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Hereditary Angioedema: Diagnosis, Management, Current State of Art and Advances

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Abstract

Hereditary angioedema (HAE) is a rare, mostly inherited disorder however 25% of patients have de novo mutations. Although it's rarity, it can be life threatening due to laryngeal involvement. Along with understanding the basis of swelling, several new treatment options aside from C1-inhibitory protein (C1-INH) replacement have been developed and are avaible on the markets. However the avaibility of approved drugs for attacks of HAE varies world wide. Treatment management requires angioedema attacks treatment, pre-procedural treatment and long term prophylaxis (LTP). C1-INH which was firstly developed and approved for on-demand treatment, pre-procedural treatment and LTP by iv route, nowadays for LTP, other developed and approved options are used by orally and sc route. Despite the new developing medications, permanent treatment such as gene therapy is needed.

Keywords: Hereditary angioedema, C1-inhibitory protein, C1-INH replacement, bradykinin, plasma kallikrein, lanadelumab,

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History of hereditary angioedema

Angioedema is known as recurrent, localized and self-limiting swelling at subcutaneous or submucosal tissue that can be resolve spontaneously in 1-3 days. Firstly in 1586, Marcello Donati[1] was termed angioedema in a patient with egg allergy. After for a long time, in 1876 John Laws Milton[2] is renamed angioedema as "giant urticaria" in a woman with swelling of her both eyes. Then in 1882, Quincke delinated angioedema in a group of patients but the term of "angioneurotic edema" was first used by Paul Strübing[3], in 1885. The term of angioneurotic affirms that edema is associated with neurotic affects. In 1888, the denomination of hereditary form "hereditary angioneurotic edema" was renamed by Osler.[4] Osler highligted the hereditary inclination of the disease based on a patient and her affected family members expansion back to five generation. In 1961, Lepow and et al.[5] found out an enzyme that inhibits Complement 1 and named it as C1-esterase inhibitor (C1-INH). In 1963, Donaldson and Evans[6,7] explained the basis of the disease with absence of C1-INH in hereditary angioedema (HAE) patients. In 1965, Rosen et al.[8] reported impaired C1-INH function with normal C1-INH level in a family and HAE was then defined as Type I and Type II. HAE type I has low both C1-INH antigen and function and Type II has normal C1-INH level but low C1-INH function. Crowder[9] was defined inheritance pattern of the disease as autosomal dominant heritage in 1917. Genetic sequences with DNA revealed that C1-INH is a member of serin protease inhibitor (SERPING1) family and located on 11q12-q13.1 position. The mutation in the SERPING1 gene was found in the mid 1980s. C1-INH protein regulates several proteases inclusive of the complement, contact-system, coagulation, and fibrinolytic pathways. Although all of these developments, until 1998, Nussburger et al.[10] stated that bradykinin was the main molecule that leads to vascular permeability and angioedema as a result of contact system activation.

Hereditary angioedema with normal C1-INH level and function (nlC1-INH-HAE) was defined in 2000s.[11,12] In 2006, Dewald and Bork[13] found out FXII gene mutations in patients with nlC1-INH-HAE, in exon 9, that encodes coagulation factor (Hageman factor). Nevertheless FXII mutations in HAE accounts for only up to 25% of European patients with nlC1-INH-HAE. Afterwards widening next-generation sequencing technologies utilization, 4 novel target genes (ANGPT1, PLG, KNG and MYOF) discovered in patients with nC1-INH-HAE.[14]

Highlights

- Hereditary angioedema is a rare autosomal dominant trait disease.
- Mutation on SERPING1 leads to C1-inhibitor protein deficiency.
- Hereditary angioedema Type I and II have low C4, and low C1-inhibitor protein level and/or function.
- Other forms of hereditary angioedema have normal C4 and C1-inhibitor protein level /function with different mutations.
- Some identified mutations causing hereditary angioedema with normal C1-inhibitor are factor XII, angiopoietin-1, plasminogen, kininogen-1, myoferlin and heparan sulfate glucosamine 3-sulfotransferase 6.
- Treatment options are replacement of C1-INH protein intravenously or subcutaneously, and targeting inhibition of bradykinin– kallikrein pathways by orally, and subcutaneously.

