SCIE DOI: 10.14744/scie.2020.01886
South. Clin. Ist. Euras. 2020;31(3):301-307

Review

Current and Future Therapy of Hereditary Angioedema

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Submitted: 17.05.2019
Accepted: 10.01.2020

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Keywords: Bradykinin; C1 inhibitor; hereditary angioedema; kallikrein.

ABSTRACT

Hereditary angioedema (HAE) is an autosomal dominant disorder, mostly due to C1 esterase inhibitor (C1-INH) deficiency, known by recurring angioedema attacks that are nonpruritic, not accompanying with urticaria, and involve the dermis, intestinal submucosa, and upper respiratory system. The angioedema attacks are not responsive to epinephrine, glucocorticoids, or antihistamine treatments. Whereas HAE patients formerly had a few therapeutic options accessible such as anabolic androgens and antifibrinolytics. Nowadays in many parts of the world there has been remarkable progress in HAE treatment for the last two decades and clinically confirmed medications are presented for prophylactic and attack treatment. Alternatives in attack therapy contain two plasma-derived C1-INH concentrates, a recombinant C1-INH product, a kallikrein inhibitor, and a bradykinin β2 receptor antagonist. Options in prophylactic therapy include other than two plasma-derived C1-INH concentrates, subcutaneous C1-INH replacement and newest subcutaneous plasma kallikrein inhibitor Lanadelumab. In spite of these progresses, HAE patients still run into some challenges of an arduous disorder that can yield to devastating angioedema attacks related with important expenses for patients and the public. Better education of HAE patients and implementation of the self-management policy for "on-demand" therapy will recuperate patients' life quality and negative effects of the disease. Herein the existing and promising therapeutic options are reviewed in the HAE management.

INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disorder, mostly due to C1 esterase inhibitor (C1-INH) deficiency, known by recurring angioedema attacks that are nonpruritic, not accompanying with urticaria, and involve the dermis, intestinal submucosa, and upper respiratory system. In this review, besides the current treatment methods in the world and in our country, the drugs and treatment methods that are currently being studied in the treatment of HAE will be discussed.

As an approach to treatment, it can be considered in the first place to prevent or reduce attacks by avoiding triggering factors, if applicable. Since it is not always possible to avoid triggers, we can divide the treatment into two main groups as prophylaxis and emergency treatment.[1,2]

Avoiding triggering factors

It includes avoiding trigger factors known to the patient, such as stress, infection, trauma, certain medications (ACE-inhibitor and oral contraceptives containing estrogen, etc.).

Thus, it is aimed to decrease drug use and increase the quality of life by preventing the factors that require drug use.[1,2]

Treatment used in prophylaxis (protection)

This type of treatment is divided into two as short and long-term prophylactic treatment. "Short-term prophylaxis" before planned operations, "long-term prophylaxis" may be required in cases where disease control cannot be achieved due to known conditions or personally, as will be explained below. The drugs used in this situation will be explained in detail below.[3–5]

Treatment used in emergency (attack, necessary-on demand-) situation

In cases where control cannot be achieved despite prophylactive treatment or attacks occurring in an unexpected situation and time with any trigger, urgent or need-based treatment may be required. An important point is to distinguish that it is an HAE attack in the patient not the other types of attacks like histaminergic and bradykininergic angioedema.[6] Again, it is known that anti-histaminic, adrenaline and corticosteroids are ineffective during attacks.[7–9]

First of all, after mentioning all the drugs reported in the literature in prophylactic and emergency treatment, the drugs used in our country will be explained below in more detail.

All drugs reported and developed in the literature

The aim is to try to control the disease by preventing the accumulation of quinine in the body that causes end products and angioedema. This is tried to be done by replacing the missing C1-INH in the body, preventing the production of kallikrein through the coagulation system/F12 or the coagulation system from overworking.[1–9]

We can classify all the drugs developed so far in prophylactic and emergency treatment into eight groups below.[10–17]

I. Antifibrinolytic drugs: Epsilon (ε)-amino caproic acid, tranexamic acid

II. Weak (anabolic) androgens: Danazol, stanozolol, oxandrolone, methyltestosterone

III. Plasma sourced products containing C1-INH: Plasma concentrates (Cinryze®/Berinert®)

IV. Partially new drugs: Ecallantide (DX88, Kalbitor®), Icatibant (Firazyr®, Icatin®) and products containing recombinant C1-INH antigen (Rhucin®/Ruconest®)

