

Treatment of Hereditary Angioedema

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■ Abstract

Hereditary angioedema due to C1-esterase inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disease.

In the last decade, new drugs and new indications for old drugs have played a role in the management of C1-INH-HAE. This review examines current therapy for C1-INH-HAE and provides a brief summary of drugs that are under development. Increased knowledge of the pathophysiology of C1-INH-HAE has been crucial for advances in the field, with inhibition of the kallikrein-kinin system (plasma kallikrein, activated factor XII) as a key area in the discovery of new drugs, some of which are already marketed for treatment of C1-INH-HAE.

Pharmacological treatment is based on 3 pillars: treatment of acute angioedema attacks (on-demand treatment), short-term (preprocedure) prophylaxis, and long-term prophylaxis.

The 4 drugs that are currently available for the treatment of acute angioedema attacks (purified plasma-derived human C1 esterase inhibitor concentrate, icatibant acetate, ecallantide, recombinant human C1 esterase inhibitor) are all authorized for self-administration, except ecallantide.

Purified plasma-derived human C1 esterase inhibitor concentrate is the treatment of choice for short-term prophylaxis.

Tranexamic acid, danazol, intravenous and subcutaneous nanofiltered purified plasma-derived human C1 esterase inhibitor concentrate, and lanadelumab can be used for long-term prophylaxis.

New drugs are being investigated, mainly as long-term prophylaxis, and are aimed at blocking the kallikrein-kinin system by means of antiprekallikrein, antikallikrein, and anti-activated FXII action.

Key words: Hereditary angioedema. C1 inhibitor. Bradykinin. Kallikrein. Treatment.

■ Resumen

El angioedema hereditario por déficit del inhibidor de la C1 esterasa (AEH-C1-INH) es una enfermedad rara hereditaria autosómica dominante. En la última década nuevos fármacos y nuevas indicaciones de antiguos fármacos han llegado al área del AEH-C1-INH. En esta revisión se valora el conjunto de fármacos disponibles para el AEH-C1-INH, junto con los fármacos en desarrollo. Los avances en el conocimiento de la fisiopatología del AEH-C1-INH han sido fundamentales para este desarrollo, con la inhibición del sistema de calicreína-cininas (calicreína plasmática, factor XII activado) como un punto caliente para el descubrimiento de nuevos fármacos, algunos de los cuales ya han llegado al mercado del AEH-C1-INH.

El tratamiento farmacológico se basa en tres pilares: tratamiento de los ataques agudos de angioedema (tratamiento a demanda), profilaxis a corto plazo o preprocedimiento, profilaxis a largo plazo.

Hay actualmente 4 fármacos disponibles para el tratamiento de los ataques agudos de angioedema (concentrado plasmático purificado nanofiltrado del inhibidor de la C1 esterasa humana, acetato de icatibant, ecalantida, inhibidor recombinante de la C1 esterasa humana), todos ellos autorizados para autoadministración, excepto la ecalantida.

El concentrado plasmático del inhibidor de la C1 esterasa humana es el tratamiento de elección como profilaxis a corto plazo.

Como profilaxis a largo plazo se puede utilizar ácido tranexámico, danazol, concentrado plasmático del inhibidor de la C1 esterasa humano intravenoso y subcutáneo y lanadelumab.

Se están investigando nuevos fármacos, fundamentalmente como profilaxis a largo plazo, dirigidos a bloquear el sistema calicreína cininas con acción anti precalicreína, anti calicreína y anti FXII activado.

Palabras clave: Angioedema hereditario. C1 inhibidor. Bradicinina. Calicreína. Tratamiento.

1. Introduction

1.1. Angioedema: Definition and Classification

Angioedema is a vascular reaction in the deep subcutaneous and/or submucosal tissue characterized by a localized and transitory increase in blood vessel permeability that produces localized tissue swelling [1]. It can be caused by mast cell mediators, such as histamine, or by bradykinin.

Angioedema can present with urticaria or not (angioedema without wheals). Angioedema without wheals is classified into hereditary angioedema (HAE) and acquired angioedema (AAE) [2]. HAE can be caused by C1-esterase inhibitor (C1-INH) deficiency (C1-INH-HAE) or can occur with normal C1-INH levels (nC1-INH-HAE) [2]. C1-INH-HAE is caused by mutations in the *SERPING1* gene (also known as the *C1NH* gene) [2,3]. Mutations in other genes (*F12*, FXII-HAE; plasminogen, PLG-HAE; angiopoietin 1, ANGPT1-HAE; kininogen 1, KNG1-HAE; and myoferlin, MYOF-HAE) have been reported to cause nC1-INH-HAE [4,5]. When no mutation is detected in families with nC1-INH-HAE, the disease is known as HAE of unknown origin (U-HAE) [2].

AAE is sometimes due to C1-INH deficiency (C1-INH-AAE) or related to the intake of angiotensin-converting enzyme inhibitors (ACEIs) (ACEI-AAE) [2].

Treatment with H₁ antihistamines at high doses (up to 4 times the marketed dose) is used to classify idiopathic AAE. If the patient improves, AAE is known as idiopathic histaminergic AAE (IH-AAE), whereas if the patient does not improve it is classified as idiopathic nonhistaminergic AAE (InH-AAE) [2]. It is very important to bear in mind that nonhistaminergic angioedema is not synonymous with bradykinin-mediated angioedema (BK-AE) and that the InH-AAE group includes mast cell-mediated angioedema that responds well to other treatments, such as omalizumab and immunosuppressants (eg, corticosteroids, cyclosporine), and BK-AE, which improves with treatments that block bradykinin receptors (icatibant acetate) or inhibit the kallikrein-kinin system (KKS) (eg, C1 inhibitor, lanadelumab) [6].

Additional forms of angioedema without wheals are angioedema induced by nonsteroidal anti-inflammatory drugs (NSAIDs) and allergic angioedema [7].

Table 1 shows the classification of angioedema.

This review addresses the treatment of C1-INH-HAE.

1.2. Epidemiology of C1-INH-HAE

C1-INH-HAE is a mostly autosomal dominant disease, although the inheritance pattern may sometimes be recessive [8]. There are 2 classes: quantitative C1-INH deficiency (type 1),

Table 1. Classification of Angioedema

Angioedema with wheals			
Allergic urticaria-angioedema			
Urticaria-angioedema induced by NSAIDs			
Spontaneous chronic urticaria/Inducible urticaria associated with angioedema			
Angioedema without wheals			
Acquired (AAE)	Allergens	Allergic angioedema	
	NSAIDs	NSAIDs-angioedema	
	ACEIs (eg, enalapril)	No other cause of angioedema	
	C1-inhibitor deficiency	No family history Onset of symptoms >40 y	Acquired angioedema related to ACEI intake ACEI-AAE
Without an identified cause	Improvement with antihistamines H ₁ (up to 4x commercial dose)	Acquired angioedema with C1-INH deficiency C1-INH-AAE	
		Idiopathic histaminergic acquired angioedema IH-AAE	
	No improvement with antihistamines H ₁ (up to 4x commercial dose)	Idiopathic nonhistaminergic acquired angioedema InH-AAE	
Hereditary (HAE)	C1-inhibitor deficiency	Mutation in the <i>C1NH/SERPING1</i> gene	Hereditary angioedema with C1-INH deficiency C1-INH-HAE
	Normal C1-inhibitor (nC1-INH-HAE)	Mutation in the <i>F12</i> gene	FXII-HAE
		Mutation in the plasminogen gene	PLG-HAE
		Mutation in the angiopoietin 1 gene	ANGPT1-HAE
		Mutation in the kininogen 1 gene	KNG1-HAE
Mutation in the myoferlin gene	MYOF-HAE		
Unknown cause	Hereditary angioedema of unknown origin U-HAE		

Abbreviation: NSAID, nonsteroidal anti-inflammatory drugs.

