Balkan Med J 2021;38:89-103

Therapeutic management of hereditary angioedema: past, present, and future

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Hereditary angioedema is a rare disease that can often be disabling or even life threatening because of the unpredictable, self-limiting, and localized swelling episodes involving cutaneous, subcutaneous, and mucosal sites. The last decades revealed a spectrum of possibilities to control the disease through the development of effective therapies that changed the life of many patients and families worldwide.

This review summarizes the current literature regarding the general management and therapeutic approach in patients with hereditary angioedema, both with and without C1 inhibitor deficiency. Medications already available in the market and new drugs in different research stages of development are addressed.

Recent decades saw a huge leap in identifying mechanisms of angioedema and developing modern safe and effective medications to both treat acute angioedema manifestations and control disease activity via prophylactic therapy. Further improvement is still needed, together with improving global accessibility of diagnostic tools and effective medications. Whether novel drugs will demonstrate a sustained cost/effectiveness ratio will be answered in the years to come when we will witness whether a majority of the patients will benefit from these major advances.

Angioedema (AE) is a chronic disease presenting with recurrent episodes of non-pruritic, subcutaneous, or submucosal swelling. These symptoms occur as a result of increased paroxysmal vascular permeability owing to endothelial disequilibrium. The syndrome AE is a heterogeneous entity with a variety of clinical phenotypes.[1] Some are often accompanied by urticaria owing to release of histamine. In minority of the cases, such as in patients with hereditary AE (HAE) and other rare forms of AE, bradykinin is believed to be the main mediator responsible for increased vascular leakage and edema formation.

Bradykinin-mediated AE is, in most cases, episodic, self-limited, and sometimes worsened by predictable triggers, such as physical trauma, psychoemotional stress, or some drugs (e.g., angiotensin-converting enzyme inhibitors [ACEIs] and estrogen-containing medication). It typically progresses over continuous hours or a few days, causing significant physical dysfunction, suffering, and pain, and can be life threatening if the upper airways are involved.[2]

The remarkable scientific progress made in the last decades of AE knowledge unveiled many of the pathomechanisms of this disease and helped in developing novel therapeutic modalities that changed the life of many patients and families worldwide. This review will focus on therapeutic modalities of HAE, both with and without C1 inhibitor (C1-INH) deficiency.

As per the current classification of AE, two major types of HAE have been recognized: one with congenital C1-INH deficiency (C1-INH-HAE) because of a pathogenic variant of the *SERPING1* gene and the other with normal C1-INH (nlC1-INH-HAE).[3,4] The latter consists of a variety of currently discovered genotypes, although others are likely to be discovered in the years to come[5-12] Furthermore, disequilibrium of bradykinin activity is considered a crucial player in most of these ultra-rare forms of AE (Figure 1).

GENERAL MANAGEMENT CONSIDERATIONS

Current progress in the understanding of HAE pathophysiology, genetics, and therapeutic strategies result in the development of treatment and monitoring personalized plans to help patients with HAE improve their quality of life (QoL). As previously discussed, HAE is a life-threatening condition with an unpredictable clinical course. Therefore, to address patients' needs, a comprehensive individualized action/management plan should be developed in cooperation between the treating physicians, patients with HAE, and patients' family members/caregivers. The aim of this plan is to engage patients in their treatment and lessen the significant burden that HAE places on patients and their families. HAE is characterized by wide variability in presentation, clinical course, response, and tolerance to treatment. Therefore, HAE treatment plans should be individualized to meet the patient's needs and to address the

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Received: February 15, 2021 Accepted: February 22, 2021 • DOI: 10.5152/balkanmedj.2021.21094

Available at www.balkanmedicaljournal.org

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Cite this article as:
Valerieva A, Nedeva D, Yordanova V, Petkova E, Staevska M. Therapeutic management of hereditary angioedema: past, present and future. *Balkan Med J.* 2021;38(2):89-103.

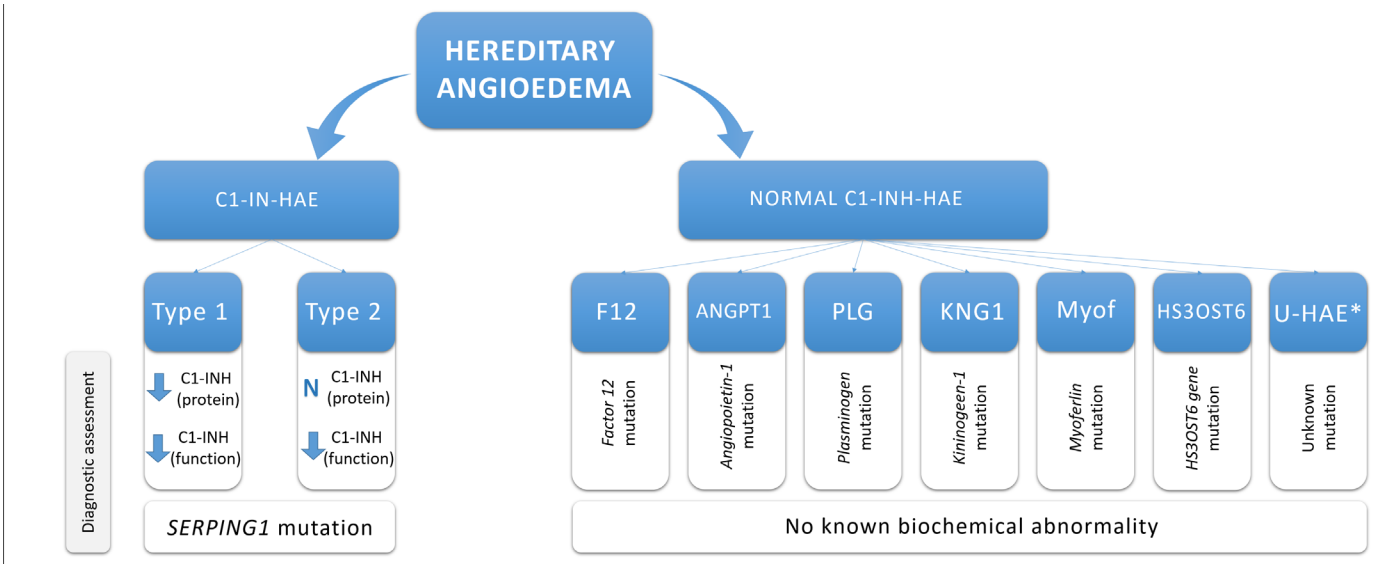

FIG.1. Genotypes of hereditary angioedema.
HAE, hereditary angioedema; C1-INH, C1 inhibitor; F12, factor 12 gene; ANGPT1, angiopoietin-1 gene; PLG, plasminogen gene; KNG1, kininigen-1 gene; MYOF, myoferlin gene; HS3OST6, heparan sulfate glucosamine 3-O-sulfotransferase 6 gene; U-HAE, unknown HAE.

heterogenous factors impacting disease course and outcomes. Furthermore, patients should be regularly followed up, and management plans should be updated in a timely manner based on the current condition of the patient. The following information should be included in HAE management plans: (a) effective on-demand treatment (ODT) options and information on how to adequately administer available drugs to treat acute HAE attacks, (b) information on the use of short-term prophylactic drugs before invasive interventions or other known acute HAE attack triggers, and (c) information on long-term prophylaxis (LTP) for certain cases, aiming to prevent onset and severity of future HAE attacks.[13]

All patients with HAE should be referred to HAE experts to confirm the diagnosis and type of HAE, develop or optimize current treatment plans, monitor and coordinate medical care, and provide comprehensive education. To achieve this goal, physicians should be familiar with recent advances in HAE diagnostic work-up, on-demand therapy, and short- and long-term prophylactic therapies. In addition, healthcare personnel and teachers and educators who take care of children with HAE should be provided with clear written information on the characteristics of the disease and instructions on how to properly use available treatment in urgent situations, especially in case of an airway attack.[14]

Initial evaluation of patients with a confirmed HAE diagnosis aims to provide important information on symptoms, disease course, treatment options, and disease/attack risk factors and outcomes. Educational materials, treatment action plans, and attack diaries should be developed, implemented, and regularly reviewed at follow-up visits. Patients should be advised to keep a diary and to enter their symptoms and therapy given regularly to monitor disease activity, need for medications, and possible adverse effects of the treatment. In addition, all patients should have an HAE identification card to guarantee prompt recognition of HAE attacks and facilitate timely and adequate treatment. Therefore, it is strongly recommended that all patients with HAE carry a specific sign (card or letter) with short information on the disease, the HAE treatment plan, and contact information of an HAE specialist.

