

Original Article

Diagnosis, Course, and Management of Angioedema in Patients With Acquired C1-Inhibitor Deficiency

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What is already known about this topic? Acquired angioedema due to C1-inhibitor deficiency (C1-INH-AAE) is a rarer disease than hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE). Clinical manifestations are similar in the 2 forms; however, onset of symptoms is later, family history of angioedema is absent, and facial edema is more frequent in C1-INH-AAE.

What does this article add to our knowledge? The diagnosis of C1-INH-AAE has improved in the recent past: 35% of the patients (27 of 77) were diagnosed in the last 5 years, and patients were diagnosed earlier than expected (within 2 years of symptom development).

How does this study impact current management guidelines? Currently available treatments for acute management of C1-INH-HAE including plasma-derived C1-inhibitor concentrate, icatibant, and ecallantide (limited clinical experience) were successfully used in C1-INH-AAE; tranexamic acid was more effective than androgens for long-term prophylaxis.

BACKGROUND: Acquired angioedema due to C1-inhibitor deficiency (C1-INH-AAE) is a rare disease with no prevalence data or approved therapies.

OBJECTIVE: To report data on patients with C1-INH-AAE followed at Angioedema Center, Milan (from 1976 to 2015).

METHODS: Diagnostic criteria included history of recurrent angioedema without wheals; decreased C1-INH antigen levels and/or functional activity of C1-INH and C4 antigen less than 50% of normal; late symptom onset (>40 years); no family history of angioedema and C1-INH deficiency.

RESULTS: In total, 77 patients (58% females; median age, 70 years) were diagnosed with C1-INH-AAE and 675 patients with

hereditary angioedema due to C1-INH deficiency (C1-INH-HAE) (1 patient with C1-INH-AAE/8.8 patients with C1-INH-HAE). Median age at diagnosis was 64 years. Median time between symptom onset and diagnosis was 2 years. Sixteen patients (21%) died since diagnosis, including 1 because of laryngeal edema. Angioedema of the face was most common (N = 63 [82%]), followed by abdomen (N = 51 [66%]), peripheries (N = 50 [65%]), and oral mucosa and/or glottis (N = 42 [55%]). Forty-eight of 71 patients (68%) had autoantibodies to C1-INH. In total, 56 patients (70%) used on-demand treatment for angioedema including intravenous pdC1-INH 2000 U (Berinert, CSL Behring, Marburg, Germany) (N = 49) and/or subcutaneous icatibant 30 mg (Firazyr, Shire; Milano, Italy) (N = 27). Eventually, 8 of 49 patients receiving pdC1-INH became nonresponsive; all had autoantibodies. Thirty-four patients received long-term prophylaxis with tranexamic acid (effective in 29) and 20 with androgens (effective in 8).

CONCLUSIONS: The incidence of C1-INH-AAE was 1 for every 8.8 patients with C1-INH-HAE. Thirty percent of the deaths were related to the disease. Treatments approved for C1-INH-HAE are effective in C1-INH-AAE, although with minimal differences. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Acquired angioedema; C1-INH deficiency; Prevalence; Treatment; Diagnosis

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Abbreviations used*ACE-I*- Angiotensin-converting enzyme inhibitor*C1-INH*- C1-inhibitor*C1-INH-AAE*- Acquired angioedema due to C1-inhibitor deficiency*C1-INH-HAE*- Hereditary angioedema due to C1-inhibitor deficiency*IQR*- Interquartile range*pdC1-INH*- Plasma-derived C1-inhibitor concentrate

observed in C1-INH-AAE are similar to those observed in the hereditary form of C1-INH deficiency (hereditary angioedema due to C1-inhibitor deficiency [C1-INH-HAE]), which is also a rare disease with an estimated prevalence of around 1:50,000 of the global population.² There are no epidemiological data on the prevalence of C1-INH-AAE in the general population, but data from limited case series suggest that it occurs less frequently than C1-INH-HAE.