Table 2. Drugs Marketed for the Treatment of C1-INH-HAE

Drug	Trademark	Company	Mechanism of Action	Half-life	Administration Route	Indications	Dose (Adults)	Dose (Children)	Regulatory Status
Tranexamic acid	Amchafibrin, Cyklokapron, Lysteda	Meda Pharma SL (Madrid, Spain), Mylan Products Ltd (Hertfordshire, United Kingdom), Ferring Pharmaceuticals Inc., Parsippany, NJ, USA)	Antiplasmin and antiplasminogen activity	2-8 h	Oral, IV	LTP	1000-3000 mg/d	20-40 mg/kg/d	Europe: Approved in some countries. FDA: not approved.
Danazol	Danotrol, Danocrine	Sanofi-Aventis (Paris, France)	Increase in hepatic C1-INH synthesis, increase in APP function	9.44 ± 2.74 h	Oral	LTP	Initial dose: 400 mg/d Maintenance dose: maximum 200 mg/d ^a 400-600 mg/d from 5 d before and up to 2 d after (spread over 2 or 3 doses)	2.5 mg/kg/d 5-10 mg/kg/d (maximum 600 mg/d) since 5 d before and until 2 d after	Europe: Approved in some countries USA: Approved
pdC1INH	Berinet	CSL-Bering (Marburg, Germany)	C1-INH replacement	32.7-62.0 h ^b	IV	On demand treatment of acute attacks	20 IU/kg	20 IU/kg	Europe: approved in Germany in 1986. Decentralized country approval. FDA: approved for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adolescent and adult patients. EMA: Approved for STP in children, adolescents and adults Europe: Decentralized approval FDA: Approved in adults and children ≥6 y [107]
	Haegarda, Bermet			1500 IU; 50.6 ± 12.35 3000 IU; 51.5 (13.52) 6000 IU; 56.2 ± 15.02	SC	STP	1000 IU 1-6 h before	15-30 IU/kg 1-6 h before	Same as for adults
pdC1INH	Cinryze	Takeda Pharmaceutical Company Ltd (Tokyo, Japan)	C1-INH replacement	56-62h ^c	IV	On-demand treatment of acute attacks	1000 IU (repeat one hour after if no improvement) ^d	12-17 y: same as for adults. 2-11 y (>25 kg): 1000 IU 2-11 y (10-25 kg): 500 IU (repeat one hour after if no improvement)	EMA: Approved for on demand treatment in children (≥2 y), adolescents and adults. EMA: Approved for STP in children (≥2 y), adolescents, and adults.
						STP	1000 IU 1-24 h earlier ^e		EMA: Approved for STP in children (≥2 y), adolescents, and adults.

Drug	Trademark	Company	Mechanism of Action	Half-life	Administration Route	Indications	Dose (Adults)	Dose (Children)	Regulatory Status
rhC1INH	Ruconest	Pharming Group NV (Leiden, The Netherlands)	C1-INH replacement	3 h	IV	LTP	1000 U twice a week ¹	12-17 y: same as for adults. 6-11 y: 500 IU twice a wk. FDA: Approved for LTP in children (≥ 6 y), adolescents, and adults. EMA: Approved for LTP in children (≥ 6 y), adolescents, and adults [108].	EMA: Approved for on demand treatment in adolescents and adults. FDA: approved for on demand treatment in adolescents and adults (limited data for laryngeal attacks).
Icatibant acetate	Firazyr	Takeda Pharmaceutical Company Ltd	B2R blockage	1-2 h	SC	On-demand treatment of acute attacks	≤ 84 kg: 50 U/kg > 84 kg: 4200 U	Adolescents: same as for adults. 12-25 kg (1.0 mL) 26-40 kg (1.5 mL) 41-50 kg (2.0 mL) 51-65 kg (2.5 mL) > 65 kg (3.0 mL)	EMA: approved for on demand treatment in children (≥ 2 y), adolescents, and adults FDA: approved for on-demand treatment in adults (≥ 18 y)
Ecallantide	Kalbitor	Takeda Pharmaceutical Company Ltd	Kallikrein inhibition	2.0 \pm 0.5 h	SC	On-demand treatment of acute attacks	30 mg administered subcutaneously in 3 doses of 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24-h period.	≥ 12 y (same as for adults)	FDA: approved for on demand treatment in patients ≥ 12 y EMA: not approved
Lanadelumab	Takxzyro	Takeda Pharmaceutical Company Ltd	Kallikrein inhibition	~ 2 wk	SC	LTP	300 mg/2 wk 6 mo \Rightarrow 300 mg/4 wk if good control (no attacks in the last 6 mo) (FDA)	≥ 12 y (same as for adults)	EMA: Approved in patients ≥ 12 y FDA: Approved in patients ≥ 12 y

Abbreviations: B2R, bradykinin type 2 receptor; C1-INH, C1-inhibitor; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; pdC1INH, purified nanofiltered plasma-derived human C1 esterase concentrate; rhC1INH, recombinant human C1 esterase concentrate; SC, subcutaneous; STP, short-term prophylaxis.

¹The maximum maintenance dose of danazol is 200 mg/d; it should be lowered to the minimum effective dose which can be as low as 100 mg 2 days per week.

²This varies according to severity of C1-INH-HAE and whether it is assessed in an asymptomatic or symptomatic period.

³Assessment has been performed in asymptomatic patients with C1-INH-HAE.

⁴The dose of Cinryze for on-demand treatment can be repeated 1 hour later; 66% of the patients needed to repeat the dose in the clinical trial [48].

⁵Although the prescribing information for Cinryze says that it can be administered 1-24 hours prior to the procedure, it should not be administered more than 6 hours before the procedure.

⁶The interval between Cinryze doses can be shortened or lengthened according to the frequency of the angioedema attacks.

⁷The dose can be repeated after 6 hours of an incomplete response (a single dose is enough in up to 85%-92% of cases) [53]. A maximum of 3 doses in 24 hours or 8 doses in 4 weeks is advised.

the most frequent, and qualitative C1-INH deficiency, with normal C1-INH levels and low C1-INH function (type 2) [2]. In a recent systematic review of epidemiological studies, the prevalence of C1-INH-HAE was estimated to vary between 1.1 and 1.6 per 100 000 inhabitants [9].