Estimated prevelance of HAE is 1-9/100.000.[15] Well known and firstly defined form is HAE with C1-INH deficiency, that has hypocomplementemia and caused by SERPING1 mutation. Afterwards nonhypocomplementemic HAE with normal C1-INH due to mutations other then SERPING1 was discovered. The known mutations to cause nlC1-INH HAE are FXII (HAE-FXII), PLG (HAE-PLG), ANGPT1 (HAE-ANGPT1), high molecular KNG1(HAE-KNG1), and myoferlin (HAE-MYOF) and lastly heparan sulfate glucosamine 3-O-sulfotransferase 6 (3-OST-6), HS3ST6. Although the majority of HAE patients with nlC1-INH may have unknown mutations, namely as HAE-U.[16]

Pathophysiology of HAE

Unlike urticaria-angioedema, underlying mechanism of edema in HAE patients' is activation of contact system or kallikrein-kinin system which leads to exaggerated bradykinin generation or signaling. Bradykinin, a potent vasodilatory mediator, enhances vascular permeability and acts as a main mediator of swelling in C1-INH-HAE and probably in nlC1-INH-HAE. C1-INH is an inhibitory protein and act as a check point protein on classical, lectin complement pathways, as well as contact system, fibrinolytic and kinin-generating pathways. Increased bradykinin engages bradykinin B2 receptors, that is mainly expressed on endothelial cells, and leads to disintegration of the adherens junction, with resultant increases pore size of endothelial cells and vascular leakage and angioedema.[17] Swelling occurrs without wheals and pathologic basis is non-histaminergic. The feature of the angioedema is chronic, non pruritic and recurrent episodes of swelling in any part of the body. Fortunately edema resolves spontaneously within 2-5 days, however larynx, tongue and uvula involvement can cause asphyxia and death. To provide to control of the plasma contact system crucial functional threshold of C1-INH is approximately 40%.[18] In C1-INH-HAE, functional C1-INH level is commonly 5-30% of the normal level. In nlC1-INH-HAE, underlying mechanism of angioedema is not fully understood but is considered that increased bradykinin plays an important role.

Diagnosis of Hereditary Angioedema

To make a diagnosis of hereditary angioedema, firstly a highly suspicion is needed. Episodic cutaneous or subcutaneous angioedema without urticaria and accompanying abdominal semptoms includes reccurrent pain, swelling of bowel walls, and vomiting in patients

with a positive family history are warning signs of HAE. Swelling may occurs at any part of the body other than abdomen and skin. During lifetime, a laryngeal attack rate is more than 50% and even if only one laryngeal attack should be accepted as a warning sign for HAE.[19,20] In cases with unresponsive to antihistamines or glucocorticoids therapy should also be watched out for HAE. In HAE with C1-INH deficiency, angioedema attacks usually proceed in childhood, and worsen during puberty with the difference of in nlC1-INH patients angioedema attacks usually begins at adulthood. Classifications of angioedema without urticaria is illustrated in **Figure 1**.

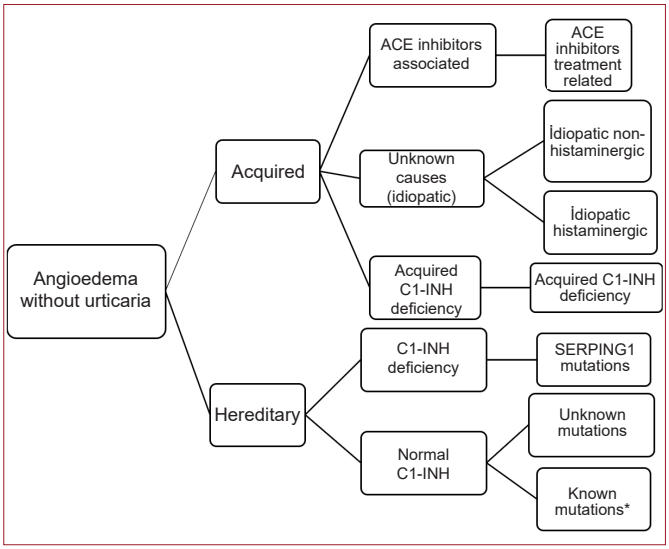

Figure 1. Classification of angioedema without wheals.

ACE inhibitors: angiotensin-converting enzyme inhibitors; C1INH deficiency: C1 inhibitor deficiency. * Mutations in the genes encoding factor XII, angiopoietin-1, plasminogen, and kininogen-1, myoferlin and heparan sulfate glucosamine 3-O-sulfotransferase 6 are associated with hereditary angioedema.