Forbidden Medication

As HAE is a disease manifesting with significant variables throughout a patient's life, it is of great importance to recognize and avoid all known possible HAE triggers. The HAE specialist should proactively ask about any existing comorbidities for which the patient currently takes concomitant treatment, and this HAE-related information must be communicated to the patients, their families, and other involved health care teams to adequately provide and coordinate medical care and services. Patients should be advised to avoid certain drugs that may worsen the disease course and provoke more frequent and severe HAE attacks, including ACEIs, hormone replacement therapy (HRT), and exogenous estrogens (e.g., estrogen-based oral contraceptives [OCs]).[15,16] Hormonal contraception with progestin-only pills may be considered because it is known to be safe for women with HAE.[17-19] Although patients with HAE are advised not to use exogenous estrogens, in some cases the risk/benefit ratio would warrant their use to improve QoL and reduce the disease burden (e.g., fertility treatments, unbearable symptoms following surgical or natural menopause). In these cases, patients should be closely monitored, HAE therapy should be adjusted as needed, and prophylaxis with C1-INH could be considered because it is shown to be beneficial.

Lifestyle

Infectious diseases and mechanical trauma are other common triggers for HAE attack, especially in children. All vaccinations are considered safe for children and should be recommended. Furthermore, influenza vaccine is associated with reduction in upper airway symptoms and potentially reduces frequency and severity of upper airway swelling, and therefore, it could be advised for all patients with HAE. Many experts recommend vaccinations for hepa-

titis A and B for patients in whom human plasma-derived products are regularly administered.[20,21]

Other non-pharmacological risk factors include psychological and physical stress, fatigue, febrile conditions, acute illness, trauma, infections, and pregnancy or menstruation[22,23] Trauma, both accidental or after dental procedures, medical interventions, or surgical procedures, may precipitate an acute swelling episode. However, most traumas are unpredictable. Therefore, excessive avoidance of suspected triggers should not be strongly recommended to not restrict activities and lifestyle and limit patients' normal lives.

Other general preventive considerations include regular dental care to reduce the need for invasive dental procedures, such as tooth extractions, and prevent the development of acute or chronic oral inflammation, which may decrease the threshold for attacks. In addition, the local primary care team, emergency departments, and hospitals should be provided with clear information on the management of specific conditions, such as pregnancy and planned surgical or dental interventions that require short-term prophylactic treatment.

Pre-Procedural Prophylaxis

Initial evaluation and regular assessments should focus on review of new and previously available HAE medication options; prescription of on-demand therapy; and review of need for short-term (pre- and peri-procedural) prophylaxis, particularly in cases of dental/oral surgery, bronchoscopy or endoscopy, endotracheal intubation or intervention in the upper airway region or pharynx, and long-term prophylactic options. Medication self-administration techniques should be communicated to all patients on prescribed on-demand drugs licensed for self-administration. Self-administration is crucial for the effectiveness of ODT because it is well known that early treatment in the course of a swelling attack is more effective and may prevent severe symptoms, further complications, and even fatal outcomes.[24-27] Training should also include a family member or close friend who is able to administer therapy when the patients themselves are unable or uncomfortable with self-administration.[28] Home therapy is associated with decrease in the severity and duration of HAE attacks, reduction of morbidity and disability, and improvement of QoL.

Family Consultation and Psychological Support

A discussion of short-term (travel) and long-term future plans, such as pregnancy, and the importance of screening all family members for HAE should be routinely performed. Pregnancy, because of associated anatomical, physiological, and hormonal changes, can mitigate, aggravate, or have no effect on manifestations, disease course, and treatment of HAE.[29] All pregnant patients with HAE should be closely monitored by an HAE expert and should be managed by a multidisciplinary team of professionals from relevant medical specialties. Although delivery is only rarely reported as an attack trigger, all women should be closely followed up for at least 72 hours after uncomplicated vaginal delivery. Care for patients undergoing cesarean section (C-section), especially if intubation is necessary, includes similar short-term prophylaxis, as in any other surgical procedure. C1-INH is the treatment choice for those cases per current recommendations. Although breastfeeding may result in an increased number of maternal attacks, it is still recommended based on its beneficial effects on the infant.[30,31]

Current guidelines recommend that all relatives, including grandparents, parents, siblings, children, and grandchildren, of patients with HAE be screened for C1-INH function, C1-INH protein, and C4 plasma levels. It is considered crucial because delayed diagnosis results in decreased QoL owing to delayed initiation of appropriate therapy and increased mortality because, although rare, the onset of the disease could be fatal because of airway involvement during the first HAE attack. All patients with HAE are indicated to have at least 1 annual medical evaluation by an HAE specialist. Newly diagnosed patients and those on LTP with attenuated androgens (AAs) should be seen more often to recognize side effects in a timely manner and re-evaluate the risk/benefit ratio. Therefore, patients on androgens should continue to be monitored twice a year with proper safety evaluation of liver function, lipid profiles, and cardiovascular risk. Follow-up visits should include review of swelling attack log (location, frequency, and severity of symptoms) and review of frequency of use, dosing, and effectiveness of treatment. If applicable, long-term prophylactic therapy should also be monitored in terms of preventive efficacy, for medication adverse effects, and for dose adjustment as needed. Furthermore, after attack resolution, patients should record and discuss with their physician the relevant HAE-specific information on the event (suspected triggering factors, dose and medication administered, time to symptom relief, and any adverse reactions).

QoL Monitoring

Health-related QoL (HRQoL) is known to be significantly decreased in patients with HAE. It can be assessed with recently developed HAE-specific QoL questionnaires (AE-QoL, HAE-QoL, and HAE Association–QoL), which measure an individual's perception of disease impact on several aspects, including physical, psychological, social, and somatic domains of functioning and wellbeing[32,33] Recent achievements in HAE care, including the development of on-demand and LTP therapies that are proven to be more effective and safer, home therapy, and self-administration, have led to consistent improvements in patients' QoL and disease burden (anxiety and depression, dissatisfaction with treatment, impairment of daily activities and economic costs).[34,35]

Patient organizations and support groups provide psychological support for patients with HAE, caregivers, and family members. They work toward providing all patients worldwide with sufficient information and resources to control their illness and lead normal lives.

ON-DEMAND THERAPY

Treatment of Acute C1-INH-HAE Manifestations

The primary purpose of acute HAE treatment is to minimize morbidity and prevent mortality owing to symptoms of AE.[36] The ability to apply ODT for episodes of swelling has been a major achievement in HAE management.[36] The advanced insight on the mechanism of swelling in C1-INH-HAE has led to the development of specific ODTs that have shown to be effective and safe in randomized, controlled studies,[20,37,38] and their efficacy and long-term safety have been confirmed in extension studies in real-world practice.[29–42]

Latest guidelines advise several on-demand HAE treatments that can be summarized as replacement therapies (C1-INH concentrates, freeze-dried or solvent detergent frozen plasma) and targeted therapies (bradykinin B2 receptor antagonist and plasma kallikrein inhibitors). The following 4 types of medications have been approved by regulatory authorities to date: C1-INH–containing products (plasma-derived C1-INH [pdC1-INH], Berinert and Cinryze, and recombinant human C1-INH [rhC1-INH], Ruconest) for intravenous (IV) administration, a bradykinin B2 receptor antagonist (icatibant [Firazyr]) for subcutaneous (SC) administration, and a plasma kallikrein inhibitor (ecallantide [Kalbitor]) for SC administration. All mentioned on-demand medications have shown to be safe and effective. Nevertheless, there is information that ecallantide can cause systemic allergic reactions (< 2%); therefore, it is recommended to be administered in a hospital setting or other facility with the ability for HAE and anaphylaxis management. Antifibrinolytic agents and anabolic androgens are not suitable for ODT.[13]

Fresh Frozen Plasma: The amount of published data on fresh frozen plasma (FFP) for treatment of HAE attacks is relatively scarce in comparison to the large amount of randomized controlled trials (RCTs) conducted for other on-demand therapies. Nevertheless, FFP remains the only available option for many patients with HAE globally, especially those in lower-middle-income countries.[43] The efficacy and safety data are mainly obtained by published case reports.