1.3. Pathophysiology of C1-INH-HAE

C1-INH is a 105-kDa glycoprotein from the serpin superfamily [2,3,10]. It inhibits several proteases of the complement system (C1r and C1s from the classical pathway, MASP1 and MASP 2 from the lectin pathway), the KKS (plasma kallikrein; FXIIa, FXIIf; high-molecular-weight kininogen, HK), the coagulation system (FXIa), and the fibrinolytic system (plasminogen, PLG) (Figure 1) [2,3,10]. The absence of plasma K inhibition produces activation of the KKS, with generation of bradykinin by cleavage from HK. Bradykinin is a proinflammatory vasodilator that binds the bradykinin type 2 receptor (B2R) on endothelial cells and produces vasodilation and liquid leakage from the vascular space into the interstitial space and localized swelling [2,3,10]. In addition, the lack of inhibition of fibrinolysis produces an increase in D-dimer [11].

Bradykinin is quickly catabolized to inactive forms (Figure 1) [12], with ACE as its main inactivator (70%). Other enzymes that catabolize bradykinin are aminopeptidase P

(APP) (20%), neutral endopeptidase (NEP), and dipeptidyl peptidase 4 (DPP4) [10,12]. Bradykinin is also metabolized by carboxypeptidase N (CPN) to des-Arg-BK, which binds to bradykinin type 1 receptor (B1R) and can also produce vasodilation [3]. In addition, des-Arg-BK is inactivated by ACE and APP.

1.4. Clinical Symptoms in C1-INH-HAE

C1-INH-HAE is characterized by recurrent, transient, and unpredictable episodes of white, cold, nonpruriginous edema without associated urticaria that resolve spontaneously in 2-3 days (sometimes in 5 days) [3,10,12,13].

The symptoms generally first manifest during the first decade of life and worsen during puberty [3,12].

Angioedema episodes can be peripheral (eg, limbs, face, genitals) or abdominal or affect the upper airway (eg, pharynx, larynx, tongue); they seldom affect other locations [14,15]. The attacks are often combined and migratory at different locations. Peripheral and abdominal attacks are the 2 most frequent [10,12].

Abdominal episodes are characterized by abdominal pain, nausea, and vomiting [16]. Pain is very disabling and may prevent the patient from walking. Hypovolemia with orthostatic hypotension, dehydration, and hypovolemic shock can develop in severe abdominal episodes [17,18]. The

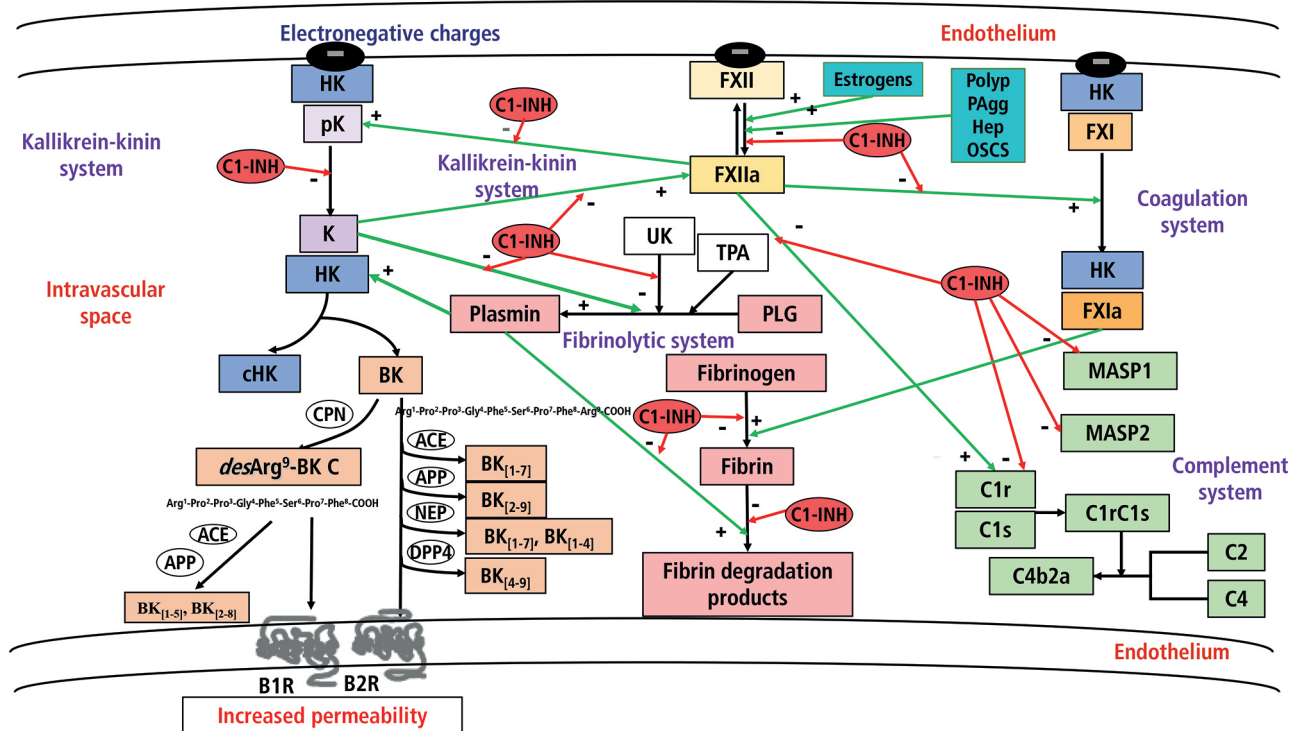


Figure 1. Pathophysiology of C1-INH-HAE. APP indicates aminopeptidase P; ACE, angiotensin converting enzyme; aFXI, activated coagulation factor XI; aFXII, activated coagulation factor XII; B1R, bradykinin type 1 receptor; B2R, bradykinin type 2 receptor; TPA, tissue plasminogen activator; BK, bradykinin; CHK, cleaved high-molecular-weight kininogen; C1, complement component 1; C2, complement component 2; C4, complement component 4; C1-INH, C1-esterase inhibitor; CPN, carboxypeptidase N; DPP4, dipeptidyl peptidase 4; FXI, coagulation factor XI; FXII, coagulation factor XII; Hep, heparin; HK, high molecular weight kininogen; K, kallikrein; MASP1, mannan-binding lectin-associated serine protease 1; MASP2, mannan-binding lectin-associated serine protease 2; NEP, neutral endopeptidase; OSCS, over sulphated chondroitin sulphate; PAgg, misfolded protein aggregates; pK, prekallikrein; PLG, plasminogen; polyP, polyphosphate; UK, urokinase.