Laboratory diagnosis

Currently, HAE is basically classifed based on C1-INH levels and Complement 4; HAE with normal C1-INH or HAE with C1-INH deficiency. HAE with C1-INH deficiency is also classifed as Type I that accounts for 85% of cases and Type II accounts for 15%. In C1-INH-HAE, C4 levels are low in both suptypes. HAE type I has low C4 and low level of C1-INH antigen and functions. HAE type II has normal C1-INH antigen level but C1-INH protein function is low. Both subtypes can not be distinguished clinically. C1-INH levels could be measured by enzyme-linked immunosorbent assay or the chromogenic assay but if avaible the chromogenic assay should be preferred because of more sensitive.[21] Complement tests should be assessed twicely, at least one month interval. In at least 10% percent of patients with C1-INH-HAE has normal C4 level and C4 level should be performed during an angioedema episode. **Table 1** shows C4 and C1-INH assesment and comparison of HAE and other forms of angioedema. Differential diagnosis should be done with allergic reactions and anaphylaxis, idiopathic angioedema, drug induced angioedema, allergic contact dermatitis, autoimmune conditions, thyroid disorders, chelitis granulomatosa and Merkersson-Rosenthal Syndrome and trichinosis. In HAE with normal C1-INH, making diagnosis needs genetic evalaution on suspected cases because of lack of spesific diagnostic tests.

Genetic testing

To make a diagnosis of HAE with C1-INH deficiency, genetic analysis is not required but in some cases HAE with normal C1-INH, detecting a genetic mutation allows for diagnosis. Although HAE has an inheritance trait patterns, approximately 25% of mutations are de novo. By this time, a total of 748 diverse SERPING1 variants associated with C1-INH-HAE have been revealed. To make a diagnosis of HAE with normal C1-INH is difficult because of absence of commercially avaible diagnostic tests and biomarkers except for known genetic mutations.[22,25] Well known genetic mutations in nlC1-INH-HAE are FXII, PLG, ANGPT1, KNG1, and MYOF. Although widen utilization of genetic sequencing, a group of non-histaminergic/bradykininergic patients can not be diagnosed. The diagnosis of nlC1-INH-HAE should be based on consensus guidelines.[26]

HAE-FXII

Gain of function mutation in prolin-rich domain of FXII gene is the most frequently detected in patients with nlC1-INH-HAE.[27,28] FXII gene mutation is inherited by autosomal dominant trait with a female predominance. FXII converts prekallikren to kallirein which is later turned into bradykinin via high molecular weight kininogen (HMWK). The clinical phenotype is similiar with C1-INH-HAE and more dependent to estrogen. Estrogen increases the quantity of FXII in the plasma.

Table 1
Assesment and comparison of C4, C1-INH on HAE and other forms of angioedema

Angioedema types	C4	C1-INH level	C1-INH function	C1q	Genetic tests
C1-INH-HAE Type I,	Low	Low	Low	Normal	SERPING1 mutation/not needed
C1-INH-HAE, Type II,	Low	Normal/elevated	Low	Normal	SERPING1 mutation/not needed
Acquired angioedema with C1-INH deficiency	Low	Normal/low	Low	Normal/low	Genetic test is not needed. Anti-C1-INH antibodies positivity
Idiopathic acquired angioedema (histaminergic or nonhistaminergic)	Normal	Normal	Normal	Normal	Not identified
ACE inhibitor-associated angioedema	Normal	Normal	Normal	Normal	Not identified
HAE with normal C1-INH	Normal	Normal	Normal	Normal	Factor XII, angiopoietin-1, plasminogen, kininogen-1, myoferlin, heparan sulfate glucosamine 3-O-sulfotransferase 6, unknown mutations

HAE: hereditary angioedema, C1-INH:C1 inhibitor protein, C4: Complement 4, ACE: Angiotensin-converting enzyme

HAE-PLG

Bork et al.[24] defined a genetic mutation in the PLG gene in patients nlC1-INH-HAE, in 2018. Plasminogen converts to plasmine that activates FXII which has a role to turn prekallikrein into kallikrein. The diversity between C1-INH-HAE and HAE-PLG is age of onset of attacks. In PLG mutations, symptoms occurs usually in adulthood with a tendency of head and neck swelling.

HAE-ANGPT1

In 2018, Baffuna et al.[23] revealed a mutation in the gene encoding Angiopoietin 1 (ANGPT1) in a family diagnosed as HAE-U. ANGPT1 does not play a role in kinin or complement pathways. ANGPT1 plays a role in diminishing vascular permeability via tunica interna endothelial cell kinase 2 signaling cascade. Deficiency of ANGPT1 or decrease ratio of ANGPT1/ANGPT2 was reported to leads to enhaced vascular permiability.[29]

HAE-KNG1

A variant in the Kininogen 1 (KNG1) gene is founded in patients with nlC1-INH-HAE. KNG1 mutation is present in both high and low molecular weight kininogen isoproteins. Autosomal dominant inheritance pattern is seen in cases and the mutation is located in a functional domain, the cleavage region for kinins including bradykinin.