In C1-INH-AAE, synthesis of the C1-INH protein is normal, but its catabolism is increased.³ C1-INH-AAE has been described in association with various diseases, most commonly with non-Hodgkin lymphoma.⁴ Other B-lymphocyte-related abnormalities, such as production of neutralizing C1-INH autoantibodies and monoclonal gammopathy of undetermined significance, are often encountered in patients with C1-INH-AAE.^{5,6} These associated conditions have been demonstrated to induce C1-INH consumption and may contribute to the disease pathogenesis.⁷⁻¹⁰ Development of C1-INH deficiency leads to activation of the contact system and consequent episodic production of bradykinin and development of angioedema, similar to that observed in C1-INH-HAE.¹¹

As in C1-INH-HAE, symptoms of C1-INH-AAE include recurrent cutaneous swellings; edema of the gastrointestinal mucosa causing temporary bowel obstruction with colicky abdominal pain, vomiting, and/or diarrhea; and life-threatening laryngeal edema. Differently from C1-INH-HAE where most patients become symptomatic within the second decade of life, symptom onset occurs after the fourth decade of life in 90% of patients with C1-INH-AAE and family history of angioedema is absent.²

Patients with C1-INH-AAE have decreased plasma levels of C1-INH, as well as C1-INH antigen and/or C1-INH function and C4 antigen below 50% of normal. Because of deep complement consumption in the classical complement pathway, C1q is also markedly below 50%, a feature rarely present in C1-INH-HAE.⁴ Furthermore, autoantibodies to C1-INH are frequently detected and may serve to confirm the diagnosis. When C1-INH autoantibodies are absent and other clinical and biochemical characteristics are not confirmatory for diagnosis, genotyping to exclude mutations in the C1-INH gene (*SERPING1*) may be necessary to rule out C1-INH-HAE.

Because clinical trials have not been performed, no therapies are specifically approved for C1-INH-AAE, although it is assumed that drugs used in C1-INH-HAE may be similarly effective in C1-INH-AAE.¹² Plasma-derived C1-INH concentrate (pdC1-INH; Berinert, CSL Behring, Marburg, Germany) and the antagonist of the bradykinin B2 receptor, icatibant (Firazyr, Shire, Milano, Italy), are used off-label to treat acute angioedema attacks of C1-INH-AAE, and tranexamic acid or androgens for long-term prophylaxis.

To improve the understanding of the landscape of C1-INH-AAE, we report data on 77 patients followed at our angioedema center in Milan.

METHODS**Patients**

Patients diagnosed with C1-INH-AAE from 1976 and followed until 2015 were included in this study. Diagnosis was based on personal history of recurrent angioedema without wheals and decreased plasma levels of C1-INH antigen and/or functional activity of C1-INH and C4 antigen below 50% of normal, similar to patients with C1-INH-HAE type I/II.¹³ Differently from C1-INH-HAE, all patients with C1-INH-AAE had no family history of angioedema and a later onset of symptoms (after age 40 years). When clinical and biochemical data were not confirmatory, genetic analysis was performed to exclude *SERPING1* mutation.

All patients included in the analysis gave their informed consent for using their data for the purpose of this study. Data collection and analysis were conducted by the patients' own physicians; therefore, patient confidentiality was well maintained. The study was approved by the local ethics committee.

Treatment policy

Similar to C1-INH-HAE, patients with C1-INH-AAE could avail of on-demand treatment for acute attacks at home. In Italy, this included pdC1-INH (since 1976) and icatibant (since 2010). Long-term prophylaxis was prescribed to patients with a history of more than 1 severe attack per month. The first choice for this was tranexamic acid 1 g thrice a day; for patients who had contraindications or failed to respond to tranexamic acid, danazol 200 mg once a day was prescribed. The doses of both treatments were reduced to minimal effective doses after patients became stable.

Data collection

For each patient, the following data were collected from medical records: sex, vital status (dead/alive), date of birth, date of symptom onset, date of diagnosis, plasma levels of functional and antigenic C1-INH, C4, and C1q, genetic test results (when performed), autoantibodies to C1-INH, location of angioedema attacks, on-demand therapy, and long-term prophylaxis.

Laboratory methods

Antigenic levels of C1-INH, C4, and C1q were quantified using radial immunodiffusion (NOR-Partigen, LC-Partigen; Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). C1-INH function was measured using a chromogenic assay (Technochrom C1-inhibitor, Technoclone GmbH, Vienna, Austria). Results were normalized as percentage of normal value (C1-INH function: normal range, 70%-130%; C1-INH antigen: normal range, 70%-115%; C4 antigen: normal range, 60%-140%). Autoantibodies to C1-INH were detected using a homemade modification of the ELISA described by Alsenz et al.^{5,14}

Statistical analysis

Data from the C1-INH-AAE patient population were summarized with descriptive statistics and results were reported as median (interquartile range) for each parameter.