Table 3. Adverse Events and Contraindications of the Drugs Used in C1-INH-HAE

Drug	Secondary effects	Precautions	Contraindications
Tranexamic acid	Muscle necrosis: – Asthenia – Myalgia – Increased CPK – Increased aldolase Dizziness, postural hypotension Nausea, diarrhea, and abdominal pain Asthenia Muscle cramps Dysmenorrhea Pruritus Theoretical risk of thrombosis		Underlying prothrombotic disease
Danazol	Residual hormonal activity Seborrhea Acne Hirsutism Voice changes Decreased breast size Vasomotor symptoms Menstrual irregularities Decreased libido Virilization Alkylation in the 17- α position Hepatotoxicity: increase in transaminases, necrosis, cholestasis, hepatic peliosis, hepatocellular adenoma, hepatocellular carcinoma Other Lipoprotein profile alterations: increased risk of atherogenesis Increased CPK-rhabdomyolysis High blood pressure Premature closure of the epiphysis (decreased growth) Increased hematocrit Weight gain	Female patients	Children (Tanner I-IV) Pregnancy Breast cancer Prostate cancer Nephrotic syndrome Alterations in liver function
pdC1INH	Theoretical risk of transmission of infectious agents ^a Thrombosis (off-label very high doses) ^b Anaphylaxis (very rare) [109]. Neutralizing anti-C1-INH antibodies ^c		
rhC1INH	Anaphylaxis in healthy volunteers with undisclosed rabbit allergy who participated in a phase I clinical trial [37]. Neutralizing antibodies have not been reported [58,110].		Rabbit allergy
Icatibant acetate	Local reactions (itching, pain, edema, and erythema in the area of administration) ^d No antibody formation has been described [111].	Active ischemic heart disease Patients with ischemic acute cerebrovascular accident in the previous 2 wk	
Ecallantide	Antiecallantide antibodies (20%) [111]. Allergic reactions. Anaphylactoid reactions (3.5%). Prolongation of partial thromboplastin time.		Self-administration is not approved because of anaphylactoid reactions.
Lanadelumab	Local reactions (usually mild) Antilandelumab antibodies (2.8% with neutralizing antibodies, but without any perceptible clinical impact) Hypersensitivity reactions [91] Interference with coagulation test: increased activated partial thromboplastin time (aPTT) ^e		

Abbreviations: CPK, creatine phosphokinase; pdC1INH, purified nanofiltered plasma-derived human C1 esterase inhibitor concentrate; rhC1INH, recombinant human C1 esterase inhibitor

^aThe risk of transmission of infections has been reduced by the selection of donors, testing of plasma donations for possible viral contaminants, the methods introduced in manufacturing to inactivate and/or remove viruses and other adventitious agents that might be present in the serum mixture, and regular pharmacovigilance [112]. No cases have been reported to date with currently marketed pdC1INH products [1,37].

^bA procoagulant effect of Berinert IV was reported at very high doses (>200 U/kg) in off-label use in newborns to prevent capillary leak syndrome after extracorporeal circulation in cardiac surgery [113,114]. This effect was not seen with the approved doses for C1-INH-HAE [1,10,37]. The United States Food and Drug Administration issued an alert on the development of 10 serious thrombotic events in patients receiving IV Cinryze [115], which was eventually attributed to the use of central venous catheters to facilitate IV self-administration [116]. The use of central venous accesses is discouraged; patients can be trained in direct intravenous self-administration.

^cNeutralizing anti-C1-INH antibodies have been detected, albeit without a loss in the C1-INH function [117].

^dAttributed to the partial agonist effect of icatibant acetate on B2R [118].

^eIncrease in activated partial thromboplastin time (aPTT) due to an interaction of lanadelumab with the aPTT assay [91].

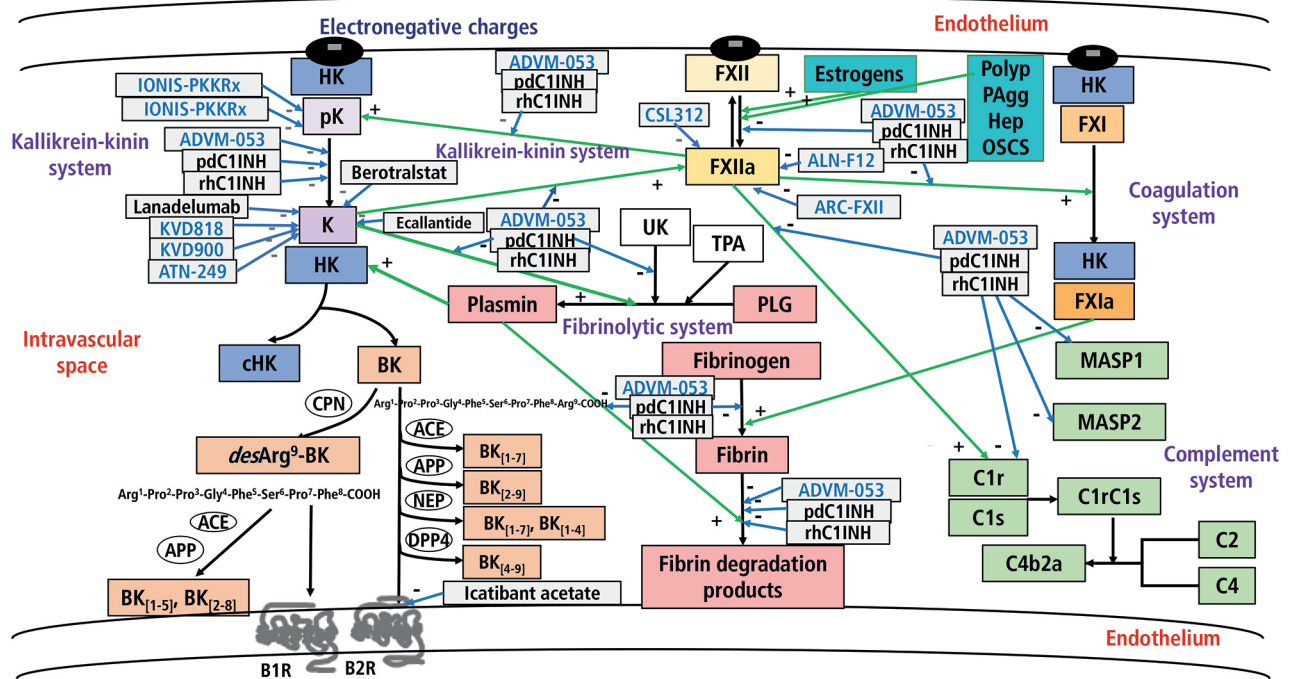


Figure 2. Mechanism of action of approved and under development drugs for C1-INH-HAE.

APP, aminopeptidase P; ACE, angiotensin converting enzyme; aFXI, activated coagulation factor XI; B1R, bradykinin type 1 receptor; B2R, bradykinin type 2 receptor; TPA, tissue plasminogen activator; BK, bradykinin; cHK, cleaved high-molecular-weight kininogen; C1, complement component 1; C2, complement component 2; C4, complement component 4; C1-INH, C1-esterase inhibitor; CPN, carboxypeptidase N; DPP4, dipeptidyl peptidase 4; FXI, coagulation factor XI; FXII, coagulation factor XII; Hep, heparin; HK, high molecular weight kininogen; K, kallikrein; MASP1, mannan-binding lectin-associated serine protease 1; MASP2, mannan-binding lectin-associated serine protease 2; NEP, neutral endopeptidase neutral; OSCS, over sulphated chondroitin sulphate; PAgg, misfolded protein aggregates; pK, prekallikrein; PLG, plasminogen; polyP, polyphosphate; UK, urokinase; pdC1INH, plasma derived human C1-esterase inhibitor concentrate; rhC1INH, recombinant human C1-esterase inhibitor.

differential diagnosis should be with acute abdomen [12], and undiagnosed patients may undergo unnecessary surgery during an abdominal attack [19].