HAE-MYOF

In 2020, a variant in the myoferlin (MYOF) gene is reported in an Italian family diagnosed with HAE-U. The gene encodes myoferlin, an integral membrane protein, and regulates vascular endothelial growth factor signaling.

HAE-HS3ST6

In 2021, a mutation encoding heparan sulfate glucosamine 3-O-sulfotransferase 6 (3-OST-6), HS3ST6, was detected in all 3 members of one family diagnosed with nlC1-INH-HAE. This mutation likely causes to defective synthesis of heparan sulfate, a glycosaminoglycan on endothelial surfaces.[30]

New biomarkers for diagnosis and prognosis of HAE were detected during the last years. These are ready to enter market, the cleavage of high molecular weight kininogen in plasma, the spontaneous amidase activity[31], the threshold-stimulated kallikrein assay[32], the fragmentation patterns of serum glycoprotein 120.[33]

Therapeutic management of Hereditary angioedema

The main causative mediator, bradikinin, is considered to lead increased vascular permiability and swelling. Edema formation occurs slower as over hours or a few days and is generally self- limited.

Some drugs such as ACEIs, hormone replacement therapy and estrogen containing pills should be avoided in all group of HAE patients.[34,35] Pills consisting of only progestin is considered safe in these patients.[36-38] Apart from some drugs, other known angioedema triggers are trauma, infectious diseases and psychoemotional stress. Surgery, endotracheal entubation, tooth extraction and endoscopic interventions are also considered mechanical trauma and should done with cautions and under short-term prophylactic therapy. Also lactation, breastfeeding, pregnancy or menstruations may cause attacks of angioedema.

All vaccinations are considered safe in HAE patients and especially, hepatitis A and B vaccines should be advised to patients in whom receive regular plasma derived C1-INH.

Approved therapies for HAE attacks by FDA has been avaible since 2009 except for fresh-frozen plasma (FFP). FFP is helpful in some cases with a risk of increasing the severity of an attack and transmission of some infectious diseases.[19] FDA and EMA approved dosing for HAE acute attack, long term prophylaxis (LTP) and short term prophylaxis (STP) treatment is summarized in **Table 2**.

On-Demand Treatment For Acute Attacks

Nowadays several treatment modalities including replacement treatment with human and recombinant C1-INH and targeted therapies which targets bradykinin receptors and plasma kallikrein are under use.

C1-INH replacement

As C1-INH deficiency was defined for the cause of HAE in 1963, development of a rescue treatment for angioedema attacks took ten years time, up to1974. Therefore the first plasma derived C1-INH concentrate (pdC1-INH) was produced by Central Laboratory of Netherlands Red Cross Blood Transfusion Service in 1974 but it was approved in 2008, in the United States. Additionally recombinant human C1-INH (rhC1-INH) was approved for marketing in Europe and USA in 2010 and 2014, respectively. It is produced from transgenic New Zealand White rabbits' milk with a distinction in the glycosylation pattern from human C1-INH protein. Probably because of this difference, plasma half life is about 2-3 hours and shorter then pdC1-INH which is 33±19 hours aproximately.[39]

The recommended dose for attack treatment and short term prophylaxis in pdC1-INH is 20U/kg intravenous and if needed a second dose can be given after 60 minutes. For rhC1-INH, the approved dose is 50 U/kg (<84 kg), or 4200U (>84 kg) and if needed a second dose can be given within 4 hours. Although rhC1-INH has short plasma-life, studies showed no more frequent infusion needs compared to pdC1-INH.[40,41] pdC1-INH can be used as intravenous route both at the hospital by a health care professional or at anywhere if adequate training is completed. Self-administering of pdC1-INH is accepted safe, well-tolerated and applicable.