RESULTS

From 1976 until 2015, 77 patients (58% females) were diagnosed with C1-INH-AAE at our angioedema center in Milan. During the same period, 675 patients were diagnosed

TABLE I. Characteristics of patients with C1-INH-AAE (N = 77)

Characteristic	
Age (y), median (IQR)	70 (64-78)
Sex, n (%)	
Males	32 (42)
Females	45 (58)
Age at symptom onset (y), median (IQR)	62 (51.0-68)
Age at diagnosis (y), median (IQR)	64 (55-72)
Delay in diagnosis (y), median (IQR)	2 (1-5)
Follow-up period (y), median (IQR)	8 (2-15)
Complement parameters,* n (%)	
C1-INH antigen	25 (9-27)
C1-INH activity	13 (4-25)
C4	9 (4-25)
C1q	21 (6-25)
Patients tested for autoantibodies to C1-INH, n (%)	73 (95)
Positive for autoantibodies to C1-INH, n (%)	48 (68)
Patients with lymphoproliferative disease (excluding MGUS), n (%)	24 (31)
Positive for autoantibodies to C1-INH, n (%)	14 (58)
Patients with MGUS, n (%)	32 (42)
Positive for autoantibodies, n (%)	22 (69)

IQR, Interquartile range; MGUS, monoclonal gammopathy of undetermined significance; N, total number of patients; n, number of patients with data.

*Values indicate activity relative to normal human plasma.

with C1-INH-HAE, giving a relative frequency of 1 patient with C1-INH-AAE for every 8.8 patients with C1-INH-HAE. Median (interquartile range) age was 70 years (63.5-77.5) and the median (interquartile range) delay between symptom onset and diagnosis was 2 years (1.0-5.0) (Table I).

Lymphoproliferative neoplasms were present in 24 patients (Table I), as recently reported.¹⁵ Of these, 20 patients had low-grade nonfollicular B-cell lymphomas, 1 had follicular lymphoma, and 3 had high-grade lymphomas. In addition, 5 patients (4 females and 1 male) had breast cancer. Two patients had other neoplasms including endometrial adenocarcinoma and urothelial adenocarcinoma (1 patient each).

Median plasma levels of functional and antigenic C1-INH, and antigenic C4 and C1q, were well below 50% of normal, as shown in Table I. Plasma functional C1-INH levels were low (ie, <50%) in all patients. Plasma C1-INH antigen levels were 50% or lower in most patients, with normal levels (100%) noted in 2 patients and reduced values in 2 patients (60% and 64%). Plasma C1q levels were normal (ie, >70%) in 14 of 73 patients (19%) tested. Plasma C4 antigen levels were lower than 50% in all except 1 patient with normal levels (74%). Overall, 73 patients were tested for autoantibodies to C1-INH, including 24 with lymphoproliferative disease; of these, 48 (68%) and 14 (58%), respectively, tested positive (Table I).

To date, 16 patients (21%) have died since diagnosis of C1-INH-AAE (Table II). Three patients died because of progression of the lymphoproliferative disease associated with C1-INH-AAE. One patient developed laryngeal angioedema and experienced prolonged asphyxia before pdC1-INH was administered. Consequently, the patient went into an irreversible cerebral coma and died 2 years thereafter. Twelve deaths were apparently unrelated to C1-INH-AAE. One of these was due to hemorrhagic complication of hepatitis C virus cirrhosis, possibly

TABLE II. Characteristics of patients with C1-INH-AAE who died during the study period

Patient characteristics	Total number of patients = 77
Number of patients who died	16
Unrelated to C1-INH-AAE	11
Related to C1-INH-AAE	1
Probably related to C1-INH-AAE treatment	1
Related to lymphoproliferative disorders	3

acquired during treatment with pdC1-INH before introduction of virus inactivation methods, when testing for viral markers in source plasma was insufficient and treatment was with preparations different from those that are now on the market.

Face was the most common location of angioedema attack, reported by 63 patients (82%), followed by the abdomen (51 patients [66%]), peripheries (50 patients [65%]), and oral mucosa and/or glottis (42 patients [55%]) (Figure 1).