Upper airway angioedema is less frequent, although approximately 50% of patients have at least 1 upper airway angioedema attack during their lifetime [3,20]. Angioedema of the upper airway is the most severe location, because of the risk of asphyxia and death [20,21] or permanent brain damage [22].

The clinical phenotype is very variable from patient to patient and within a family and does not correlate with antigenic or functional blood C1 inhibitor levels [12].

Precipitating factors have been described in 50% of angioedema attacks in patients with C1-INH-HAE [12]. The most frequent include emotional distress, physical trauma, infections, estrogens, and ACEIs. Trauma affecting the upper airway is of special importance because of the risk of asphyxia [12,23].

More than 80% of patients with C1-INH-HAE may present prodromes, that is, symptoms or signs that precede the angioedema attack [23,24].

1.5. C1-INH-HAE Activity

The activity of the disease can be measured based on 2 patient-reported outcomes (PROs): The Angioedema Activity

Score (AAS) [25] and the Hereditary Angioedema Activity Score (HAE-AS) [26].

1.6. Severity of C1-INH-HAE

The concept of severity of C1-INH-HAE covers the patient's overall experience of the disease. Severity is difficult to assess, and there is no validated instrument, although several scores have been proposed [27].

Conversely, there are several instruments to measure attack severity, some of which have been validated [27,28]. Consensus documents and guidelines on HAE recommend monitoring the severity and frequency of angioedema attacks [2,29,30].

1.7. Disease Burden in C1-INH-HAE

C1-INH-HAE generates a significant burden for the patient, in part due to its hereditary character, concern over the transmission of the disease to children, and the lack of knowledge of the disease by health care professionals, which leads to misdiagnoses and diagnostic delay [31]. Other factors that contribute to disease burden are the unpredictability of the angioedema attacks, painful attacks, the risk of asphyxia, the need for emergency interventions, concern over access to specific drugs, and adverse effects of some drugs [32]. All these factors can have a negative impact on health-related quality

Table 4. Evidence Level and Strength of Recommendations in the Most Recent International Guidelines on C1-INH-HAE

	Level of Evidence	Strength of Recommendation
International WAO/EAACI Guideline [1]	<p><i>A.</i> Randomized, double-blind clinical trial of high quality (for example, sample size calculation, flow chart of patient inclusion, intention-to-treat analysis, sufficient sample size)</p> <p><i>B.</i> Randomized clinical trial of lesser quality (for example, only single-blind, limited sample size: at least 15 patients per study arm)</p> <p><i>C.</i> Comparative trial with severe methodological limitations (for example, not blinded, very small sample size, no randomization) or large retrospective observational studies</p> <p><i>D.</i> Adapted from existing consensus document or statement based on expert voting during consensus conference</p>	<p>Strong (We recommend)</p> <p>Weak (We suggest)</p> <p>The strength of recommendation was based on the level of evidence, the balance between desirable and undesirable effects, values, and preferences</p>
International Canadian Guideline [37]	<p><i>High:</i> We are very confident that the true effect lies close to that of the estimate of the effect</p> <p><i>Moderate:</i> We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p><i>Low:</i> Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect</p> <p><i>Very low:</i> We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect</p> <p><i>Consensus:</i> If no published evidence was identified in an area, but the guideline authors determined that it was important to make a recommendation</p>	<p>Strong</p> <p>Weak</p>

of life (HRQOL). HAE-QoL is a specific validated PRO for assessing HRQOL in adult patients with C1-INH-HAE [33,34], whereas AE-QoL is a specific PRO validated for use in adult patients with any type of angioedema [35,36].

2. Diagnosis of C1-INH-HAE

The diagnosis of C1-INH-HAE is based on clinical suspicion because of the presence of recurrent and transient episodes of cutaneous angioedema attacks, abdominal pain, or upper airway angioedema, together with a family history, and should be confirmed by laboratory tests [12].

Screening for C1-INH-HAE is based on the measurement of serum antigenic C4, which is low in most cases [10,12]. Given that cases with normal C4 levels have been described, joint assessment of serum antigenic C4 and C1-INH levels and plasma functional C1-INH is advised [10,12]. Besides, C1q levels are normal, in contrast with C1-INH-AAE. However, the diagnosis should be confirmed by screening for the *C1NH* or *SERPING1* gene [10,12]. De novo mutations can be present in up to 25% of cases [10].

3. Treatment of C1-INH-HAE

Patients should avoid taking estrogens or drugs with estrogen activity and ACEI because of the risk of worsening [1,10,37].

The pharmacological treatment of C1-INH-HAE is based on 3 pillars: controlling the angioedema attacks, preventing the development of angioedema attacks under risky situations, and preventing the appearance of new angioedema attacks [1,37]. All these therapeutic strategies aim to reduce morbidity and mortality and increase HRQOL.

Several drugs have been approved and marketed for the treatment of C1-INH-HAE, with different indications, doses, safety profiles, and availability worldwide (Tables 2 and 3). Their mechanisms of action are shown in Figure 2.

3.1. Treatment of Acute Angioedema Attacks (On-demand Treatment)

The indications for the treatment of an angioedema attack have evolved over time and can be consulted in the different consensus statements and guidelines on C1-INH-HAE management [1,29,30,37-43] (see Table 4 for the criteria used for assessing evidence level and strength of recommendations). In the 2018 update of the international WAO/EAACI guideline, the authors recommend treating any angioedema attack, independently of the location (Evidence grade, D; strength of recommendation, Strong; 100% agreement) and that angioedema attacks are treated as soon as possible (Evidence grade, B; strength of recommendation, Strong; 100% agreement) [1]. For their part, the authors of the 2019 International/Canadian Hereditary Angioedema Guideline consider that effective therapy should be administered in acute attacks to decrease duration and severity (Level of evidence, High; Strength of recommendation, Strong, 100% Agreement) [37].

The 4 specific drugs used for the treatment of acute angioedema attacks in patients with C1-INH-HAE are intravenous (IV) plasma-derived nanofiltered and purified human C1-INH concentrate (pdC1INH), IV recombinant human C1-INH (rhC1INH), subcutaneous (SC) icatibant acetate, and SC ecallantide [1,3,37].

Two different IV pdC1INH concentrates are marketed worldwide. Berinert (CSL-Behring) was shown to be efficacious and safe [44,45] and is approved by various

European countries [46] and the United States Food and Drug Administration (FDA) [47]. Cinryze (Takeda Pharmaceutical Company Ltd) has also demonstrated its efficacy and safety [48,49] and is currently approved by the European Medicines Agency (EMA) [50].

Another widely available treatment worldwide is SC icatibant acetate (Firazyr, Takeda Pharmaceutical Company Ltd), a competitive B2R blocker, which has been approved by the EMA and the FDA [51,52] and has been confirmed to be efficacious and safe [53-55].

The IV recombinant human C1-inhibitor (rhC1INH) (Ruconest, Pharming Group NV), which is produced in transgenic rabbits, is efficacious [56-58] and has been approved by the EMA [59] and FDA [60].