Recently, a solid retrospective registry study on the management of acute HAE attacks was conducted at 1 Iranian National Reference center, South African centers, and private South African healthcare institutions. The study covered the period from 2001 to 2017. FFP was used to treat 98 acute HAE swellings and authors discussed that (a) FFP has proven to be effective, but time to resolution for FFP is considerably slower than time to resolution for HAE-specific therapies; (b) the rate of adverse events is about ~5%, and it could be reduced by the use of premedication; (c) the management of acute HAE attacks with FFP has its own specifics, including speed of access, treatment thresholds, hospital length of stay, dosing, and time to resolution; and (d) FFP treatment is associated with prolonged length of hospital stay and increased direct healthcare costs. Therefore, availability of HAE-specific therapies would be preferred, possibly through global access initiatives.

As mentioned, no randomized trials have been conducted, and safety reporting includes sporadic reports of HAE symptoms promptly worsening after the administration of FFP. This is possibly because FFP contains a variety of plasma factors, including factor XII (FXII), high-molecular-weight kininogen, and plasma prekallikrein (PKK), that could provide substrate for more bradykinin release, in addition to C1-INH replacement. An additional concern is the potential risk for anaphylactic reactions, which could be associated with any biological product.

ODT with FFP remains the main option for treating symptoms of HAE in case other acute therapy is not readily available. Precautions for securing airway must be taken into consideration in case upper airway swelling occurs. Administration with plasma that is solvent detergent–treated is associated with reduced viral transmission risk and, if available, may be safer to use than FFP.[44]

Replacement Therapy with C1-INH: Congenital C1-INH deficiency was first revealed as a reason for HAE in 1963 by Donaldson et al.,[45] and thereafter, C1-INH, derived from human plasma, became the first HAE-specific treatment option. In 1974, the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service produced the first plasma-derived C1-INH concentrate.[46] The first marketing authorizations for C1-INH in Europe were granted in 1985, but in the United States (U.S.), only in 2008. Still, worldwide availability is not evenly secured even nowadays.

An rhC1-INH was given marketing authorization in Europe in 2010, and Food and Drug Administration (FDA) approval was granted in 2014. The drug is associated with a sustainable production supply because it is not dependent on blood donations.

Both IV pdC1-INH and rhC1-INH concentrates are equally effective for treatment of acute HAE attacks in the different age groups (Table 1).

Currently, 2 pdC1-INHs are available: Berinert (vials of 500 and 1500 IU; CSL Behring) and Cinryze (vials of 1000 IU; Shire, now part of Takeda). pdC1-INH pharmacokinetics have demonstrated a mean plasma half-life of 33 ± 19 hours.[20] Administration can be done by a healthcare professional (HCP), or it can be self-administered when appropriate training has been provided. Both pdC1-INH products are known to be well-tolerated and safe. Current viral safety monitoring provides a secure production chain with no documented transmission of infectious agents.

Potential anticipated side effects of pdC1-INH products are injection site reactions (rare), transmission of infectious agents (theoretical), and risk of anaphylaxis (theoretical).

The approved doses for ODT are 20 U/kg IV application for Berinert and 1000 U IV for Cinryze; a second dose of 1000 IU of Cinryze may be administered if there is no adequate response after 60 minutes.

rhC1-INH (conestat-α [Ruconest]; Pharming Group NV) has the exact same amino acid sequence as human C1-INH with a difference in the glycosylation pattern because it is produced by a purification process of milk from transgenic New Zealand white rabbits.[47] This difference is considered responsible for the shorter plasma half-life of the protein (approximately 2-3 hours). However, this does not seem to impair the sustained efficacy of the drug because study results do not show more frequent rebound attacks than pdC1-INH.[48,49]. A meta-analysis of trials using pdC1-INH or rhC1-INH demonstrated that efficacy is mostly dependent on the number of the infused units and not on the pharmacokinetic parameters.[50,51] Although rhC1-INH is considered generally safe, it is important for clinical practice to avoid it in patients with a rabbit allergy because of potentially serious allergic reactions, which has happened within 3 minutes after administration in a single healthy volunteer with a pre-existent (retrospectively known), non-disclosed rabbit dander allergy.[52]

TABLE 1. Drugs for treatment of Hereditary Angioedema

Medication (Trade name and company)	Mechanism of action	Approved indication	Regulatory status	Dose and route of administration	Potential side effects
Plasma-derived nanofiltered C1-INH (Cinryze, Takeda)	Replaces C1-INH	Acute treatment (on-demand therapy) Short-term prophylaxis Long-term prophylaxis	Australia (≥ 12 years) EU (≥ 2 years) Australia (≥ 12 years) EU (≥ 2 years) Approved by FDA and EMA (U.S. and Europe) for patients ≥ 6 years; Australia, Canada (≥ 12 years)	≥ 12 years: 1000 U IV 2-11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight) ≥ 12 years: 1000 U IV 2-11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight) Pediatric (6-11 years): 500 IU every 3-4 days IV Adolescents and adults: 1000 U IV every 3-4 days	Common: hypersensitivity, rash, pruritus, erythema, injection site reactions, vomiting dizziness Theoretical: transmission of infectious agent, thromboembolic events
Plasma-derived nanofiltered C1-INH (Berinert, CSL Behring)	Replaces C1-INH	Acute treatment (on-demand therapy) Short-term prophylaxis	Australia, Canada, EU, U.S. (adult and pediatric) EU (adult and pediatric)	20 U/kg IV Adults: 1000 U IV Pediatrics: 15-30 U/kg body weight IV	Rare: injection site reactions, hypersensitivity Theoretical: transmission of infectious agent, thromboembolic events
Plasma-derived nanofiltered C1-INH (Haegarda, Berinert 2000/3000, Berinert SC, CSL Behring)	Replaces C1-INH	Long-term prophylaxis	Australia, Canada, EU (≥ 12 years), U.S. (≥ 6 years)	60 U/kg body weight twice weekly (every 3-4 days)	Very common: injection site reactions, nasopharyngitis Common: Hypersensitivity, pruritus, rash and urticaria, dizziness Theoretical: transmission of infectious agents, thromboembolic events
Recombinant human C1-INH (Ruconest, Pharming)	Replaces C1-INH	Acute treatment (on-demand therapy)	EU (≥ 2 years), U.S. (≥ 12 years)	50 U/kg IV (< 84 kg) 4200 U IV (≥ 84 kg)	Uncommon: risk of anaphylaxis in rabbit-sensitized individuals Common: headache, nausea, and diarrhea
Ecallantide (Kalbitor, Takeda)	Selective, reversible inhibitor of plasma kallikrein	Acute treatment (on-demand therapy)	U.S. (≥ 12 years)	30 mg SC injection	Most common: headache, nausea, fatigue, diarrhea, upper respiratory tract infection, injection site reactions, nasopharyngitis, vomiting, pruritus, upper abdominal pain, and pyrexia Uncommon: anaphylaxis
Icatibant (Firazyr, Takeda)	Bradykinin B2 receptor antagonist	Acute treatment (on-demand therapy)	U.S. (≥ 18 years) Australia, Canada, EU (≥ 2 years)	Adults: 30 mg SC Pediatric: 12-25 kg, 10 mg SC; 26-40 kg, 15 mg SC; 41-50 kg, 20 mg SC; 51-65 kg, 25 mg SC; > 65 kg, 30 mg SC	Very common: injection site reactions
Lanadelumab (Takhzyro, Takeda)	Fully human monoclonal antibody that inhibits plasma kallikrein	Long-term prophylaxis	Australia, Canada, EU, U.S. (≥ 12 years)	300 mg SC injection every 2 weeks A dosing interval of 300 mg every 4 weeks may be considered if the patient is well controlled (e.g., attack-free) for more than 6 months	Common: injection site reactions Rare: risk of anaphylaxis
Berotralstat (Orladeyo, Biocryst Pharmaceuticals)	Oral inhibitor of plasma kallikrein	Long-term prophylaxis	U.S. (≥ 12 years)	150 mg capsule taken orally once daily with food In patients with moderate or severe hepatic impairment, chronic administration of P-glycoprotein inhibitors or BCRP inhibitors (e.g., cyclosporine): 110 mg capsule taken orally once daily with food	Common: abdominal pain, vomiting, and diarrhea

BCRP, breast cancer resistance protein; C1-INH, C1 inhibitor; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; SC, subcutaneous; U.S., United States

Potential anticipated side effects of rhC1-INH are headache, nausea, diarrhea, and risk of anaphylaxis in individuals with a rabbit allergy.