On-demand treatment for angioedema, with either pdC1-INH or icatibant or both, was used by 56 patients (70%). Of these, 49 (88%) received intravenous pdC1-INH 2000 U, which was effective in reversing angioedema attacks within 24 hours of starting treatment. In total, 35 patients (71%) received 3 or more pdC1-INH treatments; the others received fewer than 3 treatments. In 41 patients (84%), the efficacy of pdC1-INH was consistent during follow-up. Only 8 patients (16%) became nonresponsive to pdC1-INH over time; that is, 2000 U or higher doses (up to 12,000 U) of pdC1-INH were needed to treat attacks with minimal or no response. All these 8 patients showed autoantibodies to C1-INH.

Subcutaneous icatibant 30 mg was used by 27 of 56 patients (48%) who received on-demand treatment. Eight of them were nonresponders to pdC1-INH, 15 received icatibant as first on-demand treatment, and 4 switched from pdC1-INH to icatibant because of preference for subcutaneous versus intravenous administration. In 24 patients (89%), 30 mg subcutaneous injection of icatibant was effective in reversing the angioedema attack, whereas a second or third injection was needed to reverse symptoms in the others.

In total, 45 patients (58%) received prophylactic treatment to manage their frequent angioedema attacks (>12 attacks/y). Prophylaxis was considered effective when the frequency of attacks was reduced by 50%. Overall, 34 (76%) received tranexamic acid and 20 (44%) received attenuated androgens (some patients received both treatments in different time periods). Tranexamic acid was effective in 29 patients (85%), and attenuated androgen treatment was effective in 8 (44%).

We registered thrombotic events in 4 patients on anti-fibrinolytic agents; the treatment was discontinued after the patients developed adverse events including cardiovascular adverse events (transient ischemic attack and myocardial ischemia; 2 patients), retinal thrombosis (1 patient), and deep vein thrombosis (1 patient). In 3 of these patients, the frequency and severity of angioedema recurrences increased substantially after withdrawal of tranexamic acid and could not be controlled by on-demand treatment alone; furthermore, danazol failed to control symptoms. Therefore, after complete recovery from the acute thrombotic events, antifibrinolytic treatment was resumed with concomitant oral anticoagulants. No further thrombotic

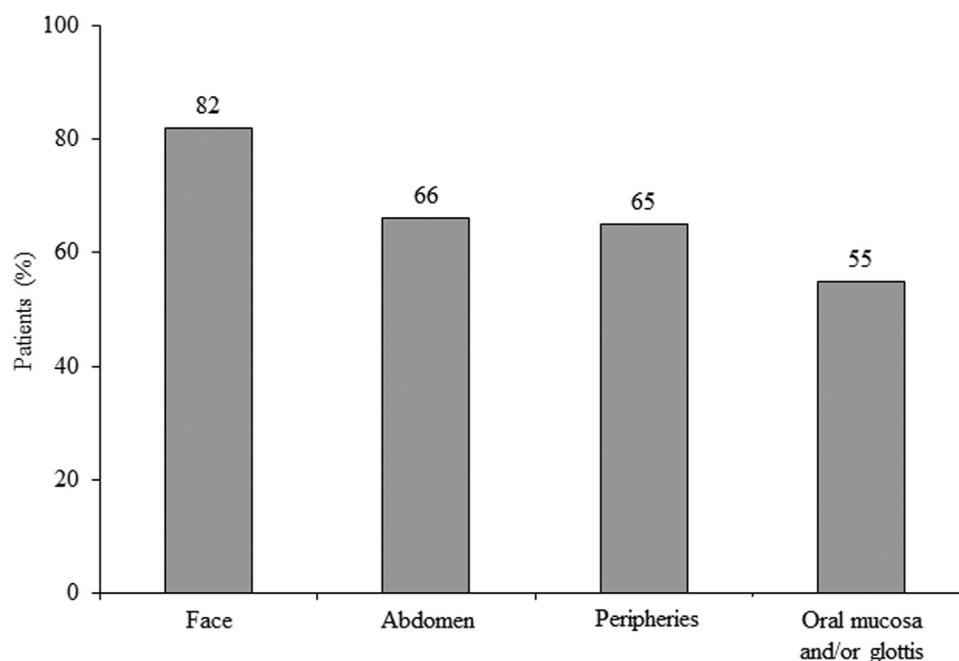


FIGURE 1. Locations of angioedema attacks in patients with C1-INH-AAE (N = 77). N, Total number of patients.

events were registered in these 3 patients with this treatment regimen for over 10 years.