V. Solvent detergent/Fresh frozen plasma

VI. Latest drugs: Subcutaneous C1-INH (Haegerda®), subcutaneous plasma kallikrein inhibitor-Lanadelumab-(Takzyhro®)

VII. Developments in clinical studies: Oral plasma kallikrein inhibitor: Avoralstat (BCX4161), BCX7353, KVD818 (KalVista Pharmacy); Containing hyaluronidase - subcutaneous C1-INH; Coagulation products that destroy FXII production (ALN-F12, ARC-F12) and monoclonal antibody against FXIIa (CSL 312)

VIII. Genetic intervention methods tried in pre-clinical studies: Ionis PKKRx and Gene therapy, which suppresses precallikrein transcription (anti-sense).[17–21]

Different pharmaceutical groups used in other countries

we can simply classify all drugs currently used actively in other countries in prophylactic and emergency treatment into six groups as follows.

A. Antifibrinolytic drugs: Tranexamic acid

B. Weak/anabolic androgens: Danazol

C. Products containing C1-INH: Plasma concentrate: Cinryze®, subcutaneous C1-INH (Haegerda®) and recombinant C1-INH antigen (Rhucin®/Ruconest®),

D. Bradykinin receptor inhibitor: Products containing Icatibant (Firazyr®, ICATIN®)

E. Plasma kallikrein inhibitors: Ecallantide (DX88, Kalbitor®) administered subcutaneously and products containing Lanadelumab (Takzyhro®) are approved drugs.[22–25]

F. Solvent detergent/fresh frozen plasma.[10–21]

In our country, there are no products containing recombinant C1-INH antigen, subcutaneous C1-INH (Haegerda®), Ecallantide (Kalbitor®) and Lanadelumab (Takzyhro®).

Treatment methods applied in our country

We can classify all the drugs currently used actively in our country for prophylactic and emergency treatment in six groups below.

I. Antifibrinolytic drugs

Although Epsilon (ε) amino caproic acid was formerly used, afterwards it was replaced by Tranexamic acid. Tranexamic acid acts by inhibiting plasminogen activation. They are weak in strenght than androgens. It may have side effects such as diarrhea, postural hypotension, muscle cramps, retinal tumor development and liver dysfunction. Before the drug is used, the treatment should be started by making researches in terms of thrombo-embolism/thrombophilia and care should be taken in this regard during its use.[1–5]

II. Weak/anabolic androgens

The most commonly used one in the whole world is Danazol. Anabolic androgens act by increasing C1-INH synthesis in the liver. In the guides, especially for men, it is stated that written consent should be obtained from the patients due to the risk of side effects. Again, it is said that it can be used in Tanner puberty stage above 5. As side effects, they can cause weight gain, virilization, menstrual dysfunction, liver enzyme elevation and hepatocellular adenoma. For starting Danazol therapy protocols (Milan and Budapest) have been reported. In Milan protocol, it is tried to start with a high dose (400 mg/day), increase up to 600 mg if necessary, and decrease the dose to 50 mg/day at monthly intervals to 5 days a week.

In the Budapest protocol, it is started with a partially low dose (200 mg/day) and the dose is increased to 400 mg if necessary, and then it is tried to be reduced to 50 mg/day, 7 days a week at intervals of 2–4 weeks. Methyltestosterone can be tried in men when desperate. Although Stanozolol has been approved by the FDA for use in children, it is not available in or country.[10–17] In our country, Danazol has an indication for HAE treatment.

Although easiness of the oral use of androgens and seem to be low-cost drugs, their co-morbidities such as muscle cramps, psychiatric problems, obesity, and hyperlipidemia, the indirect cost of treatment increases.[22]

The drug used orally other than danazol and tranexamic acid is Avoralstat, which is a plasma kallikrein inhibitor that has not been found successful in preventing attacks but has been found to increase quality of life.[23–25]

III. Plasma-derived products containing recombinant C1-INH

It can be used in relapse treatment, short-long term prophylaxis and pregnancy. Cinryze® in our country as plasma concentrate, Berinert® in other countries, in addition to this drug, intravenously administered recombinant C1-INH antigen (Rhucin/Ruconest®) and subcutaneous C1-INH preparation (Haegerda®) are available.

