Diagnosis and Treatment of Bradykinin-Mediated Angioedema: Outcomes from an Angioedema Expert Consensus Meeting

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Key Words

Angioedema · C1 inhibitor · Hereditary angioedema · Treatment · C1-esterase inhibitor

Abstract

Several types of angioedema exist beyond hereditary angioedema (HAE) types I/II; however, the diagnostic and treatment needs of these conditions are not well understood. Noticeably, there are no licensed treatments available for other forms of angioedema beyond HAE types I/II, and similarly they are unresponsive to conventional antihistamine/glucocorticoid treatment. A group of angioedema experts met in Budapest in May 2013 to discuss such issues, presenting their experience, reviewing available literature and identifying unmet diagnostic and treatment needs in three different angioedema types: HAE with normal C1-inhibitor (C1-INH; previously referred to as type III HAE); nonallergic angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema (ACEI-AAE), and acquired angioedema due to C1-INH deficiency (C1-INH-AAE). The group identified unmet diagnostic and treatment needs in HAE-nC1-INH, C1-INH-AAE and ACEI-AAE, explored remedies and made recommendations on how to diagnose and treat these forms of angioedema. The group discussed the difficulties associated with using

diagnostic markers, such as the level and function of C1-INH, C1q and C4 to reliably diagnose the angioedema type, and considered the use of genetic testing to identify mutations in *FXII* or *XPNP2* that have been associated with HAE-nC1-INH and ACEI-AAE, respectively. Due to the lack of approved treatments for HAE-nC1-INH, ACEI-AAE and C1-INH-AAE, the group presented several case studies in which therapies approved for treatment of HAE types I/II, such as icatibant, ecallantide and pasteurized, nanofiltered C1-INH, were successful. It was uniformly agreed that further studies are needed to improve the diagnosis and treatment of angioedema other than HAE types I/II.

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Introduction

Hereditary angioedema (HAE) types I/II (HAE with deficient C1-inhibitor, C1-INH, and HAE with dysfunctional C1-INH) are well-characterized forms of HAE, which can be diagnosed by low functional levels of C1-INH and, in most cases, have a positive family history. Several treatments exist for HAE types I/II, including C1-INH, the β_2 bradykinin receptor antagonist icatibant, and the kallikrein inhibitor ecallantide, which have been suc-

Fig. 1. Mechanism of bradykinin-mediated angioedema. Increased bradykinin levels lead to vasodilation, increased tissue permeability and edema. Degradation of bradykinin is mediated by kininases. ACE, which plays a role in degradation of bradykinin, can be inhibited by ACEIs. Production of bradykinin can be inhibited by ecallantide, which acts on kallikrein, or by C1-INH, which acts to inhibit formation of kallikrein and HMW kininogen. Activation of the bradykinin $\beta 2$ receptor is inhibited by icatibant. In angioedema cases where C1-INH is deficient, treatment with pnfC1-INH or recombinant human C1-INH replaces endogenous C1-INH to control bradykinin levels. Dashed lines indicate inhibition. ACE = Angiotensin converting enzyme; ACEI = angiotensin converting enzyme inhibitor; HMW = high molecular weight; C1-INH = C1-inhibitor; pnfC1-INH = pasteurized, nanofiltered C1-INH.

cessful in the treatment of HAE types I/II for many years [1]. However, for other forms of bradykinin-mediated angioedema, the diagnostic and treatment needs are less well understood. Bradykinin-mediated forms of angioedema include both hereditary, i.e. HAE types I and II, and nonhereditary forms, i.e. acquired angioedema with C1-INH deficiency [2]. During bradykinin-mediated angioedema, increased levels of bradykinin results in over-activation of $\beta 2$ bradykinin receptors and subsequently increased tissue permeability, vasodilation and edema (fig. 1). Bradykinin-mediated forms of angioedema are distinct from allergic reactions, as they do not respond to conventional therapies such as antihistamines or corticosteroids.

To address these points, a group of international angioedema experts gathered in Budapest in May 2013 to present their experience, review available literature and explore the feasibility of using medications approved for HAE types I and II in the treatment of other forms of angioedema. The HAE expert group explored three other forms of bradykinin-mediated angioedema: HAE with normal C1-INH (HAE-nC1-INH), formerly referred to as type III HAE, which can result from FXII mutations (FXII-HAE) or an unknown cause (U-HAE), nonallergic angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema (ACEI-AAE), and acquired angioedema due to C1-INH deficiency (C1-INH-AAE) [3]. For these forms of angioedema there are currently no licensed treatments available, and no improvements are observed

with conventional antihistamine/glucocorticoid treatment. Furthermore, in these forms of angioedema, C1-INH antigenic levels and function may be normal and there may be no family history which can make diagnosis of these forms difficult.

