) |
| Tranexamic Acid, n (%) | 5 (14.7) |
| C1 inhibitor concentrate, n (%) | 2 (5.9) |

n: number of cases; IQR: Interquartil range.

required pacemaker implantation due to arrhythmia. However, it is difficult to establish a causal relationship between androgen therapy and these events.

A total of 27 patients received at least one dose of mRNA vaccine, with 23 of them receiving Comirnaty/Pfizer vaccine and 4 patients receiving Spikevax/Moderna vaccine. Six patients received at least one dose of a vectored vaccine, with 3 patients receiving Vaxzevria/AstraZeneca vaccine and 3 patients receiving Johnson & Johnson/Janssen vaccine. Two patients refused COVID-19 vaccination. Data regarding the type of vaccine and number of doses administered are summarized in **table II**. None of the patients reported a prior SARS-CoV-2 infection before completing the primary vaccination.

Out the 32 patients who received COVID-19 vaccination, a total of 86 vaccine doses were administered. None of the patients reported suspected hypersensitivity reactions to the vaccine. However, twenty-one patients reported other mild adverse effects, such as pain at the administration site, myalgia, fatigue and fever.

None of the patients received pre-vaccination prophylaxis with C1 inhibitor concentrate. However, four patients were given short-term pre-vaccination prophylaxis with increased doses of danazol on the five days prior to the vaccination procedure and continued for three days after the procedure.

Among the study population, one case of angioedema attack was reported in association with COVID-19 vaccination (1 in 86 vaccine administrations, 1.2%). The affected patient was a 40-year-old woman with HAE with normal complement serum levels and C1 inhibitor function but with a pathogenic *SERPING1* mutation, and she was on long-term prophylaxis with twice weekly C1 inhibitor concentrate. The attack started 2 hours after the first dose of an mRNA vac-

***Table II*** *- COVID-19 vaccination in HAE patients*.*

| Characteristics | Total | mRNA vaccine | Vectored vaccine |
|---|---|---|---|
| Total doses, n (%) | 86 | 76 (88.4) | 10 (11.6) |
| 1st dose | 32 | 26 | 6 |
| 2nd dose | 29 | 27 | 2 |
| 3rd dose | 25 | 23 | 2 |
| Previous SARS-CoV-2 infection | 0 | 0 | 0 |
| Vaccination adverse effects | 21 | 17 | 4 |
| Hypersensitivity reaction | 0 | 0 | 0 |
| Angioedema attacks | 1 | 1 | 0 |
| Long-term prophylaxis | 27 | 22 | 5 |
| Short-term prophylaxis | 4 | 2 | 2 |

*Two patients decided not to be vaccinated against COVID-19.

cine (Comirnaty/Pfizer), with swelling localized to the abdominal region and rated as mild in severity. The patient did not require additional therapy or specialized medical care. Subsequently, the patient received the 2nd and 3rd doses of the same vaccine, without short-term prophylaxis, and there were no associated angioedema attacks.

The frequency of angioedema attacks per year showed significant variability among patients. Most patients (22 out of 32, two patients were excluded from this analysis due to missing data) experienced 0-3 attacks per year, whereas four patients experienced more than 20 attacks per year. We compared the number of angioedema attacks in the year before and after the first dose of vaccine. Eighteen patients experienced an identical number of episodes in both the year before and after vaccination, three patients had fewer episodes in the year following vaccination (two had one episode less, one had two), while 11 had more episodes (six had one episode more, one had two, one had three, one had six, one had seven, and one had eight). The average number of attacks in the year preceding vaccination was 6.2 (standard deviation 2.14, 95% confidence interval (CI) 1.82-10.55) with a median of 1.5. During the year after vaccination, the mean number of attacks was 7.1 (standard deviation 2.13, 95%CI 2.72-11.40) with an identical median of 1.5. Although a statistically significant difference was detected (p = 0.0278, Wilcoxon signed-rank test), the magnitude of the observed difference was unlikely to be clinically significant, as further discussed below.