Finally, ecallantide (Kalbitor, Takeda Pharmaceutical Company Ltd), a reversible recombinant inhibitor of plasma K₁, was shown to be efficacious in the treatment of acute angioedema attacks [61] and was approved by the FDA in 2009 [62], although it has not been approved by the EMA.

It is recommended that patients have specific medication available at home. All the drugs approved for the treatment of acute angioedema attacks (SC icatibant acetate, IV pdC1INH, IV rhC1INH) are authorized for home self-administration by the patient or a relative (after appropriate training) [46,50,51,59]. The exception is ecallantide, which has to be administered by a health care professional because of the risk of anaphylactic reactions [62].

In the international WAO/EAACI guideline the authors recommend that angioedema attacks be treated with pdC1INH, rhC1-INH, ecallantide, or icatibant (Evidence grade, A; strength of recommendation, Strong; 100% agreement) [1].

In the International/Canadian Hereditary Angioedema Guideline, the authors consider that IV pdC1INH, SC icatibant acetate, SC ecallantide, and IV rhC1INH are efficacious drugs for the treatment of angioedema attacks (Level of evidence, High; Strength of recommendation, Strong; 92.5%-100.00% agreement) [37]. Likewise, they propose that angioedema attacks be treated early to reduce morbidity (Level of evidence, Moderate; 100% agreement) and mortality (Level of evidence, Consensus; 100% agreement), both with a strong strength of recommendation and 100% agreement. The authors also propose that angioedema attacks that affect the upper airway be considered medical emergencies and treated immediately (Level of evidence, Low; Strength of recommendation, Strong; 100% agreement) [37].

3.2. Short-term Prophylaxis

Short term prophylaxis (STP), or preprocedure prophylaxis, was first described as the treatment administered prior to medical or surgical procedures to prevent angioedema episodes [19]. Currently, it also includes the preventive treatment prior to vital events (eg, exams, weddings) and during especially stressful life periods (eg, divorce), which can elicit angioedema episodes [1,37].

The treatment of choice is IV pdC1INH (Berinert, Cinryze) [46,47,50]. If pdC1INH is not available, danazol can be used for 5 days before and 2-3 days after the procedure [41].

rhC1INH was shown to be efficacious and well tolerated as STP in a case series of patients with C1-INH-HAE [63], although it is not approved for this indication.

Icatibant acetate and ecallantide are not advised for use as STP owing to their short half-life and the lack of evidence [10,41]. Moreover, icatibant acetate does not decrease bradykinin release but only blocks B2R [10,41].

The international WAO/EAACI guideline recommends STP before procedures that can trigger an angioedema attack (Evidence grade, C; Strength of recommendation, Strong; 100% agreement) [1].

For its part, the International/Canadian Hereditary Angioedema Guideline states that STP should be considered prior to dental, surgical, or medical procedures or in the case of patient-specific known triggers of angioedema attacks (Level of evidence, Low; Strength of recommendation, Strong; 100% agreement) [37]. According to this guideline, IV pdC1INH should be used as STP in patients with C1-INH-HAE (Level of evidence, Consensus; 97.37% agreement; Strength of recommendation, Strong; 92.31% agreement) [37]. Additionally, the authors recommend having specific treatment for acute angioedema attacks on hand (Level of evidence, Low; Strength of recommendation, Strong; 93.39% agreement) [37].

3.3. Long-term Prophylaxis

Long-term prophylaxis (LTP), also called routine prophylaxis, is continued or maintenance treatment aimed at decreasing the frequency, severity, and duration of the angioedema attacks [1]. It should be considered in symptomatic patients whose condition is not adequately controlled exclusively with optimal on-demand treatment, taking into account disease activity and HRQOL [1].

Efficacy outcomes for LTP in C1-INH-HAE have not been defined. Cicardi et al [64] proposed the goal of 1-2 angioedema attacks per year in 1997, when the main drugs used for LTP were attenuated androgens. While more drugs have since been approved for LTP, the experts do not agree on the treatment goals [1,37,42].

Indications for the start of LTP have evolved over the last 2 decades. In the international WAO/EAACI guideline, the authors recommend that LTP be taken into consideration when patients face life events associated with an increase in disease activity (Evidence grade, D; Strength of recommendation, Strong; ≥90% agreement) [1]. Moreover, they recommend that patients be assessed for LTP at every visit and that disease burden and patient preference are taken into account (Evidence grade, D; Strength of recommendation, Strong; 100% agreement) [1]. Furthermore, the authors of the International/Canadian Hereditary Angioedema Guideline state that LTP is adequate for some patients with C1-INH-HAE in order to decrease the frequency, duration, and severity of attacks (Level of evidence, High; Strength of recommendation, Strong; 96.7% agreement) [37].

3.3.1. Drugs used for long-term prophylaxis

3.3.1.1. Attenuated androgens: danazol (Danatrol, Sanofi Aventis)

Oral danazol, which enhances hepatic synthesis of C1 inhibitor and plasma APP activity [41,42,64], has been approved for LTP in C1-INH-HAE in some countries [65]. The

initial dose can be high to induce remission of symptoms, with a later decrease until the minimal effective dose is reached. A maximum dose of 200 mg/d is advised as the maintenance dose in order to minimize adverse effects [41,42,64]. The adverse effects of danazol are summarized in Table 3 [41,42,64]. These are mostly produced by residual hormonal action and are more severe in women, although they are minimized by using the minimal effective dose [66].

3.3.1.2. Tranexamic acid (Amchafibrin, Meda Pharma SL)

Tranexamic acid competitively inhibits activation of plasminogen, with a reduction in the transformation of plasminogen into plasmin and a decrease in fibrinolysis. The dose ranges from 1000 to 3000 mg/d divided into 2-3 oral administrations per day [41,42]. Data on its efficacy have been reported [41,42], although this is considered low in real life and is reserved for specific subgroups (females, children) [37,42,66,67].

3.3.1.3. Intravenous plasma-derived C1 inhibitor (IV pdC1INH)

IV pdC1INH (Berinert, CSL-Behring) was initially used as off-label LTP more than 2 decades ago [68-71], although it is still not approved for this indication owing to the lack of clinical trials [46].

The regular use of another IV pdC1INH (Cinryze, 1000 U every 3-4 days) decreases the frequency of angioedema attacks by 50.8% (4.24-2.09 attacks/mo, $P<.001$), their duration (from >4 h to 2 h, $P=.02$), and severity, as well as the number of acute rescue treatments [48]. Afterwards, the same dose revealed a 93.7% reduction in the frequency of angioedema attacks (0.19 attacks/mo; IQR, 0.00-0.64) in comparison with the historical attack rate in an open-label study [72]. IV pdC1INH was well tolerated during the study [48,72]. In another study, patients with >1 angioedema attack/mo were eligible for an increase in the dose of IV Cinryze (1500 IU, 2000 IU, and 2500 IU twice a week), with a reduction in the frequency of angioedema attacks and good tolerance in most patients [73]. pdC1INH acts by replacing deficient C1-INH [41,42].

Regular use of IV pdC1INH increased HRQOL measured using SF-36 [74].