Products used in C1-INH replacement therapy can be used over the age of two. C1-INH replacement therapy in exacerbations in children 10–20 units/kg, usually 500–2.000

units, if C1-INH is administered intravenously, symptoms subside in 30−60 minutes and completely disappear within 24−48 hours. In long-term prophylaxis, 1.000−2.500 units should be administered every 3−4 days, twice a week. The C1-INH preparation should be given as a slow infusion (1 mL/min). Side effects are rare and include symptoms such as anaphylactoid reaction (due to rapid infusion without bringing it to room temperature), formation of inhibitory antibodies against the product, localized rash, fever, headache, fatigue.[26,27]

Cinryze is an FDA-approved product for intravenous administration in lyophilized vials with 500 units/5 mL solvent and must be stored at +2−+8 ° C. If the body weight is less than 25 kg, 500 units, if more than 25 kg, 1.000 units are applied. It should be melted and prepared without shaking. The prepared solution can be kept at room temperature for a maximum of 8 hours. It is administered intravenously through peripheral veins. The infusion rate should not be less than 5 minutes. Its half-life in the circulation varies between 31 and 46 hours depending on the severity of the attack. Since it is a blood product, it carries the risk of transmitting some diseases like others.[10,17]

Recombinant C1-INH antigen (Rhucin/Ruconest®) is an FDA-approved preparation, especially 50 U/kg intravenously administered during attacks and has been used in the last decade. Apart from side effects such as rash and itching, there is a risk of developing anaphylaxis due to the rabbit proteins it contains.[28−31] Currently it is still not available in our country.

Subcutaneously administered plasma-derived C1-INH preparation Haegerda® can be used twice a week at 60 U/kg from adolescence. In studies, treatment could be reduced in to 5 years old.[32−37] It can not be provided in Turkey.

IV. Bradykinin β2 receptor antagonist/inhibitor

In our country, it is an alternative to intravenous C1-INH replacement, especially in attacks.

Subcutaneously applied Icatibant, is sold in foreign countries under the name of Firazyr® and it is produced and sold in our country under the name of Icatin®.

It is not suitable for prophylaxis due to its short half-life (1.4±0.4 hours) Care should be taken in terms of "rebound" effect in the treatment of attacks. Icatin is sold with a pre-filled syringe containing 30 mg/3 mL solution.

It was reimbursed with the Health Implementation Communiqué (SUT) at the beginning of 2019. It is easy to use and can be stored at room temperature. It has a better safety profile since it is not a blood product. Since the patient can administer the drug on his own, he can solve the problem of delay in accessing treatment. It is more economical. It is not recommended for use in pregnant women (category C). As a side effect, it may cause pain and burning at the injection site.[38−42]

Icatin is used for the treatment of HAE symptoms in adult, adolescent and pediatric patients (2 years of age, ≥12 kg). It is applied subcutaneously. More than 3 injections should not be administered within a 24 hour period, and if more than 8 injections per month are required, the patient should be referred to a specialist. The posology reported in adults should be 30 mg once subcutaneously, a second injection after 6 hours if necessary, and a maximum of 3 injections within 24 hours. The posology for children is based on weight. 10 mg (1 mL) between 12−25 kg, 15 mg (1.5 mL) between 26−40 kg, 20 mg (2 mL) between 41−50 kg, 25 mg (2.5 mL) between 51−65 kg, >65 kg 30 mg (3 mL) can be injected.

V. Fresh frozen plasma (ffp)

The recommended dose for FFP administration is 10−20 mL/kg, 1−2 units on average. It's generally efficient for 45 minutes. It should not be ignored that in some patients the attack due to quinine substrates (precallikrein, F12 or kininogen residue) contained in FFP may become worse.[10−18]

After mentioning all current drugs and applied treatment methods above, the treatment methods and drugs used in prophylaxis and emergency/attack treatment will be mentioned below.