DISCUSSION

This is the first study from Italy to examine the incidence and clinical characteristics in a large group of patients with C1-INH-AAE who were diagnosed and followed at a single center for nearly 40 years. On comparing the incidence of newly diagnosed acquired versus hereditary C1-INH deficiency in this center from 1975 to 2015, we found 1 patient with C1-INH-AAE for every 8.8 patients with C1-INH-HAE. We do not know how often this condition remains unrecognized; therefore, we cannot estimate the actual prevalence. We have determined earlier that the minimum prevalence of C1-INH-HAE in Italy was 1:64,935.¹³ Assuming a similar rate of diagnosis for the 2 conditions, and considering that patients with acquired C1-INH deficiency are older at diagnosis, we can presume a prevalence of C1-INH-AAE to be around 1:600,000 of the general population. All data were collected retrospectively, and this was a limitation of our study.

A nationwide study in France found 92 patients diagnosed with C1-INH-AAE between January 1991 and March 2015. Similar to our study, the median age at onset was 62 years, and face and the abdomen were the most common sites of angioedema attacks. However, the median delay in diagnosis was 10 months, which was shorter than in our study. Furthermore, a larger proportion of patients (47%) had a lymphoid malignancy.¹⁶

In most European countries, the time between onset of symptoms and diagnosis of C1-INH-HAE is more than 8 years.¹⁷ Because of its rarity, we expected a longer delay in diagnosis for C1-INH-AAE. Surprisingly, patients with C1-INH-AAE were diagnosed earlier: the median time from symptom onset to diagnosis was 2 years. At diagnosis, 9 patients were on angiotensin-converting enzyme inhibitor (ACE-I) for

treatment of hypertension. Because ACE-I acts as a trigger of angioedema attacks, these patients had a high frequency of symptoms. Because the correlation between ACE-I and angioedema is well known,¹⁸ these patients were referred to our center for testing C1-INH levels. Low levels of C1-INH were found and diagnosis of “C1-INH-AAE worsened by ACE-I” was made. Disease severity might also have motivated physicians to look for an appropriate diagnosis. In addition, rising awareness about angioedema may have contributed toward reducing the delay in diagnosis of C1-INH-AAE. Overall, 27 of the 77 patients with C1-INH-AAE (35%) were diagnosed in the last 5 years whereas new diagnoses of C1-INH-HAE were less than 10% in the same period. Thus, we speculate that the frequency of unrecognized C1-INH-AAE is decreasing significantly. This could also explain the shorter delay in diagnosis of C1-INH-AAE compared with that in previous reports.¹⁹

Although not specific for C1-INH-AAE, plasma C4 antigen testing is a sensitive tool for diagnosing C1-INH deficiency and should be the first step for screening patients with angioedema. In our study, all except 1 patient had low plasma C4 antigen levels and C1-INH antigen levels were 50% or lower in all except 4 patients. Furthermore, plasma levels of C1q antigen were 50% or lower in 81% of the patients. Decreased plasma levels of C1q antigen in combination with low plasma C4 antigen and C1-INH antigen levels help to establish a diagnosis of C1-INH-AAE because these are normal in the hereditary form of the disease and reduced in 70% patients with acquired deficiency.²

In terms of clinical presentation, the main difference between angioedema due to hereditary and acquired C1-INH deficiency is later onset of symptoms in C1-INH-AAE. Most patients with C1-INH-HAE reported onset of symptoms during puberty and almost all the patients were symptomatic before age of 20 years; only 7 (1.7%) started having angioedema after 30 years and 2 (0.5%) after 40 years. However, none of the 77 patients with C1-INH-AAE had symptoms before 40 years, confirming that

age of symptom onset is a reliable criterion to differentiate between the 2 forms of angioedema due to C1-INH deficiency. There is no clear-cut difference in the location of symptoms, and both forms present with the classical triad of cutaneous, abdominal, and laryngeal edema. Contrary to what is described in C1-INH-HAE,²⁰ facial angioedema occurred more often than angioedema of the extremities in our patients with C1-INH-AAE with cutaneous edema.