Here we report on the findings of the HAE expert meeting and summarize the thoughts and opinions of HAE experts on the key characteristics (table 1) and challenges associated with diagnosing these forms of angioedema. We present evidence from the HAE expert meeting that suggest that treatments, such as C1-INH, which are used in the treatment of HAE I/II may be beneficial in the treatment of FXII-HAE/U-HAE, ACEI-AAE and C1-INH-AAE.

Challenges Associated with Diagnosing Alternative Forms of Angioedema

During the angioedema expert meeting, participants stressed the importance of ensuring that the exact medical condition is treated. Allergic forms of angioedema are histamine dependent and can often be determined by the presence of urticaria and successful treatment with antihistamines/glucocorticoids. Since the majority of cases are histamine dependent, it was uniformly agreed that initial cases of angioedema should be treated as such and given short-term treatment with antihistamines/glucocorticoids. An alternate diagnosis should be established

Table 1. Characteristics of hereditary, nonallergic drug-induced and acquired forms of angioedema

Type of angioedema	Description	Diagnostic markers					Genetic factor	Diagnosis
		C1-INH antigenic level	C1-INH functional level	C4	C1q	Anti-C1-INH antibodies		
HAE I/II	Symptoms present in childhood and worsen around puberty. Attacks target extremities, genitourinary tract, bowel, face, upper airway. Abdominal/bowel and upper airway attacks common. Prodromal symptoms, e.g. erythema marginatum. Attacks last 72–96 h. Frequency of attacks variable. Symptoms worsened by stress/trauma, estrogens, infections.	Low in HAE type I. Normal or elevated in HAE type II	Low	Low	Normal	No	<i>C1-INH</i> gene	Family history of angioedema present in 75%. Mutation in <i>C1-INH</i> gene. Low functional levels of C1-INH and C4. Normal C1q.
HAE-nC1-INH (FXII-HAE/U-HAE)	Similar to types I/II but: Older age of onset: 20–30 years. Fewer attacks/longer attack-free intervals. Higher percentage of cutaneous, facial and upper airway attacks. Fewer abdominal attacks. Multisite attacks rare. Recurrent angioedema without wheals. Duration of attacks >24 h. Trigger factors: estrogens.	Normal	Normal	Normal	Normal	No	<i>FXII</i> gene (in some cases)	Family history of angioedema present in 58%. <i>FXII</i> mutation reported in 10–25%. Normal antigenic and functional levels of C1-INH, normal levels of C4 and C1q.
Nonallergic ACEI-AAE	Most common cause: ACEI. Incidence of ACEI-induced angioedema 0.1–0.7%. Attacks target face, tongue, lips, pharynx and larynx. Bowel and extremities less commonly affected. Risk factors: female sex, age, ethnic origin, previous drug interactions, allergies, smoking, obesity.	Normal	Normal	Normal	Normal	No	<i>XPNPEP2/APP</i> (in some cases)	Associated with ACE inhibitors. Polymorphisms in <i>XPNPEP2/APP</i> associated with higher risk. Normal antigenic and functional levels of C1-INH, normal levels of C4 and C1q.
C1-INH-AAE	Associated with lymphoproliferative disorder, autoimmune disorders, lymphoma or infection that lead to depletion of C1-INH, or associated autoantibodies against C1-INH lead to inactivation. Older age of onset: >40 years. Attacks target face, upper airway and abdomen. Multisite attacks rare.	Low/normal	Low	Low	Low (in most cases)	In some cases	None	Presence of C1-INH autoantibodies in some patients. Low or normal antigenic level and low functional level of C1-INH, low levels of C4 and C1q.

in cases that are nonresponsive to short-term treatment with antihistamines/glucocorticoids. Diagnostic tests investigating C1-INH, C1q or C4 levels could be used as a diagnostic tool; however, these may not always indicate if attacks are histamine or bradykinin induced (table 1).

HAE with Normal C1-INH

In FXII-HAE/U-HAE, antigenic and functional levels of C1-INH, C1q and C4 are normal, so diagnostic testing using these markers cannot be used. FXII-HAE/U-HAE can be characterized by recurrent angioedema attacks

without wheals, a prolonged duration of attacks, an older age of symptom onset, with the mean age of first attack 26.8 ± 14.9 years, and a higher percentage of facial attacks [2, 4]. Furthermore, key differentiating factors for FXII-HAE/U-HAE are that it can be triggered by estrogens [4, 5] and has been associated with mutations in the *FXII* gene [6–8].