Recombinant human C1-INH should not be used in patients with rabbit dander allergy because of a severe allergic reactions developed in a patients with rabbit allergy after 3 minutes of administration.[42]

Table 2
Approved dosing of medications for LTP, STP, and acute attack treatment

Medications	Plasma derived-C1 inhibitor concentrate Berinert (iv, sc), Haegarda (sc) Cinryze (iv)	Recombinant C1-inhibitor Conestat alfa Ruconest, Rhucin (iv)	Bradykinin B2-receptor antagonist Icatibant (sc) (Firazyr)	Kallikrein inhibitor: Ecallantide (sc) (Kalbitor)	Monoclonal Kallikrein inhibitor antibody Lanadelumab (sc) Takhzyro	Kallikrein inhibitor Berotralstat (orally) Orladeyo
Approval	FDA and EMA approved Cinryze for LTP ≥6 years. EMA approved Cinryze for STP and acute attack treatment in ≥2 years. FDA approved Haegarda and Berinert for LTP in ≥6 years	EMA and FDA approved for acute attack treatment in adolescents and adults	EMA approved for acute attack treatment in ≥2 years, FDA approved for acute attack treatment in ≥18 years.	FDA approved for acute attack treatment in patients ≥12 years. EMA not approved	EMA and FDA approved for LTP in patients ≥12 years	FDA and EMA approved for LTP in ≥12 years.
Dosing for acute attacks	**Adults:** Berinert :20U/kg,iv Cinryze: 1000 U **Children:** Berinert :20U/kg, Cinryze: 500 units for body weight <25 kg, 1000 units ≥25 kg	**Adults**: 50U/kg body weight for patients <84 kg. 4200 U (2 vials) ≥84 kg.	**Adults**: 30 mg sc **Children:** 10 mg if weight is 12-25kg,(1mL) 15 mg if weight is 26-40 kg (1.5 mL) 20 mg if weight is 41-50kg (2mL) 25 mg if weight is 51-65 kg (2.5mL) 30 mg if weight is >65 kg (3 mL)	**Adults:** 30 mg (3 doses of 10 mg each) given at three separate sites subcutaneously **Children:** ≥12 years, same as adults		
Dosing for STP	**Adults**: Berinert:1000U, 1-6 hours before, iv Cinryze:1000 U, 1-24 hours earlier, iv. **Children:** Berinert:15-30 U/kg, 1-6 hours before, iv					
Dosing for LTP	**Adults**: Cinryze:1000U, every 3-4 days, iv Haegarda,Berinert : 60 IU/kg, twice weekly, sc **Children:** Cinryze: 500U twice weekly (6-11 years) Haegarda,Berinert: 60 IU/kg, twice weekly, sc				300 mg, subcutaneously every 2 weeks	150 mg/day, orally

iv:intravenously, sc: subcutaneously, LTP: Long Term Prophylaxis, STP: Short Term Prophylaxis, FDA:US Food and Drug Administration, EMA: European Medicines Agency

Icatibant

Icatibant targets bradykinin B2 receptors as competitively and selectively and is used with subcutaneous manner. The mean plasma half-life is 1.4±0.3 hours for a single 30 mg/3 mL injection. In a day maximum 3 injections is recommended with 6 hours intervals. In clinical studies with icatibant were carried out maximum 8 injections in a month.[43] Icatibant is yet approved for only attacks treatment. It can be administered in anywhere with a good safety profile with only local injection site events (erythema, swelling and pain).

Ecallantide

Ecallantide inhibits plasma kallikrein as reversibly and selectively. It is recommended for only attack treatment at 30 mg (3x10 mg/ml) in subcutaneous manner and a second dose could be administered after 24 hours. By reason of reported cases with anaphylaxis after ecallantide administrations, it is strongly recommended that drug should be used at settings that can manage anaphylactic reactions. Beside from hypersensitivity reactions, other commonly reported adverse events associated with ecallantide are upper respiratory tract infection, fatigue, headache, nause, vomiting, upper abdominal pain, diarrhea, injection site reactions, pruritus and pyrexia.

Management of HAE attacks in special populations

Children

Data are limited about HAE attacks treatment in children and a few randomized controlled trials showed similar effects in decreasing the time to symptom resolution to adults. Approved medications are considered well tolerated and safe in children.[44,45] The recommended dose for attacks treatment in children is 20 U/kg, intravenous for Berinert (pdC1-INH). For Cinryze (pdC1-INH), the recommended dose for children aged ≥12 years old and >25 kg is 1000U, and 500U intravenous for children 2-11 years and <25 kg. For Rocunest (rhC1-INH), the approved dose is 50U/kg (<84 kg) and up to 4200U/kg (≥84) for children aged ≥2 years in Europe and aged ≥12 years in U.S.

Icatibant is approved for children aged ≥2 years as a single injection dosed per kg who weigh <65 kg with subcutaneous manner. Data about repeated icatibant dosing in children has not been evaluated yet.

