

REVIEW

Non-histaminergic angioedema: focus on bradykinin-mediated angioedema

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Summary

Angioedema is a result of increased vascular permeability, with subsequent extravasation of intravascular fluid into the surrounding tissues. Angioedema may be mediated by histamine, bradykinin or other mediators. Histaminergic angioedema generally presents with urticaria and/or pruritus and will respond to conventional treatment with antihistamines, corticosteroids or epinephrine. Bradykinin-mediated angioedema, which includes hereditary angioedema (HAE types I, II and III), acquired C1-INH deficiency, and angiotensin-converting enzyme inhibitor-induced angioedema does not typically present with urticaria/weals and does not respond to conventional agents such as antihistamines or corticosteroids. In recent years, several agents that prevent the generation or activity of bradykinin have been developed for the treatment of HAE types I and II and are also being evaluated in other types of bradykinin-mediated angioedema. These agents have the potential to improve outcomes for patients with different forms of bradykinin-mediated angioedema.

Introduction

Angioedema is defined as localized swelling of the deeper dermis and/or mucosa of the gastrointestinal (GI) tract and upper airways [1]. The underlying pathophysiology of angioedema is increased vascular permeability with subsequent extravasation of intravascular fluid into the surrounding tissues [1]. Angioedema may be histaminergic or non-histaminergic. Angioedema that presents with urticaria and pruritus is usually IgE mediated (i.e. allergic angioedema), whereas angioedema without associated urticaria generally suggests a non-histaminergic process [1]. Determining the aetiology of angioedema is a critical step in its treatment; allergic or histaminergic angioedema typically responds to antihistamines, corticosteroids or epinephrine, whereas non-histaminergic angioedema conditions require treatments that target other mediators of swelling such as bradykinin. Angioedema with urticaria usually responds well to antihistamines, and an appropriate trial of antihistamines (up to four times the standard dose used for allergic disorder) is always required before a clinical label of non-responsive

to antihistamines and non-histaminergic can be applied [2]. Angioedema without urticaria may be due to C1 esterase inhibitor (C1-INH) deficiency or other mechanisms resulting in excess bradykinin production and are frequently resistant to such therapy. It may respond to prophylactic therapy with replacement C1-INH, anabolic androgens, tranexamic acid, or acute treatment with C1-INH, or medications targeting bradykinin [3, 4]. This article reviews the differential diagnosis and treatment of non-histaminergic angioedema, with a focus on bradykinin-mediated angioedema, including hereditary angioedema (HAE), acquired C1-INH deficiency, and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema.

Hereditary angioedema

Hereditary angioedema is a rare inherited disorder usually due to mutations in the C1-INH gene (*SERPINC1*) that lead to low levels of functional C1 inhibitor (C1-INH) [2]. C1-INH is a serine protease inhibitor that has key regulatory functions in the activation of the

complement and contact systems and, to a lesser extent, in the fibrinolytic pathway [5, 6]. The role of C1-INH in the contact system is particularly relevant to the pathology of HAE. In the contact system, exposure of factor XII to even small quantities of factor XIIa results in a positive feedback loop, with factor XIIa activating additional molecules of factor XII. Factor XIIa also cleaves prekallikrein to kallikrein, the enzyme that cleaves high-molecular-weight kininogen to the vasoactive peptide bradykinin. C1-INH inhibits both factor XIIa and kallikrein. Therefore, inadequate levels of functional C1-INH lead to uninhibited generation of bradykinin, resulting in increased vascular permeability, vasodilation and contraction of non-vascular smooth muscle. Bradykinin is the primary mediator of swelling in HAE [6–8].

Hereditary angioedema, estimated to occur in 1 in 50 000 individuals, is an inherited autosomal dominant disorder; however, in 25% of cases, HAE is due to spontaneous mutations in *C1INH* and there is no family history of the disease [9]. HAE is typically classified as either type I or type II, although the clinical presentations and treatment of these two types do not differ. Type I, which accounts for 85% of cases, is due to a deficiency of antigenic C1-INH [10]. Type II HAE, which accounts for the remaining 15% of cases, is due to mutations that give rise to a dysfunctional C1-INH protein [10–12].