Exposure to estrogens, either during pregnancy or from oral contraceptives, has been shown to exacerbate the severity of attacks in many FXII-HAE/U-HAE patients [4, 9]. Furthermore, a subset of FXII-HAE/U-HAE patients has been shown to be estrogen-dependent, i.e. swelling only occurs at the time of estrogen exposure. Angioedema expert discussion of unpublished experience identified that 80% of French cases worsened with estrogen, 13% of cases were estrogen dependent (only occurring with contraceptive use or pregnancy), and only 7% of cases were not influenced by estrogen (as presented at the 8th C1-INH deficiency workshop [10]). However, this is in contrast to the experience of other experts at the meeting; in a Spanish cohort the majority of patients (85%) were estrogen dependent, and 15% were estrogen related (as presented at the 8th C1-INH deficiency workshop [10]). Furthermore, published data from Vitrat-Hincky et al. [5] observed that the condition of 54.5% of women worsened with estrogen, and 23% were estrogen dependent [11]. These data highlight that the influence of estrogen on FXII-HAE/U-HAE is highly variable.

Several mechanisms have been proposed for the estrogen dependence observed in FXII-HAE/U-HAE that involve the effects of estrogen on both bradykinin production and degradation. High levels of estrogen that occur during pregnancy or from oral contraceptive use have been shown to increase the level of FXII due to an estrogen response element in the gene promoter. As illustrated in figure 1, FXII, when activated, converts prekallikrein to kallikrein; the first step in bradykinin production and increased FXII could result in increased bradykinin production. Additionally, under high-estrogen conditions, levels of C1-INH have been shown to decrease, which would reduce inhibition of FXII and kallikrein and further promote increased bradykinin production (fig. 1). High levels of estrogen may also reduce the degradation of bradykinin through inhibition of angiotensin-converting enzyme (ACE) expression and possibly through a reduction of aminopeptidase P (APP) levels [12].

Although FXII-HAE/U-HAE has been associated with mutations in the *FXII* gene; mutations are only found in a small subset of patients [4] and symptoms in

patients with or without FXII mutations are similar [11, 13]. During the meeting it was reported that only 10–25% of diagnosed French patients have a FXII mutation. Furthermore, 42% of patients had no family history and disease symptoms can be highly variable. To illustrate this, a case report was presented of a female FXII mutation carrier who experienced recurrent abdominal attacks throughout puberty and pregnancy, together with some additional peripheral attacks. In contrast, her sister, also an FXII mutation carrier, only suffered attacks during pregnancy, and her mutation-carrying daughters are asymptomatic. The low percentage of FXII mutation carriers led to the question of how patients can be reliably identified by genotyping alone, and may explain the variability in incidence across other countries, for example American angioedema experts highlighted that patients with normal C1-INH levels and no family history of angioedema would not be genotyped, thus few cases of FXII-HAE/U-HAE are reported there. Diagnosis of FXII-HAE/U-HAE therefore depends upon the interplay between genetic, clinical and laboratory factors, and key criteria to monitor include recurrence of angioedema attacks, near normal C1-INH, C1q and C4, evidence of estrogen dependence and evidence of FXII mutations or family history.

ACEI-Induced Angioedema

In ACEI-AAE, levels of C1-INH, C4 and C1q are normal and attacks commonly affect the head and neck, and can involve the mouth, tongue and larynx, which can lead to fatal laryngeal obstruction. ACE is an important regulator of bradykinin levels involved in the cleavage and degradation of bradykinin (fig. 1). In the presence of ACEIs, degradation of bradykinin is dependent upon APP, neutral endopeptidase (NEP) and dipetidyl peptidase IV (DPP-IV), and the blood and tissue levels of these enzymes are important factors in the prevention of ACEI-AAE [14]. The reported incidence of ACE-AAE is 0.1–2% [14]; however, some populations, such as African Americans, women and smokers, have a higher risk of developing ACEI-AAE [2].