Treatment methods used in prophylaxis

It is possible to collect the prophylaxis under two subheadings (short and long term prophylaxis). Although the drugs used are similar, their timing and duration are different.

Short term prophylaxis treatment

Plasma-derived C1-INH replacement, FFP or short-term preventive treatment with anabolic steroids may be required to prevent the development of an attack in patients who are planned to have surgery, any intervention in the mouth area, especially tooth extraction, etc. (Table 1).[1−5,7−9] Treatment approaches that can be used after minor and major procedures are summarized in Table 1.

Long term prophylaxis treatment

Although it is recommended for use in the presence of frequent and/or severe attacks, there is no generally accepted consensus. Previous guidelines were recommended for patients who had more than one attack per month or had a history of swelling in the throat, or who were absent from work for more than 5 days a month due to an attack. In recent years, it is emphasized that each patient should be evaluated at a personal level and treatment planning (personalized-individualized-treatment) should be made according to their needs.[2]

In our country, there is only one drug Cinryze® that can be used in long-term prophylaxis treatment. Other drugs such as Berinert® are expected to come. The treatment methods that can be used in the long-term prophylaxis treatment are shown in Table 2.

The newest drug in long-term prevention treatment in the world is Lanadelumab-flyo (Takzyhro®). This product is a monoclonal antibody, functions by inhibiting plasma kallikrein and although it is not included in the guidelines, it was approved for use by the FDA on August 23, 2018.[43−45]

Table 1. Drugs recommended in current guidelines for short-term prophylaxis (10-17)

Product	Trade Name	Dose	Source	Medication	Explanation
Minor operations					
pdC1-INH	Berinert/Cinryze	20 IU/kg; 1.000Ü	Plasma	IV	If it is on hand, no other medicine is needed
Danazol	Danasin	2.5–10 mg/kg/day	–	Oral	5 days before - 5 days after the procedure
Stanazolol	Winstrol	4–6 mg/kg/day	–	Oral	5 days before - 5 days after the procedure
Traneksamik acid	Transamin	75 mg/kg/day	–	Oral	5 days before - 5 days after the procedure
Major operations (surgery, entubation etc.)					
pdC1-INH	Berinert/Cinryze	20 IU/kg; 500–1500 Ü	Plasma	IV	1–6 hours before the procedure
Solvent-detergent / Fresh frozen plasma	SDP/TDP	10mL/kg; 400–800 mL (2–4 Ü)	Plasma	IV	1–6 hours before the procedure

PI: Plasma-induced; C1-INH: C1 esterase inhibitor; IV: Intravenous; SC: Subcutan.

Table 2. Drug groups recommended in current guidelines for long-term prophylaxis (10-17)

Group	Trade Name	Dose	Medication	Explanation
pdC1-INH	Berinert/Cinryze	1.000–2.500 Ü, 2 times a week	IV	The most known druf; Plasma sourced; Available in 2 preparations
C1-INH	Haegarda	60 IU/kg 2 times a week	SC	New drug; Plasma sourced
Kallikrein inhibitor	Lanadelumab	150mg/day	SC	August 2018 FDA approved
Antifibrinolytic	Tranexynamic acid	20–50 mg/kg/day 3-6 g/day	Oral	If lack of C1-INH or if, androgen contraindicated
Antifibrinolytic	Ɛ-amino caproic acid	1–4 g, x^3/day 0.05–0.1g/kg x^2/day	Oral	It is used of lack of Tranexynamic acid
Androgens	Danazol	2.5–5 mg/kg/day ≤200 mg/day	Oral	It can not be used during pregnancy and before Tanner phase 5
Androgens	Stanozolol	0.5–2 mg/day	Oral	Attention to Virilizan effects
Androgens	Oksandrolon	0.1 mg/kg/day 10 mg/day	Oral	Attention to side effects

PD: Plasma induced; C1-INH: C1 esterase inhibitor; IV: Intravenous; SC: Subcutan, FDA: America food medicine department.