Cinryze was approved by the FDA for its use as LTP in 2008 [75] and by the EMA in 2010 [50].

Control of C1-INH-HAE under LTP with IV pdC1INH is incomplete, with disruptive angioedema attacks at the licensed dose (1000 IU twice a week) [48,76,77]. Approximately 20% of the patients taking IV pdC1INH had disruptive angioedema attacks once a month, and more than 10% experienced angioedema attacks 2-3 times a week [76].

Therefore, the dose and interval of IV pdC1INH should be individualized in real life, with some patients even administering it every 48 hours to avoid disruptive angioedema attacks [71,73,78].

Riedl et al [77] explored the satisfaction and experience of patients with IV pdC1INH for the treatment of acute attacks or LTP. Most of the responders who used a peripheral vein (62%) reported difficulty in finding a usable vein or in making the infusion work at least some of the time [77].

In addition, patients with HAE showed their preference for noninvasive routes of drug administration, preferably oral or SC [79].

3.3.1.4. Subcutaneous plasma-derived C1 inhibitor (SC pdC1INH)

Several SC pdC1INH formulations have been developed for use as LTP in C1-INH-HAE. It is important to note that SC pdC1INH should not be used for the treatment of acute angioedema attacks.

3.3.1.4.1. CSL830 (CSL-Behring)

CSL830 is a concentrated formulation of pdC1INH (500 U/mL) that is well tolerated and produces a relevant dose-dependent increase in the plasma C1-INH function [80].

A phase 3 double-blind, cross-over, placebo-controlled clinical trial (COMPACT2, NCT01912456) [81] randomized patients to SC CSL830 (40 IU/kg or 60 IU/kg) or placebo twice a week. In comparison with placebo, the frequency of angioedema attacks was significantly reduced with both CSL830 doses, with the improvement being higher in the 60 IU/kg dose. The number of angioedema attacks per month was 0.5 in the 60 IU/kg group, 1.2 in the 40 IU/kg group, and 4.0 in the placebo group ($P<.001$) [81]. Additionally, a higher proportion of patients under LTP with SC CSL830 were free of angioedema attacks than those receiving placebo (38%-40% vs 9%) [81]. The response rate (a reduction $\geq 50\%$ in the number of attacks in comparison with placebo) was 76% (95%CI, 62%-87%) in the 40 IU/kg group and 90% (95%CI, 77%-96%) in the 60 IU/kg group. Furthermore, compared with patients receiving placebo, the need for rescue medication was reduced from 5.55 times/mo to 1.13 times/month in the 40 IU/kg group and from 3.89 to 0.32 times/mo in the 60 IU/kg group. In patients with evaluable data, the median reduction in the number of normalized angioedema attacks was 88.6% (IQR, 69.6-100.0) with the 40 IU/kg dose and 95.1% (IQR, 79.0%-100%) with the 60 IU/kg dose.

The prevalence of adverse events was similar in the patients who received CSL830 and in those who received placebo, with mild local reactions being the most frequent [81].

HRQOL assessed by EQ5D was higher in patients taking CSL830 (both doses combined) [82].

The FDA approved SC CSL830 in June 2017 (Haegarda, CSL-Behring) (60 IU/Kg twice a week) for the prophylaxis of angioedema attacks in adolescents and adults with C1-INH-HAE [83,84]. This product is marketed in Europe as Berinert and is being approved at the same dose in the different countries in a decentralized way. SC Berinert came onto the market in Spain in April 2020 [85].

3.3.1.4.2. SC liquid Cinryze

Data from a phase 3 clinical trial with another SC pdC1INH (liquid Cinryze) at a fixed dose (2000 IU twice a week [NCT02584959], Takeda Pharmaceutical Company Ltd) [86], in which the primary outcome was the normalized number of angioedema attacks (NNA), showed that the least squares mean of the NNA decreased from 3.9 with placebo to 1.6 with SC pdC1INH ($P<.0001$). The NNA decreased by 79.5% (median) with SC pdC1INH in comparison with placebo, and 37.5% of the patients treated with SC pdC1INH were free of attacks, in contrast with only 8.8% of patients in the placebo arm. The rate of treatment-emergent severe adverse events was similar in both groups.

Takeda Pharmaceutical Company Ltd have not yet applied for marketing authorization for liquid Cinryze.

An indirect comparison of the 2 independent clinical trials that demonstrate the efficacy of the 2 commercial formulations of pdC1INH for LTP (IV Cinryze 1000 IU twice a week [CHANGE; NCT01005888] and SC Haegarda 60 IU/kg twice a week [COMPACT; NCT01912456]) has been published [87].

The absolute reduction in the mean monthly angioedema attack rate was 3.6 (95%CI, 2.9-4.2) for SC pdC1INH 60 IU/kg vs placebo and 2.3 (95%CI, 1.4-3.3) for IV pdC1INH vs placebo; the difference between both drugs was 1.3 (95%CI, 0.1-2.4; $P=.034$) [87]. Additionally, the mean percentage reduction in the monthly rate of angioedema attacks was significantly higher for SC pdC1INH than for IV pdC1INH (84% vs 51%; $P<.001$) [87]. The percentage of patients with reductions in the monthly angioedema attack rate of $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ vs placebo was significantly higher in SC pdC1INH than in IV pdC1INH (reduction $\geq 50\%$, 91% vs 50% [OR, 10.33; $P=.003$]; reduction $\geq 70\%$, 84% vs 46% [OR, 6.19; $P=.005$]; reduction $\geq 90\%$, 57% vs 18% [OR, 6.04; $P=.007$]). This analysis suggests that SC pdC1INH 60 IU/kg twice a week produces a greater reduction in the number of angioedema attacks than IV pdC1INH 1000 U twice a week administered as LTP [87].

3.3.1.5. Lanadelumab

Lanadelumab (DX2930, SHP643) (Takhzyro, Takeda Pharmaceutical Company Ltd) is a subcutaneous monoclonal antiplasmin K antibody approved by both the FDA [88,89] and the EMA [90,91] for LTP in patients aged ≥ 12 years who have hereditary angioedema.

The phase 3 pivotal ‘‘Hereditary Angioedema Long-Term Prophylaxis’’ (HELP) study was a placebo-controlled, randomized, double-blind clinical trial (NCT02586805, EudraCT 2015-003943-20) [92]. Patients were treated with 3 different doses of SC lanadelumab (150 mg/4 wk, 300 mg/4 wk, or 300 mg/2 wk) or placebo. The primary outcome was the number of investigator-confirmed attacks of hereditary angioedema over the treatment period. The mean differences (vs placebo) in the attack rate per month were -1.49 (95%CI, -1.90 to -1.08 ; $P<.001$) for lanadelumab 150 mg/4 wk, -1.44 (95%CI, -1.84 to -1.04 ; $P<.001$) for lanadelumab 300 mg/4 wk, and -1.71 (95%CI, -2.09 to -1.33 ; $P<.001$) for lanadelumab 300 mg/2 wk. The most frequent adverse events in the lanadelumab treatment groups were injection site reactions (34.1% placebo, 52.4% lanadelumab) and dizziness (0% placebo, 6.0% lanadelumab).