HAE attacks are characterized by non-pruritic and non-pitting swelling of subcutaneous (SC) or submucosal tissues. Many patients have prodromal symptoms such as a tingling sensation at the affected site, nausea or a general sense of fatigue occurring several hours prior to an attack [13, 14]. Erythema marginatum (a non-raised, non-pruritic serpiginous rash on the skin) may be present in one-third of cases [13, 14]. Urticaria is typically absent. Angioedema symptoms generally last 2–5 days before resolving spontaneously without treatment [6]. Initial symptoms of HAE typically emerge before the age of 20 in ~90% of patients; the median age at onset of symptoms is approximately 11 years [15]. However, these symptoms are often not attributed to HAE at the time, and it takes on average 8 years from the onset of symptoms until a proper diagnosis is made [16]. Known triggers for HAE attacks include emotional stress, infections, trauma, medical and surgical procedures, and oestrogens [9].

Swelling in HAE can affect any part of the body and may affect multiple sites at once. However, the extremities, abdomen, genitals and face are commonly affected [15]. Approximately 50% of untreated patients will have a life-threatening laryngeal attack [15]; mortality rate due to laryngeal oedema has been reported to be as high as 30% among untreated patients [3].

A third form of inherited angioedema has been identified and labelled HAE type III, or more correctly,

inherited angioedema with normal C1-INH. HAE type III is also inherited in an autosomal dominant pattern but is due to mutations outside *C1INH*, including mutations of the factor XII gene and others. To make the diagnosis of HAE III, there must be a family history of recurrent episodes of angioedema. Unlike HAE type I or II, the underlying pathophysiology of type III HAE is not well understood, but it may be mediated via bradykinin. This point remains speculative, since early studies pointed to gain-of-function mutations in FXII, which might result in increased amidolytic activity; however, this has not been confirmed in later studies [17]. HAE with normal C1-INH primarily affects women and appears later in life, with an age of onset of 26.8 years [18]. There have been reports of HAE type III occurring in males, but symptoms appear to be less severe than in females [19]. HAE type III has clinical features similar to HAE types I and II; however, recurrent facial, lip and tongue swellings are more common and abdominal attacks less frequent [17]. As with HAE types I and II, episodes can be triggered by trauma and oestrogen use. Unlike HAE types I or II, HAE with normal C1-INH is characterized by normal C4 and C1-INH protein and functional levels. Currently, therefore, a diagnosis is achieved based on the presence of non-histaminergic angioedema (as defined above with a recorded failure of high-dose antihistamines) with a positive family history and normal complement and C1-INH and is supported by abnormal FXII genetics [17]. With greater clarity regarding the genetic basis of HAE with normal C1-INH, this heterogeneous group of disorders is likely to be separated out into distinct clinical entities.

Acquired C1-INH deficiency

Acquired angioedema (AAE), or acquired C1-INH deficiency, is a very rare bradykinin-mediated angioedema that is frequently associated with lymphoproliferative disease (e.g. lymphoma, monoclonal gammopathy) or autoimmune disease (e.g. systemic lupus erythematosus) [20, 21]. In some cases, AAE is thought to be due to the development of anti-C1-INH autoantibodies [20]. It is hypothesized that autoantibodies either destabilize the C1-INH–substrate complex or render C1-INH susceptible to proteolytic cleavage [20]. Symptoms typically emerge in late adulthood, after the fourth decade of life [22], and there is rarely a family history of recurrent angioedema [23]. Clinically, symptoms of AAE resemble those of HAE type I or II, although abdominal manifestations are less common, occurring only in about half of patients [22]. Serum evaluation will demonstrate decreased C4, C1-INH protein and C1-INH function, as well as a decreased C1q. Any patient diagnosed with AAE

should undergo further testing for lymphoproliferative or autoimmune disease, including a full blood count with differential, a lymphocyte subset analysis by flow cytometry, serum protein electrophoresis, antinuclear antibodies, a chest x-ray and possibly computed tomography of the chest, abdomen, and pelvis and a bone marrow biopsy if clinically indicated [22].

ACE inhibitor-induced angioedema

Angiotensin-converting enzyme inhibitor-induced angioedema affects 0.1–6% of people taking these medications [24]. Mean time to symptom onset after starting ACE inhibitor therapy has been reported to be 1.8 years, with about 25% of patients presenting with symptoms after 1 month of therapy, many presenting after 6 months, and some presenting as late as 10 years from the start of therapy [25–28].