Ecallantide is approved for children ≥12 years with a subcutaneous manner and as the same in adults, should be administered in settings that staff has experience to treat severe hypersensitivity reactions including anaphylaxis.[46,47]

Pregnancy and breastfeeding

According to case reports series and observational studies, HAE attacks in pregnant could be managed with pdC1-INH replacement safely.[36,48] Recent data shows rhC1-INH replacement can also be used during pregnancy with well-tolerance.[49,50] Data about icatibant usage in pregnant is limited to only case reports.[51,52] There is no data about the use of ecallantide during pregnancy.

During lactation and breastfeeding, phC1-INH replacement is accepted as safe. For rhC1-INH, case series have been reported during breastfeeding. But there is no information for the use of ecallantide and icatibant during lactation.

Treatment of attacks in patients with nlC1-INH

For patients with FXII gene mutations, there is no approved medications for attacks treatment. Although, pdC1-INH and rhC1-INH replacement were found out significant reduction of resolution time of swelling compared to nontreated attacks.[22,53] Additionally icatibant has also showed good improvement of swelling in abdominal attacks of patients of FXII mutated HAE.

According to a recently published retrospective study, 23 patients with nlC1-INH-HAE were evaluated and lanadelumab, rhC1-INH, icatibant showed favorable effect on prophylaxis and acute attacks. The frequency and severity of angioedema attacks reduced with good disease control.[54]

For patients with HAE-PLG, according to a review of 111 patients, icatibant was demonstrated more effective in reduction the duration of attacks than C1-INH replacement.[55]

For patients with HAE-ANGPT1 gene, tranexamic acid was found effective as 2 patients for prophylaxis with significant reduction of severity and frequency of attacks.[23]

For patients with KNG1 gene mutations, only 1 patient with facial swelling twicely was improved with 1000U intravenous pdC1-INH infusion.

For patients with MYOF gene mutation, there is no information about effective attacks treatment of these patients.

HAE with a pathogenic mutation of the HS30ST6 gene, there is no evidence for effective attacks treatment of these patients.[30]

Prophylactic therapy

To preclude HAE attacks in certain settings, patients should be advised to receive STP or LTP. STP should be used before encountering of triggers of attacks such as a surgery or medical interventions cause to mechanical trauma and aims to decrease the risk of angioedema attacks.[49] Angioedema attacks can develop up to 72 hours after an intervention and patients should be advised to be aware of this possible risk. Even though there is no randomized controlled trials (RCT) about pre-procedural prophylaxis, a few retrospective reviews and studies reported reduction of the rate of angioedema attacks in adults and children who received prophylactic treatment.[56-59] Thus, STP before medical interventions (surgery, endoscopy, dental procedures, and intubation…) is recommended by recent guidelines and also medicine should be avaible during and after any interventions.

The recommended dose with pdC1-INH for STP is 20U/kg by intravenous route. Cinryze should be administered within 24 hours of the intervention as late as possible and for Berinert within 6 hours or if possible before the procedure.

For rhC1-INH, STP dosage is 50U/kg intravenously and administration should be done as soon as possible before procedure.

Anabolic androgens (AAs), danazol, could be used for SPT as a second-line choice and at 2,5-10 mg/kg/day dose (maximum 600 mg/day) and should be started before 5 days of the intervention and continued 2-3 days after the procedure.[58]

Fresh frosen plasma might also be used for SPT, on the other hand FFP should be preferred as a third-line therapy if C1-INH concentrates and AAs are not avaible. The recommended dose of FFP for SPT, based on published data, is 2U in adults and 10mL/kg in children before 1-2 hours of the procedure.[60,61]

According to recent data, other therapeutic medicine used for HAE treatments are not recommended for STP.

STP for children with regard to European pediatric guidelines, the recommended dose for Berinert is 15-30 U/kg within 6 hours, for Cinryze 500 U in children weight 10-25 kg within 24 hours of scheluded procedure. As same as adults anabolic androgens could be used as STP for children at a 2,5-10 mg/kg/day, mean 5mg/kg/day (maximum 600 mg/day) dose, however it is recommended for a second line choice when C1-INH concentrate is not avaible.