Polymorphisms in *XPNPEP2* [15, 16] and haplotype mutations in the *APP* gene [15, 17] have been identified as possible risk factors of ACEI-AAE; however, there is no clear genetic basis for the disease. *XPNPEP2* encodes APP, which is involved in the cleavage and inactivation of bradykinin. Polymorphisms in *XPNPEP2* have been linked with an increased risk, especially in black (African) women [15, 18]. The increased incidence reported among African Americans and women may be due to reduced

plasma activity and levels of APP [15]. On reviewing data from the University of Cincinnati on ACEI-induced angioedema, 75% of patients presenting to the emergency department were African American. Due to the complex genetic background the question remains as to whether genotyping would be beneficial in identifying high-risk patients.

The risk of ACEI-AAE is also increased in patients receiving treatment with DPP-IV inhibitors that are used to treat diabetes, or NEP inhibitors used to treat hypertension [14]. A clinical study of patients receiving omapatrilat, an NEP inhibitor currently under development, found that it was more frequently associated with angioedema than the ACE inhibitor enalapril (2.17 vs. 0.68%) [19]. A premarketing study of the DPP-IV inhibitor vildagliptin found that whilst there was no association between vildagliptin treatment alone and angioedema, use of vildagliptin alongside ACEI resulted in a small increased risk of angioedema, as shown by 14 confirmed angioedema cases amongst 2,754 vildagliptin patients compared to 1 amongst 1,819 in a comparator product (odds ratio 4.57; 95% CI 1.57–13.28) [20].

ACEI-AAE often occurs early in the course of ACEI treatment, with around 50% of cases occurring in the first week of treatment [14, 21]; however, it can occur several months or years after initial treatment [2]. While most attacks resolve within 24–48 h of discontinuation of ACEI, they can recur weeks or months after treatment discontinuation [15]. The variable time between the start of ACEI treatment and attack is another factor that can complicate the diagnosis of ACEI-AAE.

Acquired Angioedema due to C1-INH Deficiency

C1-INH-AAE is associated with lymphoproliferative disorders such as monoclonal gammopathy of uncertain significance, malignant lymphoma, neoplasm, infections and autoimmune disorders. C1-INH-AAE can be characterized by large-scale activation of complement pathways and a breakdown of C1-INH [22, 23]. A reduction in C1-INH may be via an interaction with lymphatic tissues which have been shown to consume C1-INH [24]. In some cases C1-INH-AAE may result from autoantibodies against C1-INH [22]. Anti-C1-INH antibodies bind to C1-INH and prevent the formation of C1-INH protein complexes. The presence of autoantibodies can also convert C1-INH into a substrate for proteases which results in cleavage of C1-INH [22, 24]. This leads to depletion of components of the complement system, resulting in low antigenic levels and low functional levels of C1-INH, low

levels of C4 and, in most cases, low C1q [2]. As C1-INH-AAE is associated with low C1-INH, its clinical presentation is similar to HAE types I/II. However, unlike HAE forms, C1-INH-AAE is not associated with an inherited condition so has no family history [2] and is associated with a later age of symptom onset, typically in the 4th or 5th decade of life [2]. In 4 cases presented at the angioedema expert meeting, no patients had a family history of angioedema, 2 patients had autoantibodies against C1-INH and all patients had underlying lymphoproliferative disease (3 with non-Hodgkin's lymphoma, 1 with multiple myeloma).

Diagnosis is usually made by laboratory testing that identifies low C4, C1-INH and low C1-INH function. C1q is low in most cases and helps distinguish C1-INH-AAE from HAE types I/II; nevertheless, not all cases have low C1q, making differential diagnoses difficult. In these cases, genetic analysis to differentiate the hereditary from the acquired form may assist with diagnosis [22]. The presence of autoantibodies against C1-INH may be an indicator of C1-INH-AAE [2], although they are only observed in 70% of patients [25] and thus are not always present, as demonstrated by the cases discussed by the expert group.

Unmet Treatment Needs: The Current Therapeutic Landscape

Currently, there are no approved therapies for FXII-HAE/U-HAE, ACEI-AAE or C1-INH-AAE. Participant experience and unpublished case studies discussed during the meeting showed that therapies approved for use in HAE types I/II, including pasteurized, nanofiltered C1-INH (pnfC1-INH, Berinert; CSL Behring, Marburg, Germany), ecallantide (Kalbitor; Dyax, Burlington, Mass., USA) and icatibant (Firazyr; Shire Orphan Therapies GmbH, Berlin, Germany), have successfully resolved attacks of different types of bradykinin-induced angioedema. Icatibant, ecallantide and C1-INH have been shown to be effective treatments for ACEI-AAE [15, 26], C1-INH-AAE [2, 27] and FXII-HAE/U-HAE [9] (table 2), and are currently the focus of ongoing clinical trials in the USA [28, 29]. Fresh frozen plasma (FFP) has been successfully used in the treatment of FXII-HAE/U-HAE [2, 30] and ACEI-AAE [2, 15], and has been recommended as a treatment for angioedema when no specific treatment options are available [2]. However, the use of FFP was discussed during the HAE expert meeting as, although FFP is a successful treatment option for angio-