The approved dose for ODT is 50 U/kg IV (< 84 kg) or 4200 U IV (≥ 84 kg). An additional dose may be given in adults if there is no satisfactory clinical response within 4 hours. Recently, rhC1-INH was approved in Europe in the pediatric population > 2 years.[53]

Targeted Therapy: Icatibant (Firazyr; Shire, now part of Takeda) is a selective bradykinin B2 receptor competitive antagonist for SC administration. It is an effective therapy for acute treatment of HAE attacks.[37] The mean plasma half-life is 1.4 ± 0.4 hours. It has demonstrated good tolerability and efficacy,[37] although local reactions at the injection site (erythema, swelling, and pain) have been reported by up to 97% of the patients. The approved dose for ODT with icatibant is a single 30 mg/3 mL SC injection. The maximum recommended dose is 3 injections within 24 hours. They should be administered at intervals of 6 hours. Not more than 8 injections per month of icatibant have been administered in the clinical trials.[54] The drug is approved for the treatment of acute episodes in the U.S. for patients aged ≥ 18 years and in Australia, Canada, and Europe for patients aged above 2 years.

Ecallantide (Kalbitor; Dyax, Cambridge, acquired by Shire, now part of Takeda) is a potent selective kallikrein inhibitor that reversibly inhibits plasma kallikrein. It is used for acute treatment of C1-INH-HAE Type 1 and 2 in adolescents and adults.[38,55] It is a 60-amino-acid protein produced by a recombinant technology. Ecallantide is administered as a series of 3 consecutive SC injections. Efficacy and safety of ecallantide was studied in clinical trials (EDEMA0, EDEMA1, EDEMA2, EDEMA3 [double-blind and repeat dosing], EDEMA4, and DX-88/19), where ecallantide was demonstrated to be effective (superior to placebo) in the treatment of moderate and severe HAE episodes in patients aged above 10 years, administered as 30 mg SC injection (within 8 hours of attack onset). In the mentioned studies, ecallantide provided durable relief up to 24 hours. The most common reported adverse events are upper respiratory tract infection, fatigue, headache, nausea, vomiting, upper abdominal pain, diarrhea, injection site reactions, pruritus, and pyrexia. Hypersensitivity adverse reactions were also reported in up to 10.8% (in 17.9% when infused intravenously and in 8.7% when administered subcutaneously) of patients.[58] As these reactions are within the criteria for Type 1 immediate reactions, it is strongly advisable that ecallantide is administered at facilities with experience to manage systemic anaphylactic reactions and HAE attacks. The approved dose for ODT is 30 mg (3 × 10 mg/mL) SC injections. A second dose of 30 mg could be administered for a period of 24 hours if HAE symptoms persist. FDA has approved ecallantide for ODT in the U.S. for patients aged > 12 years. Marketing authorization is not granted in Europe.

Treatment of Special Populations: Indications for ODT in children follow the same recommendations as treatment of adults, although a limited amount of RCT data are currently available for the pediatric population. ODT with pdC1-INH in children shows similar responses to adults.[59] Data from RCT in children demonstrated that these medications are effective in decreasing the time to symptom resolution and are safe and well tolerated.[60] As in adults, data suggest that early administration of pdC1-INH results in more rapid resolution of the symptoms. The approved dose for ODT in children is 20 U/kg IV for Berinert. For Cinryze, the doses are 1000 U IV for children aged ≥ 12 years and 1000 U IV (> 25 kg) or 500 U IV (< 25 kg) for children aged 2-11 years. Recently, rhC1-INH received marketing authorization in Europe for children aged > 2 years. The drug has demonstrated efficacy in 73 acute HAE attacks in children aged ≥ 5 years.[53] No safety concerns were noted during the study in this population. The approved dose of rhC1-INH for ODT is the same as in adults: from 50 U/kg IV (< 84 kg) up to a dose of 4200 U/kg IV (≥ 84 kg) for Ruconest. If necessary, a second dose could be administered (a maximum of 2 doses can be administered within a period of 24 hours). Ruconest is approved for ODT in children in Europe (aged ≥ 2 years) and in adolescents in the U.S. (aged ≥ 12 years). SC bradykinin receptor antagonist icatibant is approved for ODT in the U.S. for patients aged ≥18 years, whereas in Australia, Canada, and Europe, it is permitted for patients aged ≥ 2 years. It is approved for self-administration as a single SC injection dosed per kilogram for pediatric patients who weighed < 65 kg. Administration of repeated dosing in children has not been studied. SC kallikrein inhibitor ecallantide is approved for use in patients ≥ 12 years in the U.S., based on the data from four clinical trials .[56,57] As in adults, the drug is to be administered only by an HCP considering the possibility of systemic allergic reactions.

Data from observational studies and case reports witnessed that C1-INH products are the treatment option at first choice for HAE attacks during pregnancy.[17,29] More real-world experience to date is available for pdC1-INH, although rhC1-INH has also been reported for uneventful use in this population.[61,62] Sporadic case reports for icatibant use during pregnancy are available.[63,64] Decision for use is to be weighed against risk in case CI-INH therapy is not readily available. To date, there is no information for the use of ecallantide during pregnancy.

C1-INH is preferred for ODT during lactation and breastfeeding. More data are available for pdC1-INH, although case series with rhC1-INH have also been reported. The use of icatibant and ecallantide is not preferred during lactation.

Generally, no special considerations are recognized in the elderly. Both replacement with C1-INH and targeted therapies are indicated with regular dosing. Theoretically, increased cardiovascular risk could be taken into consideration for targeted therapies, as the bradykinin B2 receptor also participates in the control of arterial hypertension.

Treatment of Acute Manifestations in nlC1-INH-HAE

The ultra-rare nlC1-INH-HAE cases are linked to mutations in a variety of genes: FXII (*F12*),[65] plasminogen (*PLG*),[66] angiopoietin-1 (*ANGPT1*),[9] kininogen-1 (*KNG1*),[10] myoferlin (*MYOF*),[11] and heparan sulfate glucosamine 3-O-sulfotransferase 6 (*HS3OT6*) genes.[12] Some of the recognized genes are known to be involved in the metabolism of bradykinin, whereas others interfere with different endothelial permeability processes.[67] Yet, in many nlC1-INH-HAE families, the genetic background cannot be revealed (referred to as HAE-unknown).[68]

The diagnosis of nlC1-INH-HAE is challenging even for an experienced specialist, which further creates a unique set of treatment challenges because RCTs have never been conducted in such patients, although numerous open-label reports demonstrated successful treatment response to C1-INH-HAE therapies.

A recently published solid systematic review by Bork et al.,[69] including 602 reported cases coming from 220 families with genetically determined types of nlC1-INH-HAE, analyzed the clinical features (location of attacks, demographic data, triggers) and treatment responses during acute HAE attacks. The review recognized several clinical differences between distinct forms of nlC1-INH-HAE and suggested that identifying the genotype of nlC1-INH-HAE might be important to improve precision of treatment strategies.