Emergency/attack (acute, when required: on demand) treatment

It is very important for the patient deciding "What/in what kind of involvement should the treatment be given in emergency attack (acute) treatment?" A wait-and-see strategy can be used for skin swelling in the trunk and extremities, except for facial and neck involvement. In attacks involving the larynx and abdomen, there is no need to wait and attack treatment should be started quickly.[11,13]

As in every emergency case, ensuring the patient's airway

Table 3. Drugs recommended in current guidelines in acute (attack) treatment

Group	Trade Name	Dose	Source	Medication	Side effect
pdC1-INH	Berinert/Cinryze	20 IU/kg; 1.000Ü	Plasma	IV	Thrombosis, infection
rhC1-INH	Ruconest/Rhucin	50 IU/kg	Recombinant	IV	Anaphylaxis
Icatibant	Icatin/Firazyr	30 mg	–	SC	Injection reaction
Ecallantide	Kalbitor	30 mg	–	SC	Anaphylaxis
Solvent-detergent/ Fresh frozen plasma	SDP/TDP	10 mL/kg; 400–800 mL	Plasma	IV	It can increase the severity of the attack!

PD: Plasma induced, C1-INH: C1 esterase inhibitor; IV: Intravenous, SC: Subcutan.

clearance comes first. Today, especially 4 kinds of drugs C1-INH plasma concentrate, recombinant C1-INH, Icatibant and Ecallantide are used all over the world. Supportive therapy with fluid replacement and analgesics can be given, if appropriate. It may be preferred if solvent-detergent plasma is available, otherwise fresh frozen plasma can be given instead.[10–12,15–17]

Although androgens and antifibrinolytic drugs have been used in the past, they have been abandoned today as they seem less effective than new drugs. The effect of Danazol treatment begins within 1 to 2 days on average. For this reason, although it is considered not a good option in the treatment of relapses, as a general approach, it is recommended that patients in long-term prophylaxis treatment should double the dose of danazol treatment in case of an attack, despite the dose they use. Although less effective in comparison, Tranexamic acid can be tried in situations where other drugs are not available.[13,46–50]

In our country, C1-INH plasma concentrates, which have been used for the last two decades, can be given. Also, Icatibant (bradykinin receptor β2 antagonist), which is newly brought to our country, can be used as an alternative. If none is found, fresh frozen plasma can be given (Table 3).[13] Kallikrein inhibitor: Ecallantide (DX88, Kalbitor) was brought to our country at some time, it is now withdrawn from the market.[48] The treatment methods that can be used in the treatment of attacks are shown in Table 3.

Some treatment applications with the new drugs

In the reviews published in 2019, recombinant Rhucin®/Ruconest® (50 IU/kg) given intravenously in acute treatment and plasma-derived Haegarda® (60 IU/kg) administered subcutaneously in prophylaxis treatment were included in the texts.[52]

Recombinant c1-inh (rhucin/ruconest®) products: Although it has been used in adolescents since the last decade and have been introduced in the guidelines, trial studies are continuing to reduce the age of indication in treatment to 5–14 years.[28–31]

Subcutaneous c1-inh (haegarda®) product: Haegarda, one of the new alternatives for long-term prophylaxis, was approved in 2017. Dose safety studies are ongoing. Again, this plasma-derived product was compared with intravenous C1-INH replacement (Cinryze®) and was found more successful. Studies conducted to teach the use of this subcutaneous C1-INH replacement at home, have also been found successful.[32–36] Treatment trials of subcutaneous C1-INH (rHuPH20) replacement containing hyaluronidase were stopped due to the development of non-neutralizing antibodies.[37]

The most known side effects of treatment

It should be kept in mind that, intravenous blood product plasma-derived C1-INH products such as Cinryze®, Berinert® carry a risk of viral disease transmission, although have not been reported to date. It should be known that, products such as recombinant Rhucin®/Ruconest® may cause anaphylaxis as a result of the hypersensitivity reaction they may develop against rabbit proteins. Ecallantide is also known for its ability to cause hypersensitivity reactions, including anaphylaxis. Icatibant is mostly known for the reactions at the injection site.[7–17]

Future treatment in hereditary angioedema

Here, we will briefly discuss the clinical and pre-clinical drugs and methods that are being developed for the treatment. In particular, clinical studies on plasma kallikrein inhibitors continue intensely.