***Table III*** *- Clinical characteristics and management of HAE patients with SARS-CoV-2 infection.*

| Id | Age/Sex | Comorbidities | Type AEH | Severity of AEH | Long term prophylaxis | COVID-19 infection | | Attacks* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Main symptoms | Severity | During | After |
| 1 | 38M | No | I | Moderate | Danazol | Fever, myalgia, rhinorrhea | Mild | No | Yes |
| 2 | 61F | Asthma | III | Severe | C1 inhibitor | Dyspnea, myalgia | Mild | Yes | No |
| 3 | 40F | No | II | Minimal | No | Odynophagia, fatigue | Mild | No | Yes |
| 4 | 32M | No | III | Moderate | Danazol | Fever, rhinorrhea | Mild | Yes | Yes |
| 5 | 48F | Rhinitis | I | Severe | Danazol | Myalgia | Mild | No | No |
| 6 | 40F | Rhinitis | I | Minimal | No | Headache | Mild | No | No |
| 7 | 48M | MI | I | Moderate | Danazol | Myalgia | Mild | No | No |
| 8 | 23F | Rhinitis | I | Severe | Tranexamic A. | Headache, rhinorrhea | Mild | No | Yes |
| 9 | 35F | Rhinitis | I | Moderate | Danazol | Rhinorrhea | Mild | No | Yes |
| 10 | 24F | Rhinitis | I | Moderate | Danazol | Headache, myalgia, fatigue | Mild | No | Yes |
| 11 | 32M | Rhinitis and asthma | I | Moderate | Danazol | Headache, myalgia | Mild | No | No |
| 12 | 52F | No | I | Moderate | Danazol | Fever, cough, rhinorrhea | Mild | No | No |
| 13 | 40F | AI | III | Moderate | C1 inhibitor | Fever, headache, myalgia | Mild | Yes | Yes |
| 14 | 52F | No | I | Moderate | Danazol | Fever, myalgia | Mild | No | No |
| 15 | 24F | No | I | Asymptomatic | No | Fever, headache, Odynophagia | Mild | No | No |
| 16 | 45F | No | I | Moderate | Danazol | Cough, rhinorrhea, myalgia | Mild | Yes | No |

F: female; M: male; MI: acute myocardial infarction; AI: autoimmune disease; *no patient received prophylactic therapy to prevent angioedema attacks during the infection.

We did not find a significant correlation between the severity classification of HAE disease and an increase in reported attacks during the year after the first dose of the vaccine ($r = -0.245$, $p = 0.177$).

During the study period, 16 HAE patients (75% female; median age of 40 years) were diagnosed with COVID-19. All of the patients had symptomatic mild disease (**table III**). The most frequent symptoms were myalgias (9 of 16 (56%)), fever, headache, odynophagia, nasal congestion/rhinorrhea (each 6 of 16 (38%)), and fatigue (2 of 16 (13%)). None of the patients required medical intervention for COVID-19. However, in our sample, 10 out of 16 (62.5%) patients who became infected were receiving prophylactic danazol therapy, and none experienced more severe infection or complications.

Four out of 16 patients (25%) reported angioedema attacks during the COVID-19, with 3 experiencing mild and 1 moderate attacks, none of them requiring hospitalization. Treatment was necessary in two patients (one patient increased the dose of attenuated androgens and another patient received C1 inhibitor concentrate replacement), while 2 did not require any specific treatment. The most common sites of angioedema among the patients who had flares were the face and extremities.

Seven out of 16 patients (43.8%) reported flares during the COVID-19 convalescence period (which was assessed 3 months after infection), and three of them required adjustments to their prophylactic therapy and on demand treatment. Most patients (5 out of 7) experienced 1-2 attacks, while two patients experienced 4-6 attacks. We compared the number of angioedema attacks in the 3 months before and after infection. Five patients experienced an identical number of episodes in both periods, seven patients had fewer episodes in the convalescence period, while four had more episodes. The average number of attacks was 1.6 *versus* 0.5 in the 3 months before and after infection, respectively.

## Discussion

This is the first national study in Portugal to assess the impact of the COVID-19 pandemic on acute attacks in HAE patients, including the effects of SARS-CoV-2 infection and of COVID-19 vaccination.

In our study population (most of which was on long-term prophylactic therapy), both the mRNA and adenoviral vector-based COVID-19 vaccines were found to be safe and well tolerated in HAE patients, with only one patient (1.2% of administrations) reporting a mild angioedema flare, that did not require any treatment.

In our study population, we observed a very low number of attacks per year (69% reported 0 to 3 attacks per year, or less than one attack every 4 months) and only four patients experienced more than 20 attacks per year during the study period.