HAE with a Pathogenic Variant of the *F12* Gene: FXII-HAE is an autosomal-dominant inherited trait. It is more common in women, who seem to be more symptomatic than men identified as carriers of the pathogenic variant of the *F12* gene. Estrogens (menstruation, pregnancy, OCs, and HRT) seem to be of high importance as triggering or aggravating factors. Current treatment strategies for FXII-HAE include similar principles as those effective for patients with C1-INH-HAE, although no specific treatments are officially approved. It is also recommended to avoid triggering factors as much as possible and discontinue the intake of any estrogen-containing medications and ACEIs.[69] ODT with pdC1-INH and rhC1-INH concentrates was reported to be effective and demonstrated significant reduction in the duration of swelling when compared with non-treated attacks.[69,70] Icatibant has also demonstrated good effectiveness for the management of abdominal attacks in FXII-HAE, with onset of symptom improvement in 30 minutes and complete resolution by 1 hour.[71]

HAE with a Pathogenic Variant of the *PLG* Gene: This form of nlC1-INH-HAE was identified in 2018. It is linked to clinical symptoms of HAE and is an autosomal-dominant trait. Estrogens were found to play a consistently small physiological role as triggers of PLG-HAE compared with FXII-HAE. ODT experience was demonstrated by a large case review of 111 patients where indirect comparison between C1-INH concentrate and icatibant was done. Icatibant appeared to be more effective in decreasing the duration of attacks than C1-INH concentrate and demonstrated a better responder rate.[72]

HAE with a Pathogenic Variant of the *ANGPT1* Gene: This form of nlC1-INH-HAE was also identified in 2018 and is transmitted in an autosomal-dominant manner. It is a rare novel type of HAE identified by whole-exome sequencing (WES) in 2 patients from 1 family. Current reports suggest that tranexamic acid (TXA) was effective as prophylaxis in 2 patients where administration showed reduction in the frequency and severity of HAE attacks. Antihistamines and corticosteroids were not effective for acute attacks or as prophylaxis.[9]

HAE with a Pathogenic Variant of the *KNG1* Gene: This form of nlC1-INH-HAE was identified in 2019 by WES in a large family with an unknown form of HAE. It is transmitted in an autosomal-dominant manner. For this type of HAE, in 1 patient, symptom improvement was reported after IV administration of 1000 IU C1-INH for 2 facial attacks. Corticosteroids and antihistamines were ineffective.[10]

HAE with a Pathogenic Variant of the *MYOF* Gene: A new type of nlC1-INH-HAE was described recently in 3 women from an Italian family with symptoms of AE in the oral mucosa, lips, and face.[11] In this type of HAE, a mutation in the *MYOF-217S* gene was found to be the reason for abnormal protein production of myoferlin, which is associated with vascular endothelial growth factor signal transduction. No current evidence for effective treatment of this type of HAE is available.

HAE with a Pathogenic Variant of the *HS3OST6* Gene: Most recently, this novel nlC1-INH-HAE type was described recently in 3 female patients with AE symptoms.[12] The patients presented with recurrent swellings of the skin, abdominal pain attacks, tongue swellings, or laryngeal attacks. The identified mutant *HS3OT6* fails to transfer sulfo groups to the 3-OH position of heparan sulfate, which results in partial heparan sulfate synthesis. Theoretically, this affects the interactions of key molecules responsible for the vascular permeability on the cell surface. This suggests a novel pathophysiological mechanism for AE development. No current evidence for effective treatment of this type of HAE is available.

PROPHYLACTIC THERAPY

Short-term Prophylaxis

Short-term prophylaxis (STP) is indicated for patients at increased risk for an AE attack after exposure to known triggers or stressful life events. The goal of STP is to decrease the risk of swelling in patients undergoing a procedure/event that has the potential to precipitate an attack.[61]

It is known that physical trauma, caused by medical and dental procedures, can result in development of AE .[73] Patients undergoing invasive upper airway interventions, such as dental surgery and intubation, are at extremely high risk because of potential risk of upper airway swelling. However, even minor procedures can trigger AE episodes. HAE symptoms can develop from hours to several days after an intervention, and patients should be educated about the possible risk of AE within 72 hours after intervention. The characteristics of the local trauma may play an important role when considering whether to give the patient prophylactic treatment. For example, dental extraction is associated with a higher risk for AE than dental cleaning or cavity restoration. Other factors, including emotional stress, can also trigger attacks. Despite these observations, relatively little is known about the specific risk associated with certain medical, surgical, and dental procedures and the benefits of pre-procedural prophylaxis (RCTs are not available). However, several retrospective reviews, surveys, and analyses report that pre-procedural prophylaxis is associated with reduced incidence of swelling for both adults and children.[74-77] Therefore, current international guidelines recommend the use of STP before known patient-specific triggers and procedures (medical, surgical, and dental) that can induce an attack. It should be noted that irrespective of STP administration, HAE-specific ODT should be available during and after any procedure.

C1-INH-HAE: Pre-procedural C1-INH concentrate should be administered as close as possible to the beginning of the procedure (1-12 hours before the procedure). The recommended dose for pdC1-INH is 20 U/kg intravenously. STP with Cinryze is given at a dose of 1000 U within 24 hours of the procedure and Berinert at a dose of 1000 U within 6 hours of the procedure, being administered as close as possible to or immediately before the procedure.[77] rhC1-INH can be considered a reasonable choice for STP although not stated in the prescription information. It is dosed 50 IU/kg and has to be administered as close as possible to the upcoming procedure.[78]

Alternatively, anabolic androgens may be considered for STP in cases when C1-INH treatment is not an available STP option and particularly if HAE-specific acute treatments are not available. For scheduled pre-procedural prophylaxis, danazol can be used starting 3-5 days before the anticipated procedure or risk exposure and continuing 2-3 days after the intervention/procedure/event (danazol 2.5-10 mg/kg/day, maximum 600 mg/day).[76] It should be noted that side effects caused by frequent short-term administration may be similar to those seen with long-term androgen use.[16]

FFP may also be used for STP, although it is not as safe as C1-INH concentrates. It should be considered as a second-line therapy because of higher risk of blood-borne disease transmission and allosensitization. FFP can be used when C1-INH is not available and there is no sufficient time to complete a course of anabolic androgens. The optimal dose of frozen plasma for STP has not been established, but based on published data, it is usually given as 2 U in adults and 10 mL/kg in children 1-2 hours before a procedure or stressor.[79,80]

Lanadelumab, a humanized monoclonal antibody (mAb) targeted against kallikrein, is not recommended for STP, as it needs about 70 days to reach a steady-state concentration. Currently, there is no available data on the need for STP in patients who are asymptomatic under lanadelumab LTP.[81,82]

Treatment of Special Populations: Indications for STP in children follow the same guidelines as those in adults. Therefore, pre-procedural prophylaxis is recommended before medical, surgical, and dental procedures that can result in any mechanical impact to the upper respiratory tract. There are no clinical trials supporting appropriate timing and maximum dosing for STP in children. However, the European pediatric guidelines recommend prophylaxis with a dose of 15-30 U/kg of pdC1-INH (Berinert) within 6 hours or 500 U of Cinryze for children 10-25 kg within 24 hours of an anticipated procedure. Currently, there are no published data about STP in children with rhC1-INH, although the drug is licensed in the pediatric population (>2 years). Short courses of AAs, particularly danazol (2.5-10 mg/kg/day, mean dose 5 mg/kg/day, maximum 600 mg daily), are allowed as second-line treatment but only when C1-INH concentrate is not available. With either option, an on-demand therapeutic option should always be available as STP may not be successful in all cases.