Possible future treatment methods tried in the clinic

Subcutaneous plasma kallikrein inhibitor Lanadelumab (Takzyhro®): In a study of 125 patients, with this product, it was observed that it significantly reduced attacks and increased quality of life.[45]

Oral plasma kallikrein inhibitor Avoralstat (BCX4161): In the trials performed with an oral plasma kallikrein inhibitor, it was shown that it could not prevent attacks, but increased angioedema quality of life scores.[23]

Oral plasma kallikrein inhibitor BCX7353: Another oral plasma kallikrein inhibitor, in a study of 72 patients with a dose of ≥125 mg/day, was reported to reduce the number of attacks and positively affected the quality of life. In the

study, mostly side effects related to the gastrointestinal system were reported.[25]

Possible future application pre-clinically tried genetic treatment methods

Preclinical studies are based on the destruction of the production of kallikrein and coagulation F12 in the body and ultimately to prevent the formation of angioedema by reducing the accumulation of quinine in the body.[21]

Ionis PKKRx: This treatment method, produced by the company Ionis, performs kallikrein inhibition over the anti-sense oligonucleotide that suppresses the precallikrein transcription.[18,21]

ALN-F12: A product called ALN-F12, a double-stranded small RNA interference (RNAi) drug produced by Alnylam Pharmacy, is trying to be developed. It is a method intended to be used in HAE prophylaxis and based on destroying the synthesis of Factor XII.[18,21]

ARC-F12: Another drug developed by the Arrowhead Research Company and named as ARC-F12, is a product coded as ARC-F12 that acts on RNAi. Studies in mouse models have shown that the production of Factor XII is >90% inhibited with monthly injection of 4mg/kg ARC-F12. As a result of this treatment, it was reported that the swelling in the paw of the mouse was statistically significantly reduced.[18]

Gene therapy: In a study reported by Qiu et al.[51] in 2018, trial studies were conducted with the Adenoviral vector in HAE mouse models with C1-INH deficiency, and it provided C1-INH production in mice above the expected therapeutic level and this method was shown to be useful in protecting against long-term disease.[21,51]

Peer-review

Internally peer-reviewed.

Conflict of Interest

None declared.

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Günümüz ve Gelecekte Herediter Anjiyoödem Tedavisi

Çoğunlukla C1 esteraz inhibitör (C1-INH) eksikliğine bağlı meydana gelen herediter anjiyoödem (HAÖ) cilt, bağırsak submukozası ve üst solunum yolunu tutan; kaşıntı ve ürtikerle birlikte olmadan tekrarlayan anjiyoödem ataklarıyla seyreden otozomal dominant bir hastalıktır. Herediter anjiyoödem atakları epinefrin, glukokortikoit veya antihistaminik tedavisine cevapsızdır. Herediter anjioödem hastaları önceden anabolik androjen ve antifibrinolitikler gibi birkaç tedavi seçeneğine sahipti. Günümüzde birçok ülkede HAÖ tedavisinde son 20 yıldır belirgin ilerleme olmuş ve klinikte etkinliği kanıtlanmış atak ve profilaktik tedavide kullanılan ilaçlar piyasaya sunulmuştur. Atak tedavisinde alternatifler plazmadan üretilen iki C1-INH konsantresini, rekombinan C1-INH ürününü, kallikrein inhibitörü ve bradikinin β2 reseptör antagonistini içerir. Profilaksi tedavi seçenekleri plazmadan üretilen iki plazma kaynaklı C1-INH konsantresi dışında, subkutan C1-INH replasmanını ve en yeni subkutan plazma kallikrein inhibitörü Lanadelumab'ı içerir. Bu gelişmelere rağmen, HAÖ hastaları hasta ve toplum için önemli derecede maliyetle ilişkili ve yıkıcı anjioödem ataklarına yol açan bu zorlu hastalığın hala bazı ciddi sorunlarıyla karşılaşmaktadır. Hastalarının daha iyi eğitimi ve gereğinde tedavi için kendi kendine tedavi stratejisinin yerleşmesi hastaların yaşam kalitesi ve hastalığın negatif etkilerini düzeltir. Bu yazıda, HAÖ tedavisinde mevcut olan ve ümit vaat eden tedavi seçenekleri gözden geçirildi.

Anahtar Sözcükler: Bradikinin; C1 inhibitör; herediter anjiyoödem; kallikrein.