



An evidence based therapeutic approach to hereditary and acquired angioedema

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Purpose of review

Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency (HAE-C1-INH), HAE with normal C1-INH, and acquired angioedema due to C1-INH deficiency are rare but important diseases that can be associated with significant morbidity and mortality. Research into the pathogenesis of angioedema has expanded greatly and has led to new clinical trials with novel therapeutic agents and strategies.

Recent findings

Strategies for managing HAE-C1-INH are aimed at treating acute attacks or preventing attacks through the use of prophylactic treatment. Agents available in Europe for treating acute attacks include plasma-derived C1-INH concentrates, a bradykinin B2 receptor (B2R) antagonist, and a recombinant human C1-INH. In the USA, a plasma-derived C1-INH concentrate, a bradykinin B2R antagonist, and a plasma kallikrein inhibitor have been approved for the treatment of acute HAE-C1-INH attacks. C1-INH concentrates and attenuated androgens are used for short-term prophylactic treatment. Long-term prophylactic treatments include attenuated androgens, a plasma-derived C1-INH concentrate, and antifibrinolytics. Plasma-derived C1-INH and a bradykinin B2R antagonist are approved for self-administration at home.

Summary

The number of management options for HAE-C1-INH and similar conditions has increased considerably within the last few years, thus helping to alleviate the burden of these rare diseases.

Keywords

acquired angioedema, acute treatment, c1 inhibitor, c1-INH deficiency, hereditary angioedema, prophylaxis

INTRODUCTION

Recurrent angioedema is clinically characterized by episodes of edema (attacks) involving the skin, gastrointestinal tract, and other organs, including potentially life-threatening laryngeal edema. Various forms of angioedema share these clinical features. This article refers to the recent developments in managing the various forms of hereditary angioedema (HAE): HAE associated with C1 esterase inhibitor (C1-INH) deficiency (HAE-C1-INH), HAE with normal C1-INH activity (HAE-C1), and acquired angioedema due to C1-INH deficiency (AAE-C1-INH). All of these are rare conditions. The aim of the article is to describe the current advances in the field of treatment of hereditary and acquired angioedema, emphasizing the most recent and most important aspects. As most treatment advances refer to proteins and peptides, these treatments are described more extensively rather than androgens and tranexamic acid.

TREATMENT FOR HAE-C1-INH

HAE-C1-INH is associated with a deficiency of C1-INH caused by mutations of the *SERPINC1* gene. The pathogenesis of HAE-C1-INH involves activation of the kallikrein-kinin system (KKS), leading to the release of bradykinin. The mechanism of KKS activation, however, is still unknown. During an acute attack, the activation of FXII and plasma prekallikrein and the formation of the serine proteases FXIIa and kallikrein are uncontrolled. Plasma kallikrein cleaves high molecular weight kininogen resulting

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KEY POINTS

- Hereditary angioedema due to C1 esterase inhibitor deficiency (HAE-C1-INH) is a rare disease associated with recurrent edema.
- Other forms of angioedema (e.g. HAE with normal C1 esterase inhibitor and acquired angioedema due to C1 esterase inhibitor deficiency) share similar clinical features.
- Greater understanding of the pathogenesis of HAE-C1-INH has led to the development of new therapeutic agents and strategies.
- The increase in management options for HAE-C1-INH is helping to relieve the burden of the disease by providing rapid relief of acute symptoms and prevention of attacks.

in the formation of the nonapeptide bradykinin, a potent vasodilator. Bradykinin activates the bradykinin B2 receptor (B2R) located on the endothelial cells. The activation of the B2R is followed by relaxation of the smooth muscle cells of the vessels because of the production of nitric oxide by the endothelial cells. In case of angioedema, this leads to a vasodilation, increased vascular permeability, and localized fluid extravasation.