Angiotensin-converting enzyme inhibitor-induced angioedema has a predilection for the head, neck, tongue, mouth and larynx/pharynx [29]. ACE is the primary enzyme that inactivates bradykinin; therefore, ACE inhibition can result in accumulation of bradykinin in susceptible individuals, with subsequent oedema [24]. ACE inhibitor-induced angioedema is approximately five times more common among African Americans than Caucasians [28]. This ethnic preponderance may be due to the presence of genetic polymorphisms that result in lower endogenous levels of ancillary enzymes, such as aminopeptidase P, that also cleave bradykinin [30]. Although ACE inhibitor-induced angioedema may present with symptoms similar to those of HAE, patients with the former will have normal C1-INH antigen, C1-INH function and C4 levels. Patients with ACE inhibitor-induced angioedema should avoid use of all other ACE inhibitors as this side-effect is class specific. Up to half of patients who discontinue ACE inhibitors will continue to have attacks of angioedema, and 16% of these cases will not change in severity following discontinuation of the drug [25]. The propensity for angioedema to arise frequently at later time-points in therapy and the possibility of relapse despite discontinuation raise two interesting points. The first is whether the elevations in bradykinin are important or whether its metabolism is a more significant factor. The second is why those patients who decompensate on an ACE inhibitor with no prior history of urticaria or angioedema are unable to regain control of the relevant metabolic pathway [24].

In general, patients who experience ACE inhibitor-induced angioedema do not have a similar reaction to angiotensin receptor blockers (ARBs), although bradykinin levels may still be elevated in patients on ARBs [31–33].

Differential diagnosis

The presence or absence of urticaria is frequently an initial key consideration in the differential diagnosis of angioedema. Histaminergic angioedema is usually accompanied by urticaria and pruritus, whereas bradykinin-mediated angioedema typically is not. The location of angioedema may also provide some insight into the differential diagnosis. Allergic angioedema generally does not involve the GI tract unless the allergen is ingested [1], whereas abdominal involvement is a common feature of bradykinin-mediated angioedema, occurring in more than 90% of patients with HAE types I and II [15] and approximately 30–50% of patients with acquired C1-INH deficiency [22].

It is critical to ask patients and family members about any ingestion of foods that are more commonly allergenic (i.e. peanut, shellfish) and recent medication history, focusing on antibiotics, antihypertensives, analgesics, and herbal products or supplements.

Age at onset of symptoms and a patient's family history may be helpful when determining the aetiology of angioedema without urticaria. In patients with HAE, symptoms usually begin in late childhood or early adolescence during puberty, with a median age of onset of 11.2 years [15]. When patients develop angioedema that manifests in later adulthood, an underlying lymphoproliferative or autoimmune disease should be considered [22]. A family history of angioedema is present in 75% of patients with HAE with C1-INH deficiency; however, 25% of cases are due to spontaneous genetic mutations, so the absence of a family history does not exclude the diagnosis [9]. The presence of a family history is requisite for diagnosis of HAE with normal C1-INH in the absence of a specific genetic marker.

Laboratory diagnosis of angioedema without urticaria

Angioedema without urticaria and without an identifiable cause should prompt laboratory assessment of complement proteins (C4, C1-INH antigen and function, C1q). HAE types I and II are characterized by a low C4 level and low C1-INH functional activity. C4 measurement has been suggested as a screening test; however, in the presence of a strong history, a normal C4 level is insufficient to rule out the diagnosis of HAE because, in rare cases, C4 may be normal or low-normal between attacks [34]. C1-INH protein levels are low in type I HAE and normal or even elevated in HAE type II. Therefore, when diagnosing HAE, it is critical to evaluate both C1-INH protein levels and functional activity. Both HAE types I and II are also characterized by normal C1q. To ensure a correct diagnosis of HAE and avoid potential laboratory errors, complement tests should be repeated to confirm initial results. Once the

diagnosis of HAE has been established, it is not necessary to follow or repeat complement testing as it typically does not correlate with disease severity or activity. Interestingly IgM autoantibodies to C1-INH are found in patients naïve to therapy and do independently predict disease severity in terms of future attack frequency and severity; however, assays for this are not routinely available and testing is currently not part of any treatment guideline (Table 1) [35].