C1-INHs are the preferred drugs for STP during pregnancy because of their safety profile.[31,83,84] More data are available for pdC1-INH. It should be administered before any intervention, such as chorionic villus sampling and induced surgical abortion. It is recommended to manage childbirth in the hospital setting. Vaginal delivery is preferred because surgery may require endotracheal intubation. In general, not all pregnant patients with HAE are indicated for routine STP for uncomplicated vaginal deliveries, but C1-INH concentrate should be available for on-demand use in case of swelling.[18,83] However, STP could be considered before vaginal delivery in certain situations, such as a history of severe, life-threatening HAE attacks; frequent attacks during the third trimester; or a history of genital edema caused by mechanical trauma.[85] STP and epidural anesthesia are recommended before a C-section, and, whenever possible, intubation should be avoided. Intubation always requires pre-procedural prophylaxis. AAs are contraindicated in pregnant women because they cross the placenta and can cause adverse effects, such as fetal virilization, placental insufficiency, and fetal growth retardation. Therefore, before initiation of therapy with androgens, women should be advised to perform a pregnancy test. Lactation may cause more frequent HAE attacks, potentially owing to increased serum prolactin levels. Terminating lactation itself may result in reduction of attack frequency. The use of C1-INH is recommended in case pre-procedural prophylaxis is needed during lactation. Anabolic androgens are secreted into the breast milk, and, therefore, breastfeeding should be discontinued before their initiation.

nlC1-INH-HAE: There is little experience regarding STP for nlC1-INH-HAE. For patients with a confirmed diagnosis, the same approach as in patients with C1-INH-HAE may be adopted, and on-demand therapy should be provided if needed. However, as data from randomized controlled studies are not available, no conclusive recommendations regarding STP of HAE with normal C1-INH can be made.

Long-term Prophylaxis

LTP of HAE represents the regular administration of medication to prevent or decrease the frequency, severity, and duration of HAE attacks. The decision when to start with this therapeutic approach is one of the most difficult topics in patient management. Current HAE guidelines attempt to provide recommendations on which medications are suitable for LTP, although there are still no clear rules on when the right moment is to initiate it. Many factors influence this choice, and it has to be individualized based on the patient's needs. Attack frequency, severity and duration, comorbid conditions, access to emergency treatment, patient's ability to self-administer on-demand therapy, and the individual impact on QoL must be taken in consideration. Because all these factors could significantly vary over time, patients must be regularly monitored and reassessed, and the necessity to initiate, continue, or stop LTP should be repeatedly analyzed and discussed with the patient. Patients' preferences should always be taken into consideration because success of LTP can depend on their compliance and inner motivation.

It should be noted that LTP does not eliminate risk entirely, even if it has success in decreasing number and severity of attacks. Therefore, all patients receiving LTP must be informed about that risk, provided with effective on-demand therapy, and regularly trained how to use it in case an acute HAE attack occurs.

C1-INH-HAE: Medications for LTP in C1-INH-HAE include IV and SC supplementation with C1-INH, an mAb acting as selective inhibitor of plasma kallikrein (lanadelumab), and orally administered AAs and antifibrinolytics. Expert recommendations suggest that the latter two are considered second-line therapies because of long-term safety and efficacy concerns.[13] Guidelines advise that first-line therapies should be preferred whenever possible. Androgens and antifibrinolytics have to be assigned in cases when the first-line medications are not readily available or when the patient will agree with oral therapy only. In addition, the possible side effects of second-line therapies should be clearly communicated with patients.

AAs (17-a alkylated androgens) are traditionally used for many years for LTP of HAE, with danazol and stanozolol being most widely prescribed. It is suggested that they boost the level of C1-INH, although the exact mechanism is not well investigated.[86] Their effectiveness in reducing HAE attacks has been demonstrated in a pile of clinical observations, and oral route of administration facilitates their use.[87-90] The main concerns about AAs are their numerous anticipated side effects, which can affect most patients. Their adverse effects are dose dependent, with one of the most important being hepatotoxicity, including hepatocellular adenoma and, in very rare cases, carcinoma.[91,92] Menstrual disorders, hirsutism, acne, weight gain, and depression are also common.[93] AAs are contraindicated during pregnancy, because they might cause virilization of the female fetus, and in patients with androgen-dependent malignancies and hepatitis.[94,95] AAs might also interfere with many drugs' metabolism and thus can increase other adverse effects. AAs have to be used at the minimum effective dose to diminish the side effects. Usually, the treatment starts with initial induction with a higher dose for a month (e.g., danazol 400 mg to 600 mg daily; stanozolol 4 mg to 6 mg daily). Then, the dose has to be gradually reduced to the lowest dose that assures reliable prophylaxis (usually 2 mg stanozolol daily or every other day or 200 mg danazol daily or every other day). It is recommended to check patient status every 6 months, which should include laboratory tests for liver enzymes, lipid profile, complete blood cell count, alpha-feto-protein, and urine examination.[96] To detect early eventual diagnosis of liver tumors, it is desirable to perform abdominal ultrasound annually.

Antifibrinolytic agents (TXA and epsilon aminocaproic acid) have been used for LTP but with less effectiveness than other available medications. Current guidelines recommend their use only in situations where other first-line therapies are not available, and androgens are contraindicated. TXA is the preferred antifibrinolytic, because e-aminocaproic acid is related to many undesirable effects, including thrombosis, postural hypotension, muscular pain and weakness associated with an increase in creatine kinase and aldolase, anal pruritus, and myositis.[97] The daily dose of TXA is usually 1-3 g per day, up to 6 g daily. Side effects are uncommon and include abdominal discomfort, mild transient diarrhea, nausea, headache, and anal pruritus.

Replacement therapy with C1-INH is a reasonable approach to treat a congenital C1-INH deficiency, being the ultimate historical strategy to minimize the chance for acute AE attacks via normalization of plasma C1-INH levels. IV substitution was the first attempt used for LTP, which demonstrated reasonable efficacy, although with relatively poor long-term tolerability because of the need for repetitive IV applications. Drug delivery through an indwelling port system was tried and resulted in several thrombotic events, which led to the discontinuation of this practice.[98] Pharmaceutical companies tried to initiate an investigational program for hyaluronidase-enhanced SC delivery, which resulted in the formation of antihyaluronidase antibodies, and again resulted in a ban on this approach.[99] Only recently, in 2017, pdC1-INH was registered as an SC LTP option in the U.S. and Europe.

Cinryze (1000 U; Shire, now part of Takeda) was the first to receive FDA approval in 2008 as a plasma-derived, nanofiltered C1-INH with the IV route of administration for routine prophylaxis of HAE attacks in adults and adolescents. The European Medicine Agency (EMA) granted approval in 2011. Cinryze demonstrated significant reduction in the severity and continuation of attacks in ODT use when compared with placebo.[20] These findings were further confirmed in an open-label extension (OLE) study, where the patients were treated up to 2.6 years.[100] LTP with Cinryze was highly effective, sustainable, and safe in most patients with C1-INH-HAE. The dose regimen approved by Regulatory Authorities for LTP is 1000 U IV every three to four days.[100] Escalation of the dose (up to 2500 IU twice weekly) and the number of applications (3 times per week) have demonstrated improved efficacy for patients who are still symptomatic, although the administered usual dose is 1000 IU twice weekly. The indication for Cinryze was expanded in 2018, when the medication was approved by both FDA and EMA for LTP in children aged 6-11 years, on the basis of the favorable the outcomes in a Phase 3 study.[101] Berinert 500 and 1500 U (CSL Behring), another IV pdC1-INH, is currently not approved for LTP, although widely used off-label. The analysis of the data collected in an international registry showed that Berinert administered as LTP for HAE was efficacious with a very good safety profile and led to a decrease in the rate of attacks that required on-demand therapy, usually observed in the beginning of LTP initiation.[102] There are several thromboembolic events reported by patients receiving IV pdC1-INH, evaluated as being related to the use of port catheters or with underlying risk factors for thrombotic events, rather than the drug itself.[98] Still, the official summary of product characteristics for Cinryze and Berinert recommends carefully following the patients with available risk factors for thromboembolic events. Ruconest, an rhC1-INH, is not currently approved for LTP; however, it showed a clinically important decrease in the frequency of HAE attacks and demonstrated a good safety profile when applied for routine prophylaxis once or twice weekly.[49]

Maintaining long-term venous access for LTP with IV C1-INH is challenging, and many patients have had difficulties with IV self-infusions.[103] In addition, they expressed concerns about damaging their veins with long-term repetitive IV injections and expressed dissatisfaction because of long infusion time. These concerns could be overcome by the highly concentrated human pdC1-INH approved in the U.S. and Europe for SC injection (Berinert 2000/3000; Haegarda). At a dose 60 IU/kg, SC C1-INH demonstrated a significant decrease in attacks versus placebo and a reduc-

tion in the need for on-demand medication by a median of 100% during 16 weeks of treatment. The substantial and sustained prophylactic effect was further displayed in an OLE study, where most of the patients became attack-free.[104] In addition, improvements in multiple HAE-related HRQoL impairments were observed.[105] SC C1-INH is well tolerated with a very good safety profile; the most common adverse events were nasopharyngitis, hypersensitivity, dizziness, and localized injection site reaction.[104] Presently, the concern about this LTP approach is the long-term sustainability of drug manufacturing because of the large amounts of donor plasma needed for the production process of these products.