For pregnant, C1-INH concentrate is only accepted with well-safety profile as the same dose in adults. Vaginal delivery should be preferred, because of however in case of ceserian section, STP and epidural anesthesia are strongly recommended. Intubation always has to done under STP. In vaginal delivery setting, STP is not routinely recommended but C1-INH concentrate should be present for on demand use if needed. But in certain cases such as frequent attacks during third trimester or a history of serious, life-threatening angioedema attacks or a history of vaginal edema caused by mechanical trauma, STP should be preferred.[62] Anabolic androgens are contraindicated during pregnancy and breastfeeding, because of crossing placenta and milk. If C1-INH is not avaible during breastfeeding period, AAs could be used for STP after discontinuation of breastfeeding.

There is not any randomized controlled studies about STP in case of HAE with nlC1-INH, therefore any strong recommendations can not be made. However based on little experience regarding SPT, the same management with C1-INH-HAE is accepted for cases with nlC1-INH-HAE.

Long term prophylaxis

The aim of LTP is reducing the frequency, duration and severity of episode of HAE. There is no certain rules for whom and when will to start LTP but LTP management should to be individualized based on case's needs. Although regular LTP does not make sure the risk of angioedema attacks completely, patients should be warned about the risk and also obtained on-demand therapy. Many factors such as attacks severity and frequency and a history of life threatening attacks, access to emergency treatment and patient's decision should be taken into account to commence LTP.

C1-INH-HAE

Options for LTP in C1-INH-HAE are C1-INH concentrate replacement by intravenous/subcutaneous route, lanadelumab, a selective inhibitor of plasma kallikrein with subcutaneous route and, orally AAs, transexamic acid and plasma kallikrein inhibitor.

C1-INH concentrate replacement is considered as a first choice for LTP. The recommended dose of Cinryze for LTP is 1000 U every 3-4 days by intravenous route for adults.[63] Recently Cinryze and Berinerts have approval for LTP by intravenous and subcutaneous manner, respectively. Rocunest has not approval for LTP but when it was administered one or twice weekly for prophylaxis, it was reported a good safety profile and a decrease in the frequency of angioedema attacks.[41] Studies showed routine administration of C1-INH by intravenous route could cause several thrombotic events, therefore physician should be careful about the risk factors and symptoms.[64] Long term intravenous prohylaxis has some difficulties such as displeasure of repetitive intravenous access, long infusion time and maintaining long term venous access.

Haegarda (in USA) is the first subcutaneous C1-INH concentrate, was approved at the dose of 60 IU/kg twice weekly by the FDA in 2017 for LTP in patients 6 years age and older. Berinert (subcutaneous form in Europe) showed a consequential decrease (95% reduction)[18] in the rate of attacks compared to plasebo. C1-INH administration by subcutaneous route is well tolerated with a good safety profile.[65] Nasopharyngitis, hypersensitivity, dizzines, and localized injection site reactions are the most common reported adverse events of subcutaneous C1-INH administraiton.[66]

Lanadelumab is the first human monoclonal antibody that inhibits plasma kallikrein reversibly for approximately 2 weeks. It is approved for LTP at a dose 300 mg, subcutaneously, every 2 weeks and if cases are stable for 6 months, injections interval could be change as 300 mg every 4 weeks.[67-69] Lanadelumab is well-tolerated with a good safety profile. According to HELP study, injection site pain (42.%), viral upper respiratory tract infection (23.8%), headache (20.2%), injection site eritema and bruising (9.5% and 7.1%, respectively) and dizzines (6%) are the most common reported advers event related to the drug.[70] HELP study showed a rapid onset of effect and continuous effectiveness in decreasing frequency of HAE attacks.[70] In 2% percent of active drug group had developed increased aspartate and alanine transaminase levels while zero on placebo group. These were asymptomatic and transient and did not require drug discontinuation. Lanadelumab can increase activated partial thromboplastin time but has not been associated with abnormal bleeding.

Berotralstat is the first orally used, plasma kallikrein inhibitor that is approved for LTP as once daily in adults and ≥12 years old by FDA in 2020 and EMA in 2021. The approved dose 150 mg once daily showed a good safety profile and effectiveness. Berotralstat should be taken with foods. The most common reported adverse events are abdominal pain, vomitting, diarrhea and back pain in 10% percentage of cases and alleviated with continued use. A phase 3, placebo controlled study called APeX-2, carried out on 121 adults and adolescents for two different doses, 110 and 150 mg once daily. The study demonstrated a significant decrease in the rate of attacks for both doses compared placebo.[71]