Similar to HAE types I and II, acquired C1-INH deficiency is characterized by low C1-INH plasma levels, low C1-INH functional activity and low C4 levels. However, in about 75% of patients, C1q levels are also low, a diagnostic marker of this disorder [22]. In patients with normal C1q but with a clinical profile consistent with acquired C1-INH deficiency, the presence of antibodies to C1-INH in high titres can confirm the diagnosis. Once the diagnosis is confirmed, patients should undergo testing for autoimmune and lymphoproliferative disease.

C1-INH level and function, C4 level and C1q level are normal in ACE inhibitor-induced angioedema and HAE type III, making family and medical history key components in the diagnosis [9]. In type III HAE, a positive family history is requisite to make the diagnosis.

Figure 1 summarizes the diagnostic process when evaluating patients with angioedema without urticaria [36].

Treatment of bradykinin-mediated angioedema

Bradykinin-mediated angioedema conditions do not respond to antihistamines, corticosteroids or epinephrine, and this may be a clue to the diagnosis. A trial of up to 4 times the standard licensed allergy dose of an antihistamine is needed before angioedema can be said to be non-histaminergic clinically [2]. Bradykinin-mediated angioedema will respond to therapies that indirectly or directly inhibit the formation, accumulation or activity of bradykinin, including bradykinin receptor antagonists, tranexamic acid and C1 esterase inhibitor (Table 2).

HAE types I and II

Management of HAE involves prompt treatment of acute attacks and when necessary, prophylaxis. Prophylaxis may be required in the short term to reduce the risk of swelling in a patient undergoing a stressor or procedure likely to produce an attack or in the long term to decrease the number and severity of attacks. In late 2011, evidence-based recommendations for the management of HAE types I and II were published based on an expert consensus conference in Gargnano, Italy [37]. With regard to acute attacks, these guidelines

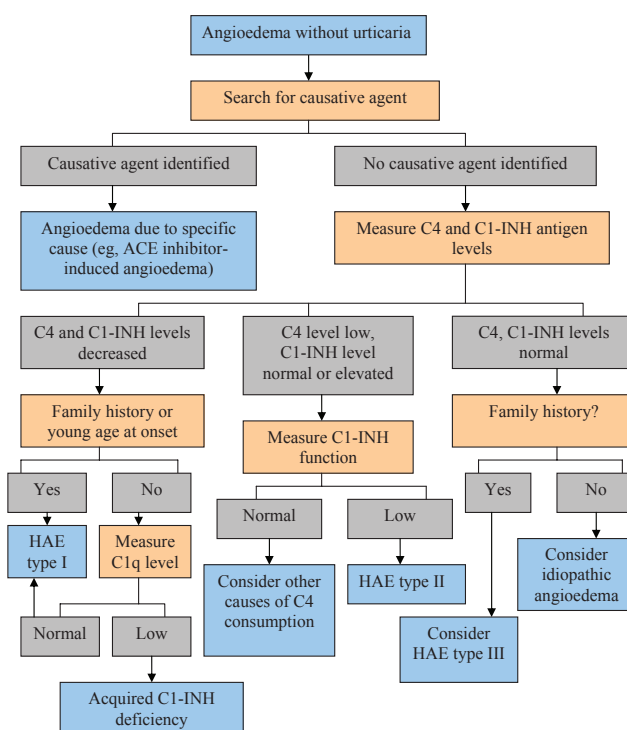


Fig. 1. Differential diagnosis of angioedema without urticaria [9, 36], ACE, angiotensin-converting enzyme; C1-INH, C1-inhibitor; HAE, hereditary angioedema.

recommend that (1) all patients have access to at least one of the specific medications approved for on-demand or acute treatment of HAE attacks; (2) whenever possible, patients should have on-demand medication available at home and be trained to self-administer these medications (this recommendation is based on observational studies that show higher efficacy with home treatment vs. hospital-based treatment); (3) all attacks, regardless of location, should be eligible for treatment as soon as they are recognized by the patient; and (4) in the case of laryngeal attacks, patients should report to the hospital if initial treatment is not effective [37]. Long-term prophylaxis, according to the Gargnano consensus document, is appropriate for patients in whom on-demand treatment is insufficient to minimize the suffering related to the disease [37]. Several therapeutic options are available for the acute and prophylactic treatment of HAE types I and II (Table 3). No one acute treatment is recommended over another in the guidelines due to the lack of head-to-head comparative trials. These medications differ with respect to mode of administration, dosing, side-effects, ability to be self-administered and cost. The costs of treatment vary from patient to patient as they are based on the number and frequency of attacks, route of administration, ability to self-administer medication, need for additional health-care resources and other factors. Selection of medica-

tion should be made in careful consultation with the patient and his/her caregivers based on the patient's individual needs.