Similar to that observed in patients with C1-INH-HAE, more than half of the patients with C1-INH-AAE experienced at least 1 episode of laryngeal edema and 1 died because of that, despite an established diagnosis and appropriate treatment. The patient called the 24-hour emergency telephone number reporting initial symptoms of laryngeal involvement and was recommended to present immediately at the nearest hospital with her own pdC1-INH for treatment. She arrived at 15 minutes and was immediately admitted to the emergency room where she developed respiratory arrest. After an unsuccessful attempt to intubate due to laryngeal edema, a tracheostomy was performed. The patient was then infused with pdC1-INH. Because of anoxic cerebral injury, the patient did not come out of coma and died after 18 months. There is no evidence for correlating the patient's death to delayed or inappropriate therapeutic intervention. Nevertheless, the risk associated with laryngeal edema and the importance of prompt treatment are well described in C1-INH-HAE and should be considered similar for C1-INH-AAE.^{21,22}

Acquired C1-INH deficiency therapy might be more problematic than hereditary deficiency because of differences in treatment efficacy. Despite the absence of controlled studies for this disease, the treatment has been derived from that for C1-INH-HAE and comprises reversal of attacks with on-demand therapy and reduction of attack frequency with long-term prophylaxis. pdC1-INH is by far the most largely used treatment for acute management. It has been used by patients with C1-INH-AAE in Europe as soon as it became available in the 1980s.^{23,24} In Italy, it was used at a dose of 1000 U/attack, similar to that used in C1-INH-HAE, before the clinical trial with Berinert showed that the appropriate dose was 20 U/kg.^{23,25} After observing the slow response of some patients with C1-INH-AAE and considering the faster C1-INH catabolism characterizing these patients, we increased the dose in our clinical practice to 2000 U.^{3,9} Since early 1980s, 49 of our patients with C1-INH-AAE were treated with 2000 U of pdC1-INH as first-line on-demand treatment for acute attacks. We did not register any drug-related adverse events and, specifically, any arterial or venous thromboembolic events. One patient died from complications related to hepatitis C that was probably contracted with pdC1-INH. The plasma products used by that patient were manufactured by Immuno Vienna and the Netherlands Red Cross; we have no unequivocal evidence that either was the source of the infection. Forty-one of the 49 patients had prompt response to treatment, and the response was consistently maintained in the 35 patients who needed repeated infusions. In 8 patients, the response to pdC1-INH was initially good and became progressively unsatisfactory (ie, no or partial response) after several infusions: in 3 patients this occurred at the very first infusion, in 3 at the second infusion, and in 1 patient each at the third and fourth infusions. Unsatisfactory response ranged from slow response (more than 4 hours before significant improvement) to complete inefficacy. Until 2010, no alternative treatment was available for this subgroup of patients and therefore

pdC1-INH continued to be used for treating acute attacks; none of these patients required invasive treatment for laryngeal edema. Interestingly, all 8 patients resistant to pdC1-INH had detectable autoantibodies to C1-INH in their plasma. Alsenz et al⁹ showed massive cleavage of C1-INH in antibody-positive patients receiving pdC1-INH. Nevertheless, out of 34 antibody-positive patients receiving repeated infusions of C1-INH, only 8 became resistant. Long-term prophylaxis with danazol is not effective in these patients. Attenuated androgens increase plasma levels of C1-INH and although efficacy does not require detectable parallel increase in C1-INH plasma levels, significant upregulation of C1-INH gene can be demonstrated during danazol treatment.^{26,27} Thus, we believe that in a minority of patients with C1-INH-AAE, probably because of avidity of autoantibodies, C1-INH catabolism is particularly elevated, leading to no/reduced efficacy of therapies involving replacement of the deficient protein.

After the bradykinin receptor antagonist icatibant became available in Italy in 2010 for on-demand treatment of C1-INH-HAE, it was used for the treatment of patients with C1-INH-AAE who did not respond to pdC1-INH. All these patients had complete response, which was maintained over repeated use. Our overall experience with icatibant comes from 27 patients treated with this drug. The majority responded to 1 injection, with only 11% of the patients needing a second or third injection to achieve complete attack resolution. The only adverse events reported with icatibant use were transient injection-site reactions such as pain, burning sensation, and erythema. These reactions were self-limiting and did not occur with every icatibant injection in the same patient.

Ecaltantide, a recombinant peptide highly specific for inhibiting plasma kallikrein, was registered in the United States in 2009 for the treatment of C1-INH-HAE.²⁸ It may also be indicated for patients with C1-INH-AAE and its mechanism of action escapes the effect of C1-INH antibodies. Our experience with this drug is extremely limited because it is not registered in Europe. We used it in 2 patients in the earliest clinical trial with this drug in 2003. The experience was favorable and is reported along with that of another patient who received the same treatment several times.²⁹ All 3 patients achieved symptom resolution within hours of ecaltantide administration. The drug was well tolerated without serious adverse events.