C1-INH is a serine protease inhibitor and inhibits not only the C1r and C1s components in the complement system, but also FXIIa, kallikrein, and FXIa in the KKS and coagulation systems (Fig. 1). In an acute attack of HAE-C1-INH, the KKS (contact system) is activated leading to increased bradykinin formation and its sequelae. C1-INH deficiency is not necessarily associated with recurrent angioedema. In a series of 514 individuals with C1-INH deficiency, 45 had never experienced clinical symptoms of HAE-C1-INH [1]. This and the alternation between symptomatic and asymptomatic phases show that, in addition to C1-INH deficiency, other factors (currently unknown) also seem to play a role in eliciting an attack.

Treatment goals in HAE-C1-INH comprise the avoidance of asphyxiation and the reduction of the attack frequency and severity. In addition to drug treatment, numerous other measures are necessary to reach these goals [2–4].

There are two treatment strategies in HAE-C1-INH. The first is to treat acute swellings (on-demand treatment) and the second is to prevent attacks (short-term or long-term prophylaxis). A range of targeted and nontargeted treatments are available (Table 1) [5,6]. The approval status of medications for HAE-C1-INH in Europe and the USA is shown in Table 2.

TREATMENT OF ACUTE ATTACKS

During acute HAE-C1-INH attacks, the first therapeutic objective is to attenuate or stop the process of KKS activation. This can be achieved by the administration of a protease inhibitor that binds plasma kallikrein and factor XIIa. It has been shown that therapy to replace C1-INH (which inhibits both factor XIIa and kallikrein) can abort acute attacks of HAE-C1-INH. Similar results have been shown using various substances that inhibit kallikrein alone.

A second objective of therapy for acute HAE-C1-INH attacks is to inhibit bradykinin action by blocking the bradykinin B2R on the endothelial cells. For this purpose, a synthetic molecule similar to bradykinin, but that does not cause vasodilation and vasopermeability, has been developed.

C1-INH concentrates

Since 1973, C1-INH concentrates derived from human plasma have been shown to be effective in treating and preventing all kinds of HAE-C1-INH attacks. Three licensed C1-INH concentrates are currently available (Table 1).

Berinert

Berinert is a pasteurized and nanofiltered C1-INH concentrate, which was first licensed in Germany in 1979. The randomized, double-blind, placebo-controlled International, Multicenter, Prospective Angioedema C1-INH Trial 1 (IMPACT1) study [7] evaluated the efficacy of Berinert in 125 patients with HAE-C1-INH. Patients were randomized to 10 or 20 U/kg body weight Berinert given intravenously or placebo to study its efficacy in abdominal attacks and facial swellings. The median time to onset of relief was significantly shorter with 20 U/kg of Berinert than with placebo (0.5 vs. 1.5 h). At a dose of 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 vs. 1.5 h), and the difference did not reach statistical significance. The conclusion was that Berinert given intravenously at a dose of 20 U/kg is an effective treatment for abdominal and facial attacks in patients with HAE-C1-INH [7].

Three large uncontrolled clinical studies [8–10], which included thousands of attacks, found that a fixed dose of 500 U was highly effective in the majority of patients (98, 81, and 68.6%, respectively).

The potentially life-threatening nature of laryngeal attacks, and facial attacks which can evolve into laryngeal edema, require a body weight-adjusted dose of 20 U/kg to be used. In attacks that are not potentially life-threatening (i.e. those with swellings of the extremities and abdominal attacks), the dose