Acute therapy. Therapies approved for acute treatment of HAE include plasma-derived C1-INH (Berinert[®], CSL Behring, Marburg, Germany; Ceter[®], Sanquin, Amsterdam, the Netherlands; or Cinryze[®], ViroPharma Incorporated, Exton, PA, USA), recombinant C1-INH (Ruconest[®] or Rhucin[®], Pharming, Leiden, the Netherlands), icatibant (Firazyr[®], Shire, Jersey, JE, USA) and ecallantide (Kalbitor[®], Dyax Corp., Cambridge, MA, USA, approved in the United States, but not in Europe).

Plasma-derived C1-INH concentrates have a well-established efficacy and safety record and generally bring about resolution of symptoms in 30–90 min [38]. Recent North American clinical trials have established a dose of 20 U/kg as effective for the Berinert product [39]. This product has been shown to relieve attacks at facial, abdominal and laryngeal sites when administered at a dose of 20 U/kg, with a median time to onset of symptom relief of 0.46 h [40]. The labelling for Berinert contains a self-administration option, whereby the product can be administered by the patient after appropriate training by a healthcare professional.

A plasma-derived, pasteurized, nanofiltered C1-INH concentrate (nfC1-INH, Cinryze[®]) is approved for acute and prophylactic treatment of HAE in Europe. The efficacy of nfC1-INH for the acute treatment of HAE attacks was evaluated in a randomized, double-blind, placebo-controlled, parallel-group study [41]. A total of 71 subjects were randomized to receive nfC1-INH ($n = 36$) or placebo ($n = 35$) and 68 patients were evaluable. The median time to the beginning of unequivocal relief of the defining symptom of the HAE attack was 2 h vs. > 4 h for placebo ($P = 0.02$) [41]. In an open-label, multicentre trial [42], patients were eligible to receive 1000 U for HAE attacks at any location, with a second dose allowed if symptoms did not improve within 60 min. In all, 101 patients were treated

with nfC1-INH for a total of 609 acute attacks. Median time to onset of symptom relief was 45 min and none of the 84 laryngeal attacks treated with nfC1-INH required intubation [42]. The nfC1-INH product may be self-administered after appropriate training from a healthcare professional.

A recombinant human C1-INH product (rhuC1-INH, Ruconest[®]), manufactured by expressing the human C1-INH protein in the milk of transgenic rabbits, is approved in Europe for the acute treatment of HAE in adults. The efficacy and safety of rhuC1-INH (50 and 100 U/kg) have been evaluated in two independent randomized, double-blind, placebo-controlled studies conducted in Europe and North America. The 100 and 50 U/kg doses of rhC1-INH resulted in a statistically significant reduction in the median time to first symptom relief vs. placebo ($P < 0.001$ and $P = 0.013$, respectively) and in the time to minimal symptoms vs. placebo ($P < 0.001$ and $P = 0.001$, respectively) [43]. Patients must test negative for the presence of IgE antibodies against rabbit allergens before using the product [43]. IgE antibody testing should be repeated annually or after 10 treatments, whichever occurs first. Self-administration of this product is not recommended. The half-life of rhuC1-INH is considerably shorter than that of plasma-derived C1-INH (3 h vs. > 20 h), which limits the use of this product to the acute setting.

Given the availability of several products and recommended licensed doses, Hack et al. [44] evaluated the licensing studies to determine the target C1-INH level that would result in the greatest efficacy. They demonstrated that 50 U/kg of C1-INH provides greater efficacy at 4 h and although all studies reached their target end-point, the use of 50 U/kg or greater achieved higher response rates. Analysis of resolution of symptoms revealed that pdC1INH at doses of 20 or 25 U/kg reduced time to resolution by approximately 50%, whereas rhC1-INH at 50 or 100 U/kg reduced time to resolution by about 80% [44]. Currently 20 U/kg is the recommended standard therapy and this may require revision in the guidelines in light of this and emerging data.