Anabolic androgens and transexamic acid should be used as a second-line choice for LTP unlike other options are not avaible. Danazol and stanozolol are the mostly used worldwide. The exact mechanism of AAs is not clear, however it is considered they enhance the level of C1-INH.[72] AAs are used orally and in several studies they were provide a reduction in HAE attacks.[73-76] The most important side affects related to AAs are hepatotoxicity, hepatocelular adenoma and carsinoma and may develop dose dependent.[77,78] Other common side affects are acne, hirsutism, menstrual disorders, weight gain and depression.[79] AAs are contraindicated in pregnants and in cases with hepatitis and androgen dependent malignancies.[80,81] Danazol should be started at 400-600 mg daily, then dose should be tapered to the lowest effective dose that maintain to prevent or reduce HAE attacks, usually at 200 mg daily or every other day. Patients under AAs treatment should be checked for liver enzymes, lipid profile, urine examination, alpha-feto-protein, and complete blood cell count every 6 months and abdominal ultrasound yearly.

Antifibrinolytic agents (tranexamic acid and epsilon aminocaproic acid) is the last option in cases with HAE for LTP in circumtance that other medications are not avaible and AAs are contraindicated. Tranexamic acid (TXA) is the most preferred drug because of less side effects compared to epsilon aminocaproic acid. The recommended dose for TXA is 1-3 gr/day up to 6 gr daily. Abdominal discomfort, diarrhea, headache, nause are the most reported side effects related to tranexamic acid.

LTP in special populations

pdC1-INH, Cinryze is approved for LTP in children ≥6 years old, at a dose of 500 U for 6-11 years old and 1000 U for 12-17 years old every 3-4 days. Berinert is approved for LTP for children ≥6 years old via subcutaneous manner. Berinert is provided a good safety profile and effective treatment for LTP in patients aged <17 years old in OLE and COMPACT studies.[82-84] AAs should not used for LTP in children because of adverse events.

In pregnant for LTP pdC1-INH should be preferred as the first line therapy according to current guidelines. Any newborn abnormatilies related to exposure of pdC1-INH during pregnancy has not been showed up to date in researches.[85-88] AAs must not used for LTP in pregnant and also have to be stopped before a planned pregnancy at least 1 month. TXA is the last option for LTP in pregnant otherwise pdC1-INH is not avaible. In lactation and breastfeeding period, pdC1-INH should be preferred firstly.[36]

nlC1-INH-HAE:

There is not enough data based on randomize controlled trials about LTP for nlC1-INH- HAE and approved medicine to these cases. According to experimental data, TXA showed a significant reduction of attacks in FXII- HAE, PLG-HAE and ANGT1-HAE for LTP.[23,55] Also AAs and progestin provided a significant decrease of angioedema attacks in FXII-HAE patients. Data are not avaible in patients with nlC1-INH-HAE, although medicine that could inhibits bradykinin may be an effective treatment options in these cases. Also studies about progestins therapies were reported a benifical effect for prophylaxis in HAE with normal C1-INH.[22]

Novel treatments in development

Several drugs are under investigation with phase 1,2,3 trials. An oral bradykinin B2 receptor antagonsit (PHA121) that blocks bradykinin within 15 minutes and inhibition lasts at least 12 hours showed effectiveness for both acute and prophylactic treatment in phase 1 clinical tirals.[89]

Garadacimab is a IgG4 type human recombinant monoclonal antibody, that binds to the FXIIa with catalytic site and blocks its proteolytic activity. Garadacimab is administered by subcutaneous manner. In a phase 2 trial, the frequency of attacks was reduced compared with placebo with mean percentage reductions with three doses of garadacimab were 89, 99, and 91 and the drug was well-tolerated.[90] Currently, Garadacimab phase 3 trials is carrying on with 60 participants for prophylactic treatment efficacy and safety.

Other targeted therapies under investigation are ALN-F12 and ARC-F12 and inhibit Factor XII which is developed by using small interfering RNA (siRNA) technology.[91]

Another targeted therapy is IONIS-PKK-LRx which targets plasma prekallikrein and provides downregulation of prekallikrein mRNA synthesis and knock outs the gene encoding prekallikrein by using CRISPR/Cas9 technology.

A one-time intravenous injection of Adeno-associated virüs gene transfer vector inserts an extrachromosomal copy of the SERPING1 gene to induce in vivo production of C1-INH are also in preclinical development in mouse models.[92]

Conclusion

New treatment options for acute attacks and long-term prophylaxis for C1-INH-HAE are developed last years and the avaibility of drugs that can be used oral and subcutaneous route may increase patients quality of life and reduce the need of admission of hospital. New treatments under development such as gene therapy and other targeted therapies promise future for patients.

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