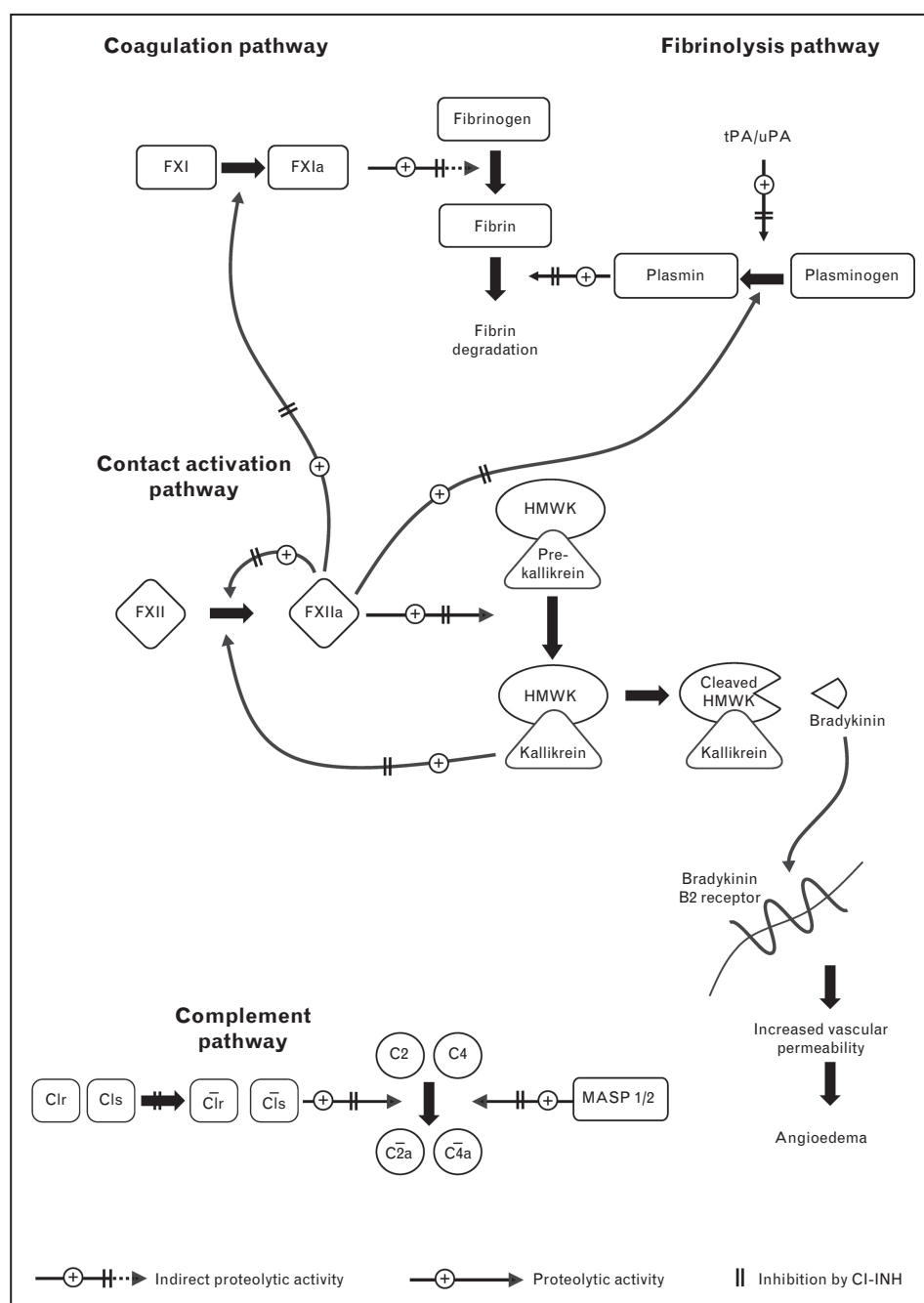


FIGURE 1. Action of C1 inhibitor in the kallikrein–kinin and complement systems, and in fibrinolysis and coagulation.

can be adjusted to the patient's individual requirements; administration of a lower, fixed dose of 500 or 1000U per attack may be sufficient [4]. Self-administration of intravenous C1-INH is one of the most important aspects of treatment in HAE-C1-INH [11]. Berinert is licensed for self-administration at home [12]. In a few patients receiving Berinert for a long period of time, a slow increase in attack frequency (i.e. disease activity) has been observed [13–15].