Icatibant, a bradykinin B2 receptor antagonist, is administered as a 30-mg SC injection. The product (Firazyr[®]) is approved in Europe and the United States for the acute treatment of HAE in adults; it has not been evaluated in children < 18 years of age. Icatibant may be self-administered after appropriate training by a healthcare professional. Icatibant has been evaluated in three randomized, double-blind, controlled phase III trials (For Angioedema Subcutaneous Treatment [FAST]-1, FAST-2, and FAST-3) in adult HAE patients with moderate to very severe cutaneous and/or abdominal symptoms [45, 46]. In FAST-1, the median time to clinically significant relief of the index symptom (the primary

Table 1. Complement levels in different forms of bradykinin-mediated angioedema

	C1-INH level	C1-INH function	C4 level	C1q
HAE type I	< 30%	< 30%	Low	Normal
HAE type II	Normal/ elevated	< 30%	Low	Normal
HAE type III	Normal	Normal	Normal	Normal
Acquired C1-INH deficiency	Low	Low	Low	< 30%
ACE inhibitor-induced angioedema	Normal	Normal	Normal	Normal

HAE, hereditary angioedema; C1-INH, C1 inhibitor; ACE, angiotensin-converting enzyme.

Table 2. Medical management of bradykinin-mediated angioedema

Angioedema type	Treatment*	Treatment considerations
HAE types I and II	Treat acute attacks with C1-INH (plasma-derived or recombinant) or icatibant. Administer prophylactic doses of C1-INH before major medical procedures Initiate long-term prophylaxis if attacks not adequately controlled with acute treatment	Laryngeal oedema requires immediate treatment ACE inhibitors and oestrogen-containing medications should be avoided
HAE type III	No approved agents Danazol prophylaxis may help prevent attacks	Does not respond to antihistamines or corticosteroids Icatibant may be of benefit Icatibant may be of benefit
Acquired C1-INH deficiency	Treat underlying lymphoproliferative or autoimmune disease if appropriate High doses of C1-INH may be of benefit Prophylaxis with antifibrinolytics or attenuated androgens may be of benefit	
ACE inhibitor-induced angioedema	Stop ACE inhibitor treatment Provide supportive care	ACE inhibitors should not be used. Icatibant may be of benefit Medical alert bracelet is recommended

*Includes only agents approved in the EU.

HAE, hereditary angioedema; C1-INH, C1-inhibitor; ACE, angiotensin-converting enzyme.

end-point) was not significantly different between icatibant and placebo (2.5 h vs. 4.6 h; $P = 0.14$). In the recent FAST-3 trial, however, icatibant was found to significantly reduce the median time to onset of symptom relief vs. placebo (2.0 h vs. 19.8 h; $P < 0.001$) [46]. In FAST-2, median time to clinically significant relief of the index system was significantly shorter with icatibant vs. tranexamic acid (2 h vs. 12 h; $P < 0.001$) [45]. The most commonly reported adverse reactions were injection-site reactions, which occurred in almost all patients; however, most were mild to moderate in intensity and resolved spontaneously.

Ecallantide, a plasma kallikrein inhibitor that is administered subcutaneously, has also demonstrated efficacy as acute treatment in patients with HAE [47]. In a two double-blind, phase III studies, 143 unique patients were treated with ecallantide 30 mg SC ($n = 70$) or placebo ($n = 73$) within 8 h of an acute attack. The primary end-point was change from baseline in mean symptom complex severity (MSCS) score 4 h after dosing. Based on an integrated analysis of the two trials, the change in MSCS score at 4 h was significantly greater in the ecallantide-treated group (-0.97 ± 0.78 vs. -0.47 ± 0.71 ; $P < 0.001$). Hypersensitivity reactions, including anaphylaxis, have been reported to occur in 2.7% of patients treated with SC ecallantide in clinical trials [48]. In the United States, ecallantide (Kalbitor®; Dyax Corp) must be administered by medical personnel. This product is not yet approved for use in Europe. The potential for anaphylaxis during therapy has been an unfortunate drawback to this medication, as it requires that adrenaline, corticosteroids and antihistamines be part of the management. It also

limits what would otherwise be an attractive self-administration SC therapy to one that must be given in a monitored healthcare setting.

Prophylactic therapy. Long-term prophylaxis may be necessary for patients whose attacks cannot be adequately controlled with acute therapy alone or in whom quality of life is compromised by attacks. Current options for prophylaxis include attenuated androgens (e.g. stanozolol, danazol) and C1-INH therapy [37].