Most of the patients in our study reported a comparable number of angioedema attacks both before and after COVID-19 vaccination. Specifically, 56% of patients experienced the exact same number of episodes in both years in our study, while the remaining patients reported only minor variations in the number of episodes. Most published studies only analyze the number of angioedema attacks reported after administration of COVID-19 vaccines (13). One study compared the number of angioedema attacks a month before and after the first, second and third doses of COVID-19 vaccines, and concluded that COVID-19 vaccination did not increase the frequency of HAE attacks (14).

Although we did observe a small increase in the average number of angioedema attacks during the years before and after vaccination, this difference is unlikely to be clinically significant, as the context of the COVID-19 pandemic likely introduced numerous uncontrolled variables in our retrospective study. For example, the implementation of lockdowns and reduced mobility and professional exposures, and the well-known reduced number of infections, may have led to a lower incidence of angioedema attacks in the year before vaccination. Additionally, reduced access to medical care before mass vaccination may have influenced the reporting of episodes. It is also possible that increased awareness of health issues after vaccination may have contributed to a higher reporting of episodes. COVID-19 pandemic significantly limited the availability of HAE medical care worldwide (8). This was primarily due to the strain on healthcare resources caused by the pandemic, as well as the implementation of social distancing measures, which have prevented on-site clinical visits and treatments for HAE patients.

Regarding COVID-19 infection, all HAE patients in our study who contracted COVID-19 were symptomatic but experienced only mild symptoms. Importantly, our study sample consisted of predominantly female patients with a median age of 40 years, who had no additional risk factors for severe COVID-19 disease (15). Our findings support previous research indicating that HAE patients typically experience mild COVID-19 symptoms and infrequent angioedema attacks during infection, even in the absence of short-term prophylactic therapy (7-9, 16).

In our cohort, 75% (12/16) of the patients did not report angioedema flares during SARS-CoV-2 infection. This rate is not statistically different from those reported in previous studies by Can Bostan *et al*. (50%, 5/10) (7), Belbezier *et al*. (69%, 9/13) (17), and Grumach *et al*. (62%, 8/13) (9). It is noteworthy that 13 out of 16 patients were on long-term prophylactic treatment, which may have contributed to the low incidence of angioedema flares during the infection. Of the three patients without long-term prophylaxis who developed COVID-19, none experienced angioedema attacks during the infection, and only one patient reported an attack during the convalescence period.

During the COVID-19 pandemic, there were concerns about the use of danazol, an attenuated androgen, due to its potential to inhibit the antiviral immune response to SARS-CoV-2 or alter the expression of the TMPRSS2 receptor, which is used by the virus. Some experts recommended caution or discontinuation of danazol in HAE patients who become infected with SARS-CoV-2 (18), however, none of 62.5% patients on prophylactic danazol that were infected experienced more severe infection or complications.

Several studies suggest that HAE patients in the convalescent phase of COVID-19 are more susceptible to experiencing acute angioedema attacks (7, 17). Within our study population, 43.8% of patients reported angioedema attacks during the convalescence period of their COVID-19 disease. This rate is similar to that reported in a cohort of 13 patients, where four patients (30.8%) experienced HAE attacks during their COVID-19 convalescence, and the difference is not statistically significant (15). Most patients experienced an equal or smaller number of episodes during the convalescence period compared to the same time period before infection, indicating that convalescence does not appear to significantly increase the risk of attacks.

In conclusions, this study provides further evidence that HAE patients do not have an increased risk of acute attacks during COVID-19 vaccination and can safely receive the vaccine against COVID-19 without requiring short-term prophylaxis. Our findings also suggest that COVID-19 symptoms are not more severe in HAE patients, which is consistent with other international studies with small samples. We observed a small increase in the number of reported attacks in the year following vaccination that is unlikely to be clinically significant, as the context of the COVID-19 pandemic likely introduced numerous societal/professional/psychologic uncontrolled and possible confounders variables during the pandemic/lockdowns.

This is the first study in Portugal to investigate the differences in the frequency of angioedema attacks in HAE patients related to COVID-19 infection and vaccination. Further studies will be required to assess the long-term impact of COVID-19 vaccination and SARS-CoV-2 infection on the frequency and severity of angioedema attacks in HAE patients.

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None.

**Contributions**

ICF: investigation, data curation, methodology, writing - original draft, conceptualization, visualization. BT: conceptualization, methodology, resources, writing - review & editing. NS, EA, CL: resources. FSR: resources, methodology, writing - review & editing. AT-B: supervision. EF: conceptualization, resources, writing - review & editing, supervision.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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