Lanadelumab (Takhzyro; Shire, now part of Takeda) is the first mAb approved in the U.S. and European Union (EU) for prophylaxis of HAE attacks. It is a fully human, κ-light-chain, monoclonal immunoglobulin G1 with high affinity to plasma kallikrein and with a long half-life (~ 2 weeks).[106,107] The Phase 3 HELP study investigated 3 dose regimens administered SC 150 mg every 4 weeks, 300 mg every 4 weeks, and 300 mg every 2 weeks.[81] All of them significantly reduced HAE attacks during the 26-week treatment period where the highest concentration was most effective (86.9% reduction in attacks) and subgroup analyses showed that this was not dependent on age, gender, body weight, and baseline HAE clinical characteristics. Ad hoc analysis of the HELP study demonstrated a rapid onset of action and maintained effectiveness in reducing the rate of HAE attacks.[82] The OLE HELP study investigated the long-term safety (primary endpoint) and efficacy of lanadelumab for a period of up to 2.5 years and ended in November 2019. An interim analysis of the results showed a continuous decrease in HAE attack rates in subjects who were treated for a mean period of 19.7 months (0-26.1 months).[108] The safety profile of lanadelumab is good, and no significant safety signals have been registered across the trials conducted so far. The most common side effects for lanadelumab reported through the HELP study were injection site pain (42.9%), viral upper respiratory tract infection (23.8%), headache (20.2%), injection site erythema (9.5%), injection site bruising (7.1%), and dizziness (6.0%). The severity was mild to moderate. Two hypersensitivity reactions were reported by one patient, representing intermediate symptoms of oral tingling and itching. The events were of mild or moderate intensity and resolved with no additional therapy or premedication.[81] An interim analysis of the OLE HELP study confirmed the good safety profile that was comparable across all subgroups, with adverse events observed in half the patients (n = 106). The most frequently reported side effect was mild injection site pain.[109] The starting dose of lanadelumab is 300 mg SC every 2 weeks. For patients who achieved good control after a certain period, a dosing regimen of 300 mg every 4 weeks could be applied.

Berotralstat is an oral, once daily, inhibitor of plasma kallikrein that was approved by FDA in December 2020 for prophylaxis of HAE attacks in adults and adolescents ≥ 12 years under the trade name Orladeyo (Biocryst Pharmaceuticals). Application for approval was submitted to EMA in April 2020 and is under evaluation. The Phase 2 study, called APeX-1, investigated the effectiveness, safety, and tolerability of several doses (62.5 mg, 125 mg, 250 mg, and 350 mg once daily) of berotralstat in 75 patients with HAE.[110] There was a significant decrease in the number of HAE attacks for the daily doses of ≥ 125 mg compared with placebo, with a 73.8% difference at 125 mg ($P < .001$). Improvement of QoL scores was demonstrated in the 125-mg and 250-mg dose regimens ($P < .05$). The most frequently observed adverse events were gastrointestinal, mainly of grade 1, especially in the two highest berotralstat dosages. These positive results were further confirmed in the Phase 3 study, called APeX-2.[111] The trial was placebo-controlled and enrolled 121 patients aged ≥ 12 years who were randomly assigned to receive berotralstat 110 mg, 150 mg, or placebo. A significant decrease in the number of attacks was observed for both 110 mg and 150 mg doses compared with placebo. This effect began within the first month of medication administration and was maintained during the whole 24-week period of the study. Berotralstat at a dose of 150 mg showed the most favorable benefit-to-risk ratio. There were no serious adverse events (SAEs) related to the drug, and the most frequently occurring adverse events were abdominal pain, vomiting, diarrhea, and back pain. An OLE trial, APeX-S (NCT03472040), is currently ongoing and investigating the long-term-safety, effectiveness, and sustainability of treatment response with berotralstat.

Treatment of Special Populations: Indications for starting LTP in children should follow the same recommendations as for adult patients.[112] The therapy should be flexible, and patients should be followed regularly to reflect the changes in hormones and lifestyle typical for children and adolescents. One of the main issues in the management of children is the lack of RCTs that involve patients from this age group for most of the therapies. pdC1-INH is the preferred therapy for LTP in children on the basis of the available results from RCTs and their OLE studies demonstrating its efficacy and tolerability.[101,113] Cinryze is approved in the EU and U.S. for LTP in children ≥ 6 years old since 2018. The dose regimen is 500 U every 3-4 days for children 6-11 years old and 1000 IU every 3-4 days for adolescents (12-17 years old). SC C1-INH (Haegarda, Berinert 2000/3000) was initially approved for adolescents aged ≥ 12 years and recently, in September 2020, the FDA granted approval for children aged ≥6 years. The extension of the use was made based on the data from the COMPACT study and its OLE study that included 10 patients aged < 17 years treated for up to 2.55 years. The results demonstrated that SC C1-INH was efficient with a good safety profile as LTP in children and adolescents, as it was in adults with HAE. Both lanadelumab and berotralstat have approval for adolescents (e.g., subjects aged ≥ 12 years). The aforementioned 3 medications provide another option for young patients in whom the regular venous access required for application of pdC1-INH for prophylaxis may not be well tolerated. Androgens are not recommended for children because of many potential effects and interference with normal growth and hormonal development.

Indications for LTP might appear during pregnancy, especially if the frequency of HAE attacks increases. The current guidelines recommend pdC1-INH as the preferred medication for LTP during pregnancy, mainly on the basis of case reports, observational studies, retrospective analyses, and expert opinions, because performing RCTs with pregnant women is extremely rare because of ethical reasons.[13,61] The data available so far suggest that pdC1-INH is well tolerated and not related to any newborn abnormalities.[30,31,83,84] A recently published subgroup analysis of COMPACT OLE showed

that four women exposed to SC C1-INH during the first trimester had uneventful pregnancies and delivered healthy babies.[114] Androgens are contraindicated during pregnancy because of the risk of virilization of the female fetus. In addition, treatment with AAs has to be stopped at least 1 month before a planned pregnancy.[17] LTP with antifibrinolytics during pregnancy is considered medically indicated only when pdhC1-INH is unavailable.[17] Lactation and breastfeeding might increase the frequency of HAE attacks, with elevated prolactin levels being suspected as a triggering factor. In case LTP is indicated during this period, pdC1-INH is suggested as a treatment of choice.[17] Androgens and antifibrinolytics are not recommended because they pass into breast milk and can have detrimental effects on the baby.[13]

nlC1-INH-HAE: Currently, no RCTs for LTP in patients with nlC1-INH-HAE are available, and there is no specific treatment approved for this group. However, there are positive experiences with antifibrinolytics, progestins and AAs, and C1-INH. A good effect of LTP with progestins was observed in 16 female patients with FXII-HAE after discontinuing estrogen-containing OCs.[70] The mean reduction in attack rate was 99.8%. Similar results with progestins in patients with FXII-HAE were observed by other groups.[115,116] TXA and AAs have also demonstrated effectiveness in reduction of attacks in FXII-HAE patients; some achieved almost complete disease control, others partial improvement. In patients with PLG-HAE, TXA appears to be the most effective drug compared to progestins and AAs.[72] In the recently determined other type of nlC1-INH-HAE, i.e., ANGPT1-HAE, two patients treated with TXA for prophylaxis experienced decrease in attack rate and severity.[9] There are few case reports on the effect of pdC1-INH in reducing attack frequency in pregnant patients with nlC1-INH-HAE.[117]

RESEARCH PIPELINE: NOVEL DRUGS UNDER DEVELOPMENT

KVD900/824

This class of investigational drugs developed by the pharmaceutical company KalVista present selective small-molecule inhibitors of plasma kallikrein, tailored for ODT (KVD900) and oral prophylaxis (KVD824) of AE attacks in adolescent and adult subjects with C1-INH-HAE Type 1 or 2. Phase 2 studies for LTP with KVD824 and Phase 3 studies for ODT with KVD900 are currently being initiated.[118]

KVD824 was evaluated in two Phase 1 studies in adult healthy volunteers. Pharmacodynamics of KVD824 have demonstrated that KVD824 inhibits plasma kallikrein activity at levels exceeding equivalent concentrations for berotralstat, the currently approved once daily oral plasma kallikrein inhibitor. KVD824 achieved adequate plasma concentrations with sustained plasma kallikrein suppression over a 12-14–hour time interval. These data support further investigation of KVD824 as an orally administered treatment with adequate plasma kallikrein suppression to potentially prevent or reduce the occurrence of HAE attacks. The doses of modified-release KVD824 to be given in this trial were well tolerated in a previous clinical trial comprising 16 subjects who received single doses of KVD824 up to 900 mg and 21 subjects who received at least 600 mg twice a day for 14 days (Study KVD824-102). All adverse events observed in these studies were of mild and of short duration. No Grade 3 (severe) or SAEs were reported.