Attenuated androgen therapy has been shown in several studies to substantially reduce the frequency of attacks [49–51]. Dosing must be adjusted empirically, with the eventual goal of achieving the lowest effective dose [9, 52]. In a long-term survey of 118 patients with HAE treated long term with danazol, 95% responded to therapy. However, adverse events occurred in about 78% of patients and led to discontinuation in 25% of patients [51]. Attenuated androgen therapy is associated with numerous dose-dependent side-effects, including weight gain, virilization, muscle pains and cramps, headaches, depression, fatigue, GI side-effects (i.e. nausea, vomiting and constipation), menstrual irregularities, lipid abnormalities and hepatic side-effects (e.g. cholestatic jaundice, peliosis hepatis and a risk for hepatocellular adenoma) [52, 53]. Virilization side-effects may be especially problematic for female patients with HAE. Patients should be counselled on the potential side-effects of attenuated androgen therapy. In addition, liver function tests need to be performed every 6 months along with a lipid profile, CBC and urinalysis. An abdominal ultrasound is recommended annually by some experts in the management of adults

Table 3. Therapeutic options for the acute and prophylactic treatment of hereditary angioedema (HAE) types I and II

Agent	Dose/administration	Adverse event profile*	EU approval status
Plasma-derived pasteurized C1-INH (Berinert®; CSL Behring)	20 U/kg body weight by IV injection	Subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhoea and vomiting	Approved for acute treatment
Plasma-derived, pasteurized, nanofiltered C1-INH (Cinryze®; ViroPharma)	Acute treatment: 1000 U IV Short-term prophylaxis: 1000 U within 24 h before medical, surgical or dental procedure Routine prevention: 1000 U every 3 or 4 days by IV infusion	Upper respiratory tract infection, sinusitis, rash and headache; hypersensitivity reactions may occur	Approved for acute treatment and preprocedural and routine prevention in adolescents and adults
Recombinant human C1-INH (Ruconest®; Pharming)	50 U/kg body weight by IV injection for adults < 84 kg 4200 U for adults ≥ 84 kg	Headache and vertigo	Approved for acute treatment in adults
Icatibant (Firazyr®; Shire)	30 mg by SC injection	Injection-site reactions, rash, nasal congestion, dizziness, headache, asthenia, nausea and abdominal pain	Approved for acute treatment in adults
Ecaltantide (Kalbitor®; Dyax Corp)	30 mg SC administered in three 10-mg (1 mL) injections. If an attack persists, an additional 30-mg dose may be administered within a 24-hour period	Headache, nausea, diarrhoea, pyrexia, injection-site reactions and nasopharyngitis; hypersensitivity reactions may also occur	Not approved
Attenuated androgens (e.g. danazol, stanozolol)	Danazol (≤ 200 mg/day) or stanozolol (≤ 2 mg/day) orally; use lowest effective dose	Weight gain, virilization, muscle pains and cramps, headaches, depression, fatigue, GI side-effects (i.e. nausea, vomiting, constipation), menstrual irregularities, lipid abnormalities and hepatic side-effects	Used for HAE prophylaxis
Antifibrinolytics (e.g. tranexamic acid, EACA)	Tranexamic acid: 20–50 mg/kg per day, divided as two or three daily doses	Dyspepsia, myalgia, muscle weakness, elevated serum creatine phosphokinase or aldolase, hypotension, fatigue and retinal changes	Used for HAE prophylaxis

*Adverse event profile data were obtained from the Summary of Product Characteristics or the US Prescribing Information of each product. C1-INH, C1-inhibitor; GI, gastrointestinal; IV, intravenous; SC, subcutaneous; EACA, epsilon aminocaproic acid.

receiving daily doses of danazol ≥ 200 mg (or equivalent) [9]. Treatment of children using anabolic androgens should be avoided if possible.