Table 2. Evidence of treatment in hereditary angioedema with normal C1-INH, ACEI-induced angioedema and acquired angioedema

Type of angioedema	Treatment					Other treatment considerations
	Antihistamines/ corticosteroids	FFP	Icatibant	Ecaltantide	PnfC1-INH	
HAE-nC1-INH (FXII-HAE/ U-HAE)	Antihistamine treatment was ineffective in 15 patients who received treatment for 67 attacks [6]. Corticosteroid treatment was ineffective in 27 patients who were treated for 186 attacks [6].	Successfully used to treat swelling in a 65-year-old patient [30].	Successfully used to treat acute attacks in 3 patients with treatment success observed within 1–2 h [35]. Self-administration was successful in the treatment of abdominal and laryngeal attacks [36].	Successfully used to treat a 65-year-old patient following initial treatment with FFP/C1-INH [30].	Successfully used to treat angioedema acute attacks in 6/7 patients. Treatment was ineffective in 1 patient with abdominal attack [6]. C1-INH was successfully used to treat 2 cases of severe laryngeal attacks [11] and for 3 short-term prophylaxis treatments during childbirth [11]. Data from the COBRA registry indicated that of 16 attacks treated with C1-INH, 75% improved within 1 h.	Progesterone, danazol and tranexamic acid have been used prophylactically [9].
Nonallergic ACEI-AAE	Mild cases may respond to antihistamine or corticosteroid treatment; however, moderate-to-severe cases do not [15].	Successfully used to treat lip and tongue swelling in a 43-year-old patient [37]. Successfully used in 7 cases that were not responsive to antihistamines, corticosteroids or epinephrine [38].	Rapidly resolved symptoms and shortened attack duration [39, 40]. In phase III FAST trial, 89.8% of attacks were successfully treated with a single injection of icatibant [41]. Currently in clinical trials to assess efficacy [29].	Theoretically a potential treatment [26]; data presented during the HAE expert meeting shows that ecaltantide could resolve facial/throat swelling in a 54-year-old patients. No published data available from clinical trials; however, ecaltantide is currently in phase II clinical trials in the USA to assess safety and efficacy [28].	Successfully used to treat tongue swelling in a 61-year-old patient within 30 min [31] and has been used to treat lingual and buccal attacks. Currently in phase III clinical trials in Germany to assess the time to onset of relief [32].	Withdrawal of ACEI is key to management of ACEI-AAE and many patients do not have further attacks following ACEI withdrawal [15].
C1-INH-AAE	Use of antihistamines or corticosteroids is not recommended.	No use reported in the literature.	Effective in the treatment of 47/48 attacks in 8 patients [27]. Successfully treated facial and laryngeal attacks in a patient who was nonresponsive to C1-INH [33].	Successfully used to treat facial attacks in 2 patients in patients who were nonresponsive or partially nonresponsive to C1-INH [33].	Data presented at the HAE expert meeting indicated that C1-INH was used for short-term prophylaxis during dental procedures or surgery. Patients may be less responsive or require higher doses due to C1-INH autoantibodies.	Treatment of underlying lymphoproliferative disorder with anti-CD20 antibody, e.g. rituximab, chemotherapy, e.g. cyclophosphamide [24] or plasmapheresis may control angioedema symptoms [42]. Androgens and antifibrinolytics may be used prophylactically [2, 24, 33]. Tranexamic acid is an effective treatment for C1-INH-AAE and is recommend for attack prophylaxis [3].

edema due to the presence of angiotensin II in plasma that acts to degrade bradykinin [15], it should be used with caution for acute treatment of angioedema attacks due to the presence of substrate, which may exacerbate swelling [2, 15]. In countries where other options are available, FFP is not recommended due to the presence of substrate and because it carries a small risk of viral transmission [2, 3], as with other plasma-derived products.