Cinryze

Cinryze is a nanofiltered plasma-derived C1-INH. Two randomized, double-blind, placebo-controlled trials have been performed in patients with acute attacks. One study used a parallel group design in which 71 patients with acute HAE attacks were randomized to Cinryze ($n=36$) or placebo ($n=35$). The study [16] demonstrated that, compared with placebo, treatment with Cinryze within 4 h of the onset of an attack resulted in a greater than two-fold

Table 1. Drugs currently available for treating hereditary angioedema due to C1 esterase inhibitor deficiency (HAE-C1-INH)

Drug	Brand name	Company	Mechanism of action	Dosage (treatment for acute attacks)	Dosage (prophylaxis)	Route of administration	Self-dosing	Potential side-effects
Plasma-derived nanofiltered C1-INH	Berinert	CSL Behring GmbH, Marburg, Germany	C1-INH replacement	20 U/kg body-weight (possibly lower dosage in skin swellings and abdominal attacks; see text)	STP: Adults: 1000 IE; children 1.5–30 IE/kg BW, 1 h before surgery, LTP: n.a.	Intravenous	Yes	Rare: anaphylactic reactions, Theoretical: blood-borne infection
Plasma-derived nanofiltered C1-INH	Cinryze	Shire, Basingstoke, UK (formerly ViroPharma Inc, Exton, PA, USA)	C1-INH replacement	1000 U, possibly a second dose of 1000 U after 1 h	STP: 1000 U, 1 h before surgery, LTP: 1000 U every 3–4 days	Intravenous	Yes	Rare: anaphylactic reactions, Theoretical: blood-borne infection, In LTP, thrombotic events were observed in a few patients [5]
Icatibant	Firazyr	Shire, Basingstoke, UK	Antagonism of bradykinin B2 receptor	30 mg	n.a.	Subcutaneous	Yes	Very common: transient erythema, wheal, and pain at injection site
Recombinant C1-INH	Ruconest, Rhucin	Pharming Group NV, Leiden, The Netherlands	C1-INH replacement	50 U/kg or 4200 U	n.a.	Intravenous	No	Uncommon: anaphylactic reactions in rabbit-sensitized patients
Ecallantide	Kalbitor	Dyax Corp., Burlington, MA, USA	Kallikrein inhibition	30 mg (in 3 injections of 10 mg each)	n.a.	Subcutaneous	No	Uncommon: anaphylactic reactions, antidrug antibodies
Danazol	Various	Various	Unknown	n.a.	50–200 mg/day	Oral	Yes	Common to rare: numerous, dose-dependent side-effects: weight gain, menstrual abnormalities, headaches, depression, muscle pains and cramps, elevated liver enzymes, hypertension, lipid profile alterations, hepatocellular tumors, and others [6]
Tranexamic acid	Cyklokapron	Meda Pharma GmbH, Bad Homburg, Germany	Inhibition of plasminogen activation	n.a.	Adults: 1 g twice-daily (from 0.25 g twice-daily to 1 g three times daily) Children: 20 mg/kg twice-daily (from 10 mg/kg twice-daily to 25 mg/kg three times daily)	Oral	Yes	Common: nausea, diarrhea, vertigo, postural hypotension, fatigue, muscle weakness with elevated muscle enzymes, Uncommon: thrombosis

Table 2. Approval of treatment options for hereditary angioedema due to C1-INH deficiency in Europe and the USA

	Approved in Germany and Europe since	Approved in the USA since	Approved for
Plasma-derived C1-INH			
Berinert	1979 (for the treatment of HAE attacks)	2009 (for the treatment of HAE attacks)	Adults and children
Cinryze	2011 (for the treatment and prevention of HAE attacks)	2008 (for the prevention of HAE attacks)	Adults and adolescents
Bradykinin B2 receptor agonist			
Icatibant (Firazyr)	2008	2011	Adults (18 years old and older)
Recombinant C1-INH			
Conestat alfa Ruconest	2010	Currently not approved	Adults
Plasma kallikrein inhibitor			
Ecallantide (Kalbitor)	Currently not approved	2009	USA: 16 years old and older
Nonprotein therapies			
Danazol	Approved in a few countries only	Approved	Adults
Tranexamic acid	Approved in a few countries only	Not approved for HAE	Europe: Adults and children

C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema.

decrease in the time to beginning of unequivocal relief of the defining symptom of the HAE attack.