Routine prophylaxis with nfC1-INH (Cinryze® 1000 U infusion every 3–4 days) has been found to reduce the frequency, duration and severity of attacks in patients with moderate to severe HAE [41]. In a double-blind, crossover study, 24 subjects with HAE were randomized to receive prophylaxis with nfC1-INH or placebo (two times per week) for 12 weeks and then crossed over to the opposite treatment for another 12 weeks [41]. Among the 22 evaluable subjects, the average number of attacks per 12-week period was 6.26 during nfC1-INH treatment vs. 12.73 during placebo treatment ($P < 0.001$). The number of days of swelling over a 12-week period decreased from 29.6 days to 10.1 days (a decrease of 66%; $P < 0.0001$). The average duration of attacks was 2.1 days during nfC1-INH treatment and 3.4 days during placebo treatment ($P = 0.002$) [41]. Many patients can be taught how to self-infuse C1-INH,

which has the potential to provide several benefits including better control over disease, decreased hospital use and shorter time from attack onset to treatment [54]. The benefits need to be explained to the patient in light of relevant risks, including those related to venous access (bleeding, bruising, thrombosis and phlebitis) and those of blood products (transmissible infection).

Antifibrinolytic agents such as tranexamic acid and epsilon-aminocaproic acid (EACA) are sometimes used as long-term prophylaxis but are less effective than attenuated androgens [9]. These agents are primarily used in children in whom androgen therapy is contraindicated. The dosage of tranexamic acid varies between 20 and 50 mg/kg per day, divided as two or three daily doses [9]. Side-effects include dyspepsia, myalgia, muscle weakness, elevated serum creatine phosphokinase or aldolase, hypotension, fatigue and retinal changes. Patients should undergo testing of liver and renal function every 6 months while on therapy [9].

HAE type III

As inherited angioedema with normal C1-INH is very rare and less well understood than types I and II, the most appropriate treatments are not well known at this point. However, it appears that HAE type III is not responsive to corticosteroids or antihistamines [55], but attacks may be controlled with danazol prophylaxis [56], icatibant [57], progesterone and avoidance of oestrogen-containing medications.

Acquired C1-INH deficiency

Treatment of acquired C1-INH deficiency focuses on treatment of the underlying disease process. C1-INH concentrates are used for acute attacks for patients with acquired C1-INH deficiency, but higher doses of C1-INH are usually required [22]. Acquired C1-INH deficiency is a bradykinin-mediated angioedema and may respond to agents that directly inhibit bradykinin. Bork and colleagues studied the efficacy of icatibant in four patients with acquired C1-INH deficiency who received treatment for 23 acute attacks (19 facial swellings, two tongue swellings and two abdominal pain attacks). Treatment with icatibant was found to reduce the time to symptom relief compared with untreated attacks [58]. Similar success has been reported by Cicardi et al. [59]. Patients with acquired C1-INH deficiency usually benefit from prophylaxis; attenuated androgens are less effective in this type of angioedema than in hereditary C1-INH deficiency and antifibrinolytics are more effective and preferred in this setting [22].

ACE inhibitor-induced angioedema

Treatment of ACE inhibitor-induced angioedema involves discontinuation of the offending drug and emergency acute management of angioedema. Intubation may be necessary [1]. ACE inhibitor-induced angioedema is associated with significant healthcare resource utilization [60, 61]. As this type of angioedema is also mediated by bradykinin, agents that directly inhibit bradykinin, such as icatibant and ecallantide, may have a role in the acute treatment of this condi-

tion, although no controlled studies have been performed with these agents. Future studies are therefore warranted to determine their potential in reducing morbidity and healthcare utilization and costs from this specific and common type of angioedema.

Summary

In the differential diagnosis of angioedema, several factors must be considered, including the presence or absence of urticaria, age of onset, location of symptoms, presence or absence of a family history and symptom triggers. Determining the aetiology of angioedema is a crucial step in the management of this condition. Bradykinin-mediated angioedema conditions, including HAE, acquired C1-INH deficiency, and ACE inhibitor-induced angioedema generally respond to agents that target bradykinin. In recent years, several agents that either directly or indirectly prevent the generation or accumulation of bradykinin have been developed for the treatment of HAE types I and II.

In healthcare economic terms, a patient with HAE costs the wider economy an average of £26 548 per annum in direct and indirect costs, with 68% of direct costs attributed to hospitalization for severe attacks; for mild attacks, 75% of costs are indirect due to missed work, lost productivity and income [62, 63]. Other forms of angioedema account for more than 22 000 hospitalizations in the United States per annum; a similar rate would be expected across Europe [63], the direct and indirect costs averaging £584M per annum. The wider use of newer agents in HAE and other types of bradykinin-mediated angioedema may help drive down these costs, which reflect the high burden of unmet need in the community.

Conflict of interests

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