The KVD900 Phase 2 study was a randomized, double-blind, placebo-controlled, crossover clinical trial evaluating the efficacy and safety of KVD900 for ODT for HAE attacks. The trial was completed by 53 adult patients with HAE from 25 clinical sites in the U.S. and Europe. During the first part of the two-part trial, patients received a single, open-label 600 mg dose of KVD900 for the evaluation pharmacokinetic and pharmacodynamic properties. All patients then entered the double-blind step to assess the efficacy of KVD900 compared with placebo in a two-attack, crossover design. Attacks treated with KVD900 resulted in significantly reduced use of rescue ($P = .001$), with 15% of KVD900-treated attacks rescued compared with 30% on placebo at 12 hours, and the effect was maintained at 24 hours ($P = .0005$). KVD900 significantly reduced time to onset of symptom relief ($P \leq .0001$) with a median time of 1.6 hours versus 9 hours for attacks treated with placebo. There were no SAEs reported in the trial, and no patients withdrew because of adverse events. In the open-label phase, eight treatment-emergent adverse events (TEAEs) were experienced by 5 patients. In the crossover phase of the trial, 3 TEAEs were experienced by 3 patients (5.2%) following administration of KVD900, and 2 TEAEs were experienced by 2 patients (3.6%) following administration of placebo.

ATN-249

ATN-249 is a novel, oral, small-molecule kallikrein inhibitor. ATN-249 was studied first in a human double-blind, placebo-controlled safety, tolerability, and pharmacokinetic study to evaluate a single ascending dose in 48 healthy subjects. A total of 30 volunteers received 50 mg to 800 mg, and 12 subjects received placebo. A part of the 100-mg cohort received the drug under fasted and fed conditions.[119]

A Phase 2 study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of ATN-249 for LTP of HAE is expected to begin.

PHA121

PHA121 (PHA-022121; Pharvaris) is an oral, potent antagonist of the bradykinin B2 receptor, thus it uses the same mechanism as icatibant. The molecule is under development for on-demand and prophylactic treatment of HAE and other bradykinin-mediated diseases. Data from the recently completed Phase 1 study (randomized, double-blind, placebo-controlled, multiple ascending dose) in healthy volunteers confirm PHA121's oral bioavailability and rapid action. The trial included 38 healthy subjects dosed twice daily (BID) for 10 days in 4 sequential dosing cohorts, ranging from 12 to 50 mg. During the study, PHA121 was well tolerated up to the highest dose of 50 mg BID. Results demonstrated that PHA121 has been observed to be safe and well tolerated at the doses studied to date. The total incidence and type of TEAEs were similar between the active drug and placebo groups. Lab safety, vital signs, and electrocardiogram parameters remained within reference ranges in all subjects.[120]

Garadacimab (CSL312)

Garadacimab (investigated as CSL312) is a newly developed mAb to inhibit Factor XIIa and is under investigation for prophylactic therapy of HAE. Announced data from a Phase 2 clinical trial show that the drug decreased total attacks compared with placebo in patients with C1-INH-HAE.[121] The study included 32 adults with HAE who were randomized to receive garadacimab (either 75 mg, 200 mg, or 600 mg) or placebo once monthly for three months. Decreased attack rate was observed with 88.68%, 98.94%, and 90.50% for distinct treatment groups versus placebo, respectively. The drug was well tolerated, with injection site reactions being the most common TEAE (12.5%).

An orphan drug designation for prophylaxis of bradykinin AE was granted by FDA in May 2020 (including both hereditary and acquired AE).

IONIS-PKK

IONIS-PKK is an antisense oligonucleotide (ASO) targeting PKK to control severe bradykinin-mediated AE .[122] Ionis developed two ASOs, IONIS-PKKRx, and IONIS-PKK-LRx, to target the production of PKK. Both therapies work through the same mechanism. Of note, PKK-L is a version of PKK that has been chemically modified to have a more potent effect in humans and it allows for the same pharmacological effect at a lower dosing.

Completion of the Phase 1 study in healthy subjects demonstrated a dose-dependent decrease of up to 95% in PKK. Development is planned to continue because of demonstrated safety and tolerability.

A recent report by Cohn et al.[123] showed advantages of the drug in 2 patients with difficult to manage bradykinin-mediated AE (a compassionate-use pilot study). Patients were given SC unconjugated parent drug, IONIS-PKKRx, weekly for 3-4 months. Thereafter, patients continued therapy with IONIS-PKK-LRx (80 mg) every 3-4 weeks for an additional 7-8 months. Decrease in number of attacks was observed with no safety concerns. These pilot findings provide proof-of-concept data supporting the use of ASOs as a treatment for HAE.

Gene Therapy

A murine model of C1-INH deficiency gave promising pilot results for studies in humans. Adeno-associated virus (AAV) vectors have been investigated for hemophilia B[124,125] and hemophilia A,[126] being able to provide sufficient levels of factor IX and factor VIII, respectively.

In individuals with HAE, it is difficult to normalize C1-INH synthesis in cells that concurrently produce a dysfunctional C1-INH protein. Adverum investigates an AAV-based gene therapy for the treatment of C1-INH-HAE constructed to erase HAE's underlying pathomechanism by normalizing functional C1-INH synthesis. This drug is designed as a potentially single-administration treatment. The Phase 1/2 clinical study has been discontinued. Although ADMV-043 was demonstrated to be well tolerated, results for protein synthesis could not reach reasonable levels.

Another study with ADVM-053 in patient-derived fibroblasts led to restoration of C1-INH synthesis. Despite this, Adverum has not submitted an application before the FDA for an Investigational New Drug designation.[127]

In conclusion, studies in the recent decades made a huge leap in identifying mechanisms of AE and in developing modern safe and effective medications to treat acute AE manifestations or control disease activity via prophylactic therapy. Future efforts must be concentrated to improve disease awareness and to develop comprehensible diagnostic tools, and, possibly, prognostic biomarkers to recognize early disease manifestations. Technology-based smart algorithms, harmonized registries, and data sharing will help improve specialist and individual/caregiver collaboration in the name of better patient care and understanding the patient's true needs. Advances in pharmacological treatment aim to provide a normal lifestyle through improvement of preventive strategies and improved safety, efficacy, and tolerability of medications for all patient groups (adults, children, pregnant, and elderly). Future aspirations must focus on improving global accessibility of diagnostic tools and effective medications and possibly genetic cures for distinct genotypes of HAE.

Author Contributions: Concept - A.V.; Design - A.V.; Supervision - A.V., M.S.; Materials - A.V., D.N., V.Y., E.P., M.S.; Data Collection and/or Processing - A.V., D.N., V.Y., E.P., M.S.; Analysis and/or Interpretation - A.V., D.N., V.Y., E.P., M.S.; Literature Review - A.V., D.N., V.Y., E.P., M.S.; Writing - A.V., D.N., V.Y., E.P.; Critical Review - A.V., D.N., V.Y., E.P., M.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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