Similar to patients with C1-INH-HAE, those with acquired deficiency whose symptoms cannot be controlled by on-demand treatment undertake long-term prophylaxis.³⁰ Drugs available for this purpose are antifibrinolytic agents, attenuated androgens, and pdC1-INH. We have no personal experience with pdC1-INH for long-term prophylaxis. This is due to fear of inducing resistance, similar to that in patients receiving on-demand treatment. As such, there is no scientific support or clinical evidence to back this assumption, and in a limited number of patients, favorable experience with pdC1-INH for long-term prophylaxis has been reported.³¹ We considered long-term prophylaxis for those patients who had experienced 2 or more severe episodes of angioedema that could not be controlled by on-demand treatment. With these criteria, slightly more than half of our patients needed prophylactic treatment. Because of limited efficacy of attenuated androgens in our patients (<50% responders), the antifibrinolytic agent tranexamic acid is our first-line approach for long-term prophylaxis. The evidence of efficacy for this class of drugs is derived from small clinical studies

performed in patients with C1-INH-HAE in the early 1970s, but because of the availability of more effective treatments, their use in these patients is now very limited.³²⁻³⁴ Antifibrinolytic agents target plasmin and their efficacy seems to be higher in acquired than in hereditary form of C1-INH deficiency.³⁵ In the present study, only 15% of the patients receiving tranexamic acid for long-term prophylaxis failed to achieve 50% reduction in the attack frequency, thus highlighting high efficacy of the treatment. Long-term treatment with tranexamic acid is associated with the risk of thrombosis, similar to that with any antifibrinolytic agent. Most patients with C1-INH-AAE are 50 years or older. Thus, they are frequently hypertensive and may have various cardiovascular risk factors. The literature does not provide clear-cut evidence for the risk of thrombosis with long-term antifibrinolytic treatment.³⁶⁻⁴² Our data cannot answer the question either because the number of patients on antifibrinolytic treatment in this study is too small to draw conclusions that may be applied to a setting with thrombotic risk driven by a large number of independent variables. The fact that none of our patients had irreversible thrombosis-related complications during treatment with tranexamic acid supports, upon careful evaluation of risk-benefit balance, an acceptable safety profile of this treatment. Furthermore, the causes of the thrombotic events in our study may well be related to the older age of the patients.

In conclusion, our case series indicates that C1-INH-AAE is a rarer disease than C1-INH-HAE; the incidence will probably increase in the future because of more appropriate diagnosis. Accurate merging of clinical and biochemical parameters provides solid diagnostic criteria. It should still be considered a syndrome because it occurs in different settings, but increasing knowledge on lymphocyte abnormalities underlying the condition may identify unifying mechanisms in the future. Affected patients may die because of laryngeal edema, but life-threatening risk is reduced to almost zero with appropriate diagnosis and treatment. Despite the absence of drugs specifically licensed for treating this condition, growing experience will help to establish a specific therapeutic algorithm.