The long-term safety of lanadelumab was studied in the HELP study and in an open-label phase [93,94].

With regard to the drugs used as LTP, the 2018 international WAO/EAACI guideline recommends that androgens be considered a second-line treatment (Evidence grade, C; Strength of recommendation, Weak; 50%-70% agreement) [1], although pdC1INH as LTP is recommended as first-line treatment (Evidence grade, A; Strength of recommendation, Strong; 50%-70% agreement) [1]. This point was intensely debated, as shown by the percentage of agreement, probably because of the lower availability of pdC1INH and its high cost. In the guideline, the authors also recommend that LTP be adapted in terms of dose and interval to minimize disease burden (Evidence grade, D;

Strength of recommendation, Weak; 100% agreement) [1]. It is important to remember that lanadelumab had not been approved anywhere when this guideline was discussed and, consequently, was not included.

For its part, the International/Canadian Hereditary Angioedema Guideline states that pdC1INH and lanadelumab are efficacious treatments for LTP in C1-INH-HAE type 1 and 2 (Level of evidence, High; 100%-90.3% agreement; Strength of recommendation, Strong; 100%-92.5% agreement) [37], whereas attenuated androgens are considered efficacious in some patients with C1-INH-HAE (Level of evidence, Moderate; Strength of recommendation, Strong; 90.32% agreement). The authors recommend SC pdC1INH and SC lanadelumab as first-line treatment for LTP in patients with C1-INH-HAE type 1 and 2 (Level of evidence, Consensus; 90% agreement; Strength of recommendation, Strong; 97.37% agreement) [37]. In addition, they recommend that attenuated androgens and antifibrinolytics should not be used as first-line treatment in patients with C1-INH-HAE type 1 and 2 (Level of evidence, Consensus; 89.47% agreement; Strength of recommendation, Strong; 88.89% agreement) [37].

The management of C1-INH-HAE during pregnancy was reviewed [66,95].

A consensus on the management of children with C1-INH-HAE was published [67].

3.3.2. New drugs under development for the treatment of C1-INH-HAE

Several drugs are under development for the treatment of C1-INH-HAE; most are for LTP, and only a few are for on-demand treatment [96,97].

On the one hand, existing approved drugs are being studied for new indications (eg, IV rhC1INH for LTP or with a label extension for children, SC pdC1INH in children); on the other, new drugs that block proteases usually inhibited by C1-INH (pK, K, FXII) are being developed with the aim of inhibiting the KKS and bradykinin release (Figure 2).

Some of these drugs act by replacing absent C1-INH by exogenous drug administration (rhC1INH) or by restoring endogenous production of C1-INH with gene therapy. These drugs act at all stages that are inhibited by C1-INH (Figure 1 and 2).

The IV rhC1INH (Ruconest, Pharming Group NV) was studied in a phase 2 clinical trial (NCT02247739) and was shown to be efficacious and well tolerated as LTP in C1-INH-HAE [98].

Gene therapy consists in restoring the body’s own C1-INH production by modifying the patient’s genes. Adverum Biotechnologies have developed an adenovirus vector (AAV8) for transferring the *C1NH* gene (ADVM-053: AAVrh.10hC1EI) and introducing an extra chromosomal gene copy in the cells in order to correct C1-INH deficiency. Preclinical studies in a murine model showed protection against the increase in vascular permeability [99]. However, development of ADMV-053 was stopped because protein expression with gene therapy for α -1-antitrypsin deficiency with ADM-043 was not clinically significant, despite the good safety and tolerance profile.

Other drugs act by inhibiting prekallikrein, with a subsequent decrease in plasma K, inhibition of KKS, and

a decrease in bradykinin release. IONIS-PKCRx (IONIS Pharmaceuticals Inc) is a second-generation SC chimeric antisense single-stranded oligonucleotide designed to selectively bind and reduce the mRNA of prekallikrein in the liver [96,97]. A phase 1 clinical trial was completed (NCT03263507) with a dose-dependent reduction in prekallikrein and a good safety profile [100]. A phase 2 clinical trial with ligand-conjugated IONIS-PKCLRx is being performed in C1-INH-HAE (NCT04030598). IONIS-PKCRx and IONIS-PKCLRx have been used in a compassionate-use pilot study in 2 patients [100].

Most drugs under development exert an anti-plasma K action, thus enabling them to inhibit the KKS.

Berotrastat (BCX7353) (BioCryst Pharmaceuticals, Inc), an oral bioavailable synthetic small molecule that inhibits plasma K, proved to be safe in a phase 1 clinical trial (NCT02448264), with only gastrointestinal symptoms and a maculopapular rash as adverse events [101]. Subsequently, berotrastat 125 mg daily was efficacious as LTP in C1-INH-HAE, with a significant reduction in the confirmed angioedema attack rate [101]. Finally, oral berotrastat once daily demonstrated a significant reduction in the attack rate at both 110 mg (1.65 attacks/mo; $P=.024$) and 150 mg (1.31 attacks/mo; $P<.001$) relative to placebo (2.35 attacks/mo) in a phase 3 study (APeX 2) [102]. The most frequent treatment-emergent adverse events that occurred more with berotrastat than placebo were abdominal pain, vomiting, diarrhea, and back pain. There were no drug-related serious treatment-emergent adverse events. The most favorable risk-benefit profile was observed at 150 mg/d. Oral berotrastat is also being studied for the treatment of acute angioedema attacks (NCT03240133).

KVD900 (KalVista Pharmaceuticals Ltd) is also a selective and potent inhibitor of plasma KK with oral bioavailability [96,97]. Another oral potent and selective inhibitor of plasma KK is ATN-249 (Attune Pharmaceuticals) [97].

Finally, other drugs under development address blocking of FXII.

CSL312 is a totally humanized IgG4 monoclonal antibody that blocks activation of factor XII, thus inhibiting its proteolytic activity and the transformation of prekallikrein into K. This in turn prevents KKS activation and bradykinin release [96,103]. A phase 1 clinical trial with SC and IV administration was completed in 2017 (ACTRN12616001438448p) [104]. A randomized, placebo-controlled, parallel-arm, phase 2 clinical trial to investigate the clinical efficacy, pharmacokinetics, and safety of CSL312 as prophylaxis to prevent attacks in individuals with HAE is under way [105].

Other drugs targeting FXII include ALN-F12 (Alnylam Pharmaceuticals) [106] and ARC-FXII (Arrowhead Pharmaceuticals) [97].

4. Conclusions

Treatment of C1-INH-HAE has evolved quickly in the last 2 decades, with new drugs for acute attacks and long-term prophylaxis. New treatments under development point to a very promising future for affected patients.

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Conflicts of Interest

Dr T. Caballero has received grant research support and/or speaker/consultancy fees from BioCryst, CSL-Behring, Novartis, Octapharma, Pharming NV, and Takeda. She has also received funding to attend conferences/educational events from CSL Behring, Novartis, and Takeda. Dr Caballero is/has been a clinical trial/registry investigator for Biocryst, CSL Behring, Novartis, Pharming NV, and Takeda and is a researcher in the IdiPaz research program.

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