In an open-label study, 101 patients were treated for a total of 609 acute HAE attacks. Overall, 87% of attacks achieved unequivocal relief from the defining symptom within 4 h of Cinryze dosing. In fact, in 95% of attacks, clinical relief was observed and the patients were discharged home within 4 h [16]. Cinryze also provided relief from acute attacks of HAE-C1-INH in children [17[•]]. Self-administration of Cinryze significantly decreased attack duration, pain medication use, and graded attack severity [18].

Icatibant

Icatibant (Firazyr) is a novel, competitive, and selective B2 receptor antagonist for subcutaneous injection in patients with HAE-C1-INH [19–21].

In an initial Phase II open-label study [22], 15 patients with 20 HAE attacks were treated with icatibant either intravenously or subcutaneously. This was the first study to demonstrate the clinical usefulness of antagonizing the binding of bradykinin to the bradykinin receptor-2 in HAE-C1-INH.

The safety and efficacy of icatibant have been further assessed in three randomized, double-blind, controlled, prospective, multicenter phase III studies: two were placebo-controlled and the third used oral tranexamic acid as the comparator. In the For Angioedema Subcutaneous Treatment (FAST-1) study [23], placebo controlled and performed in 56 patients, the primary endpoint was the median time to clinically significant relief of symptoms.

Twenty-seven patients received icatibant and twenty-nine patients received placebo. The primary endpoint was reached in 2.5 h with icatibant vs. 4.6 h with placebo. The difference was not significant ($P=0.14$).

The FAST-2 study [23] was performed in 74 patients and was almost identical in design. Thirty-six patients received icatibant and 38 patients received tranexamic acid. The median time to clinically significant relief of symptoms was 2.0 h with icatibant vs. 12.0 h with tranexamic acid. The difference was significant ($P<0.001$). In a further randomized, double-blind, controlled, prospective phase III multicenter study (FAST-3) [24], 43 patients were randomized to icatibant and 45 patients to placebo. The primary endpoint, time to onset of symptom relief, was significantly shorter with icatibant (2.0 h) than with placebo (19.8 h; $P<0.0001$) [24].

An observational study [25[•]] showed that acute attacks of HAE-C1-INH resolve faster following early treatment with icatibant compared with late treatment. Like Berinert, icatibant is licensed for self-administration. In a recent study [26[•]], 97 patients self-administered icatibant for HAE-C1-INH attacks. Most patients (91.7%) found self-administration preferable to the administration in the clinic.

Ecallantide

Ecallantide is a 7.054-kDa recombinant protein comprising 60 amino acids, produced in the yeast *Pichia pastoris*. It is a potent and selective inhibitor of

kallikrein, and acts by blocking its binding site. The plasma half-life is approximately 70 min when administered intravenously and 2 h when administered subcutaneously.

The safety and efficacy of ecallantide were evaluated in the randomized, double-blind, placebo-controlled Evaluation of DX-88's Effect in Mitigating Angioedema (EDEMA3 and EDEMA4) trials [27,28]. The effects of ecallantide were evaluated in 168 patients using a Mean Symptom Complex Severity Score (MSCS) and a Treatment Outcome Score (TOS). The results of this study showed that the drug is highly effective in patients with laryngeal attacks [29] and in the treatment of HAE-C1-INH attacks of children [30]. Side-effects included hypersensitivity and, in a few patients, anaphylaxis. A second dose was required in 12% of treated attacks [31].