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REFERENCES

- Caldwell JR, Ruddy S, Schur PH, Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. *Clin Immunol Immunopathol* 1972;1:39-52.
- Cicardi M, Zanichelli A. Acquired angioedema. *Allergy Asthma Clin Immunol* 2010;6:14.
- Melamed J, Alper CA, Cicardi M, Rosen FS. The metabolism of C1 inhibitor and C1q in patients with acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 1986;77:322-6.
- Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am* 2006;26:669-90.
- Cicardi M, Beretta A, Colombo M, Gioffre D, Cugno M, Agostoni A. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema. *Clin Exp Immunol* 1996;106:475-80.
- Jackson J, Sim RB, Whelan A, Feighery C. An IgG autoantibody which inactivates C1-inhibitor. *Nature* 1986;323:722-4.
- Hauptmann G, Petitjean F, Lang JM, Oberling F. Acquired C1 inhibitor deficiency in a case of lymphosarcoma of the spleen: reversal of complement abnormalities after splenectomy. *Clin Exp Immunol* 1979;37:523-31.
- Schreiber AD, Zweiman B, Atkins P, Goldwein F, Pietra G, Atkinson B, et al. Acquired angioedema with lymphoproliferative disorder: association of C1 inhibitor deficiency with cellular abnormality. *Blood* 1976;48:567-80.
- Alsenz J, Lambris JD, Bork K, Loos M. Acquired C1 inhibitor (C1-INH) deficiency type II: replacement therapy with C1-INH and analysis of patients' C1-INH and anti-C1-INH autoantibodies. *J Clin Invest* 1989;83:1794-9.
- Malbran A, Hammer CH, Frank MM, Fries LF. Acquired angioedema: observations on the mechanism of action of autoantibodies directed against C1 esterase inhibitor. *J Allergy Clin Immunol* 1988;81:1199-204.
- Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet* 1998;351:1693-7.
- Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis and approach to treatment for angioedema: consensus report from HAWK. *Allergy* 2014;69:602-16.
- Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, Cancian M, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis* 2015;10:11.
- Alsenz J, Bork K, Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 1987;316:1360-6.
- Castelli R, Wu MA, Arquati M, Zanichelli A, Suffritti C, Rossi D, et al. High prevalence of splenic marginal zone lymphoma among patients with acquired C1 inhibitor deficiency. *Br J Haematol* 2016;172:902-8.
- Gobert D, Paule R, Ponard D, Levy P, Frémeaux-Bacchi V, Bouillet L, et al. A nationwide study of acquired C1-inhibitor deficiency in France: characteristics and treatment responses in 92 patients. *Medicine (Baltimore)* 2016;95:e4363.
- Zanichelli A, Magerl M, Longhurst H, Fabien V, Maurer M. Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. *Allergy Asthma Clin Immunol* 2013;9:29.
- Beltrami L, Zanichelli A, Zingale L, Vacchini R, Carugo S, Cicardi M. Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. *J Hypertens* 2011;29:2273-7.
- Jolles S, Williams P, Carne E, Mian H, Huissoon A, Wong G, et al. A UK national audit of hereditary and acquired angioedema. *Clin Exp Immunol* 2014;175:59-67.
- Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 2008;63:751-7.
- Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012;130:692-7.
- Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 2001;161:714-8.
- Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206-15.
- Bork K, Witzke G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 1989;83:677-82.
- Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009;124:801-8.
- Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;295:1444-8.
- Pappalardo E, Zingale LC, Cicardi M. Increased expression of C1-inhibitor mRNA in patients with hereditary angioedema treated with Danazol. *Immunol Lett* 2003;86:271-6.
- Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 2010;363:523-31.
- Patel NS, Fung SM, Zanichelli A, Cicardi M, Cohn JR. Ecallantide for treatment of acute attacks of acquired C1 esterase inhibitor deficiency. *Allergy Asthma Proc* 2013;34:72-7.
- Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014;69:602-16.
- Levi M, Choi G, Picavet C, Hack C. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 2006;117:904-8.
- Frank MM, Sergeant JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. *N Engl J Med* 1972;286:808-12.
- Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. *N Engl J Med* 1972;287:452-4.

34. Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;66:192-6.
35. Cugno M, Cicardi M, Agostoni A. Activation of the contact system and fibrinolysis in autoimmune acquired angioedema: a rationale for prophylactic use of tranexamic acid. *J Allergy Clin Immunol* 1994;93:870-6.
36. Taparia M, Cordingley FT, Leahy MF. Pulmonary embolism associated with tranexamic acid in severe acquired haemophilia. *Eur J Haematol* 2002;68:307-9.
37. Dalmau A, Sabate A, Koo M, Rafecas A, Figueras J, Jaurieta E. Prophylactic use of tranexamic acid and incidence of arterial thrombosis in liver transplantation. *Anesth Analg* 2001;93:516.
38. Berntorp E, Follrud C, Lethagen S. No increased risk of venous thrombosis in women taking tranexamic acid. *Thromb Haemost* 2001;86:714-5.
39. Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. *Thromb Haemost* 1993;70:238-40.
40. Woo KS, Tse LK, Woo JL, Vallance-Owen J. Massive pulmonary thromboembolism after tranexamic acid antifibrinolytic therapy. *Br J Clin Pract* 1989;43:465-6.
41. Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H. Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. *BMC Pregnancy Childbirth* 2009;9:29.
42. Upadhyay SP, Mallick PN, Jagia M, Singh RK. Acute arterial thrombosis associated with inadvertent high dose of tranexamic acid. *Indian J Crit Care Med* 2013;17:237-9.