During the HAE expert meeting several case studies on the use of C1-INH in alternative angioedema types were presented. For FXII-HAE/U-HAE, there are limited data available on the therapeutic efficacy of treatments [26]; however, C1-INH has been shown to be moderately or very effective in most patients when used to treat laryngeal attacks [11], for short-term prophylaxis [11] or when used to treat acute attacks in patients with FXII mutations [6]. In the case study reported at the angioedema expert meeting, a patient with the FXII mutation was successfully treated with pnfC1-INH for edematous attacks during pregnancy and for short-term prophylaxis during delivery. French patients who suffered frequent attacks (≥ 7.2 /year) were treated with pnfC1-INH (7%) and a small number of patients received pnfC1-INH prophylactically. The national French registry, COBRA (the French National Center for Bradykinin-Mediated Angioedema), includes patients with FXII-HAE/U-HAE who have been treated with pnfC1-INH. So far, 16 attacks have been successfully treated, with 75% of patients showing improvements within the first hour after administration.

Several case reports of ACEI-AAE were presented at the angioedema expert meeting. The effectiveness of pnfC1-INH was illustrated in a case study [31] and in a small open-label study where lingual and buccal attacks resolved. A randomized, double-blind, multicenter phase III trial of pnfC1-INH in ACEI-AAE is currently underway in Germany to assess the time to complete resolution of signs and symptoms of acute ACE-induced angioedema of the upper airway tract compared to placebo when given on top of standard treatment [32].

For C1-INH-AAE, all 4 unpublished cases discussed at the meeting were successfully treated with pnfC1-INH and 2 patients were prophylactically treated with pnfC1-INH prior to dental procedures. Additionally, it was noted that some patients, particularly those with autoantibodies, required higher doses of pnfC1-INH. This could be due to patients with autoantibodies becoming resistant to C1-INH treatment [2, 22, 24]; in these patients, C1-INH-AAE can be successfully treated with icatibant or ecallantide [27]. C1-INH-AAE is linked to lymphoprolif-

erative diseases, and it has been observed that cytotoxic treatment of the lymphoproliferative diseases associated with C1-INH-AAE variably reverses the complement impairment, leading to improvement of the angioedema symptoms [24].

The question of why C1-INH treatment would be effective in forms of angioedema in which C1-INH levels are normal was raised by some angioedema experts. During the discussion participants proposed that, mechanistically, treatment with C1-INH concentrate might prevent further production of bradykinin, although it was suggested that there may be a latency in response due to the time taken to metabolize preexisting bradykinin (fig. 1).

Discussion

The angioedema expert group identified unmet diagnostic and treatment needs in FXII-HAE/U-HAE, ACEI-AAE and C1-INH-AAE. In particular, they noted that diagnostic markers such as levels of C1-INH, C4 or C1q cannot be reliably used to differentiate between angioedema types. For FXII-HAE/U-HAE and ACEI-AAE the levels of C1-INH, C4 and C1q are normal but complementary testing may be useful to provide a differential diagnosis from HAE types I/II. The presentation of C1-INH-AAE is similar to HAE type I/II, so differentiating these types can be difficult using diagnostic markers; low C1-INH and C4 levels are expected, but C1q may be normal. If the C1q level is normal (~30% of cases) [33], genetic testing can distinguish between C1-INH-AAE and HAE types I/II; however, mutation of the C1-INH gene cannot be detected in 8–10% of cases of HAE types I/II [34]. The presence of autoantibodies in C1-INH-AAE may be a useful diagnostic marker, although these are not present in all cases.

The expert consensus was that more definitive testing is essential for angioedema, not only to determine bradykinin- from histamine-induced angioedema, but also to distinguish different types of bradykinin-induced angioedema. Definitive treatment for FXII-HAE/U-HAE and other angioedema types will require tests that can confirm the diagnosis. Whilst there are currently no approved therapies for FXII-HAE/U-HAE, ACEI-AAE and C1-INH-AAE, evidence presented during the HAE expert meeting indicated that therapies such as C1-INH, icatibant and ecallantide can be effective. Further data from clinical studies are needed to confirm the efficacy of the medications discussed above

in bradykinin-induced diseases other than HAE types I/II; however, several promising trials in ACEI-AAE are currently ongoing.

- FXII-HAE/U-HAE has a positive family history, symptom onset is most often at age 20–30 years, it is largely associated with estrogens and is observed in patients with or without mutation in the *FXII* gene.

Key Clinical Points

The following key clinical points were agreed upon at the meeting:

- ACEIs are the leading cause of drug-induced angioedema.
- C1-INH-AAE is not associated with a hereditary C1-INH deficiency, is often associated with a C1-INH autoantibody and a low C1, and occurs most commonly in patients aged >40 years.

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