Recombinant C1-INH

A recombinant human C1-INH (rhC1INH) has been developed for the treatment of HAE attacks. It is obtained from the milk of transgenic rabbits. The cloned human *C1INH* gene was inserted into a mammary-gland-specific expression vector under the control of an S1 casein promoter. The construct was introduced into fertilized New Zealand white rabbit oocytes by microinjection in order to generate a line expressing high levels (12 mg/ml) of secreted rhC1INH. Rabbits have a short reproductive cycle and can produce sufficient quantities of rhC1INH.

Two separate randomized, double-blind, placebo-controlled clinical trials were conducted in Europe and North America. In Europe, a randomized, double-blind, placebo-controlled Phase III study was conducted with 32 patients. All instances of treatment with rhC1INH were successful, with no relapses. A second randomized, double-blind, placebo-controlled study with rhC1INH was conducted at several sites in the USA and Canada. In total, 38 acute HAE attacks (laryngeal, facial, abdominal, urogenital, and peripheral) were treated in 38 patients who had been randomized to one of two doses of rhC1INH (100 or 50 U/kg) or to placebo. The median time to the beginning of relief of symptoms and the median time to minimal symptoms obtained with both doses of rhC1INH were clinically meaningful and statistically significantly reduced relative to placebo [32]. An open-label extension study [33] revealed continued efficacy of rhC1-INH and no increase in adverse event was reported after repeated dosing for subsequent attacks. In a recent additional Phase III randomized, placebo-controlled trial, 44 patients with HAE-C1-INH were randomized to rhC1-INH

and 31 to placebo (isotonic saline) [34]. The median time to onset of sustained relief from symptoms was 90 min in patients treated with rhC1INH and 152 min in patients treated with placebo, and significantly shorter in patients treated with rhC1INH ($P=0.031$).

All mentioned medications for acute attacks of HAE-C1-INH are highly effective. Plasma-derived C1-INH concentrates and recombinant C1-INH have to be administered intravenously. The rate of attack recurrences is very low. Icatibant and ecallantide are administered subcutaneously; however, in about 10% of treated attacks, a second injection is necessary to control the attack. Currently, only plasma-derived C1-INH and icatibant are licensed for home-based self-administration. Most of the agents are not licensed for use in children or in pregnancy [3,4].

PREVENTION OF ATTACKS

A partial or complete prevention of clinical symptoms of HAE-C1-INH can be achieved by direct replacement of deficient C1-INH. There are other long-term prophylaxis regimens for HAE-C1-INH, such as attenuated androgens and the plasminogen inhibitor tranexamic acid. In both kinds of treatment, the exact mode of action is not fully understood. Tranexamic acid may be less effective than attenuated androgens [35].

Attenuated androgens

Attenuated androgens have been used since 1976, and so there is extensive understanding of their efficacy and safety. Attenuated androgens are highly effective in preventing HAE attacks [6,36]; however, their long-term use may be associated with numerous side-effects, and close monitoring of patients is mandatory.

C1-INH concentrates

The C1-INH concentrates Cinryze and Berinert have been used for the prevention of HAE-C1-INH attacks, but only Cinryze is currently approved for this use. The efficacy and safety of Cinryze have been evaluated in a multicenter, double-blind, placebo-controlled, crossover study [37]. Patients were enrolled if they had been experiencing two or more HAE attacks per month. A total of 20 patients completed the study. The mean number of HAE attacks in each 12-week treatment period was significantly lower for patients receiving Cinryze than for those receiving placebo. The recommended prophylactic dose of Cinryze is

1000 U every 3–4 days. In an open-label study [38], patients showed a 94% reduction in the number of monthly attacks. Some patients are not adequately controlled with this dose, however. In a recent study [39[¶]] with escalating doses of Cinryze, it was shown that a dose escalation up to 2500 U every 3–4 days reduced the attack frequency and was well tolerated.

Beriner is currently not licensed for long-term prophylactic use. Beriner's high efficacy in long-term prophylaxis has been reported in case reports and small case series since 1989 [40–42]. A series of 14 patients received one or more weekly intravenous injections of Beriner for an average of 9 years [15]. The most important benefit of this treatment was a reduction in symptom intensity: the vast majority of attacks were only mild or very mild. The percentage of attacks that were severe was 93.3% without prophylaxis and 3.8% with prophylaxis. In some patients, an increased amount of Beriner was required to prevent attacks. Some patients reported rapidly developing attacks and skin swellings at multiple locations, reflecting increased HAE-C1-INH activity. However, none of the patients reported any loss of effectiveness during the treatment with Beriner.

Recombinant C1-INH

In an open-label observational study [43], 25 patients with HAE-C1-INH received 50 U/kg rhC1INH once weekly. The study revealed that the attack frequency appeared to be reduced. The half-life of rhC1INH is 1.6 h. Although this finding cannot be considered definitive, one possible explanation for the efficacy of rh-C1-INH in long-term prophylaxis despite its short half-life might be that even short and transient restoration of C1-INH plasma level can be sufficient for stabilize the KKS for some time.

COSTS OF HEREDITARY-ANGIOEDEMA-SPECIFIC TREATMENTS

The HAE-specific treatments with plasma-derived or recombinant C1-INH, icatibant, or ecallantide are expensive. In some patients with many attacks, annual per patient medication can exceed 100 000 Euros. In the USA, each of the manufacturers of the HAE-specific agents has implemented copayment assistance programs. Home-based self-administration may reduce the treatment costs associated with HAE-C1-INH.

TREATMENT FOR HEREDITARY ANGIOEDEMA WITH NORMAL C1-INH

HAEnC1 was first described in 2000 and was initially termed 'HAE with normal C1 inhibitor occurring

mainly in women' or 'HAE type III' [44]. To date, four mutations present in exon 9 of the *F12* gene have been identified in patients with HAEnC1. These code for the proline-rich region of coagulation factor XII [45–47]. Most patients with HAEnC1, however, do not have mutations in the *F12* gene [48[¶]].

HAEnC1 is even rarer than HAE-C1-INH. To date, only case reports or small case series have been published. No randomized controlled studies have been reported. C1-INH concentrates, icatibant, ecallantide, danazol and tranexamic acid have been used to treat HAEnC1 within these case studies and small patient series [48[¶]].

TREATMENT FOR AAE-C1-INH

AAE-C1-INH is also rarer than HAE-C1-INH. The onset of clinical symptoms usually occurs after the age of 40. In about 70% of patients, there is an underlying lymphoproliferative disease, an uncontrolled clonal proliferation of B cells including monoclonal gammopathy of unknown significance and malignant lymphoma, and, more rarely, numerous other conditions. In these patients, C1-INH deficiency results from increased C1-INH catabolism. The exact pathomechanism is still unclear, although neutralizing autoantibodies against C1-INH have been found in some patients. AAE-C1-INH has been reported only in small case series and as individual case reports. The objective of therapy is to treat the AAE attack and the underlying disease. Effective treatment of acute attacks has been reported with C-INH concentrate, icatibant, and ecallantide. Tranexamic acid and attenuated androgens have been used prophylactically [49–51]. In some of the patients who needed treatment with rituximab for the underlying hematologic disorders, a partial or complete remission of AAE-C1-INH has been observed [50].

CONCLUSION

In the last few years, a number of drugs have been developed, either for the treatment of acute attacks of HAE or for long-term prophylaxis of the disease. Hopefully, these drugs will diminish the burden of hereditary and acquired angioedema by reducing the risk of asphyxiation and by reducing the number of severe attacks.

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Conflicts of interest

K.B. is a consultant to CSL Behring and to Shire.

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- of special interest
- of outstanding interest

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