

Hereditary angioedema: treatment options and availability. Balance between patients' needs and stakeholders' plans

Opcje terapeutyczne i ich dostępność we wrodzonym obrzęku naczynioruchowym: pomiędzy potrzebami pacjentów a planami decydentów

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Summary

Hereditary angioedema is a rare and disabling disease characterized by severe, acute, self-limiting edema of the subcutaneous and mucosal tissue. The disease carries significant mortality when the upper airways are involved. It is determined by a transient dysregulation in vascular permeability with a sudden increase in fluid extravasation. The most common genetic defects recognized on the SERPING1 gene leads to complement C1-inhibitor deficiency (C1-INH-HAE). In the last few years mutation on the factor XII gene, the angiopoietin, and the plasminogen genes were recognized to cause angioedema with normal C1-INH levels (nC1-INH-HAE). However, it is not uncommon to have family history of angioedema and unknown genetic defect. The burden of the disease on the individual patients is unpredictable since the number, location and severity of the attacks spans from silent disease to an extremely high number of attacks during lifetime. Nowadays effective and safe treatment for the C1-INH-HAE forms are available and new drugs are under investigation both for the on demand therapy and for the prophylaxis of the attacks. Acute treatments has been proved to reduce severity and duration of attack, prophylaxis reduces the number of attacks thus positively affecting the quality of life and reducing the indirect costs of the disease. Unfortunately, the costs of the medications are high limiting the accessibility and availability of treatment in different countries. This paper reviews the treatment options and the differences in the availability of the medications in three European countries, with practical suggestions for the management of the disease.

Keywords: hereditary angioedema, treatment, prophylaxis, C1 inhibitor, bradykinin receptor antagonist, kallikrein inhibitors

Streszczenie

Wrodzony obrzęk naczynioruchowy jest rzadką, upośledzającą funkcjonowanie chorobą charakteryzującą się ciężkimi, ostrymi, samoo ograniczającymi się obrzękami tkanki podskórnej i podśluzówkowej. W przypadku zajęcia górnych dróg oddechowych, schorzenie obarczone jest znaczącą śmiertelnością. Choroba jest determinowana przejściową dysregulacją przepuszczalności naczyniowej ze nagłym wzrostem ilości wynaczynionego płynu. Najczęściej spotykane defekty genetyczne występujące w genie SERPING1 prowadzą do niedoboru inhibitora składowej C1 układu dopełniacza (C1-INH-HAE). W ostatnich kilku latach poznano mutację genów czynnika XII, angiopoietyny i plazminogenu powodujące obrzęk naczynioruchowy z prawidłowym poziomem C1-INH (HAEnC1-INH). Jednakże, nie jest sytuacją niezwykle występowanie rodzinnego wywiadu w kierunku obrzęku przy nieznanym defekcie genetycznym. Obciążenia związane z chorobą u poszczególnych pacjentów są trudne do przewidzenia, ponieważ liczba, lokalizacja i ciężkość napadów w ciągu życia zmienia się: od okresów remisji, do okresów ze skrajnie częstymi objawami. Obecnie dostępne są skuteczne i bezpieczne formy leczenia C1-INH-HAE, a w trakcie badań są nowe leki, zarówno do doraźnej, jak i profilaktycznej terapii napadów obrzęku. Leki stosowane w stanach ostrych mają potwierdzone działanie zmniejszające ciężkość i czas trwania napadów, a leki stosowane w profilaktyce zmniejszają częstość napadów wpływając pozytywnie na jakość życia i redukując pośrednie koszty choroby. Niestety koszty leczenia są wysokie i ograniczają jego dostępność w wielu krajach. W niniejszej pracy dokonano przeglądu możliwych opcji terapeutycznych i ich dostępności w trzech krajach europejskich, poszerzonego o praktyczne sugestie dotyczące leczenia choroby.

Słowa kluczowe: wrodzony obrzęk naczynioruchowy, leczenie, profilaktyka, C1-inhibitor, antagoniści receptora bradykininowego, inhibitory kalikreiny

INTRODUCTION

Hereditary angioedema (HAE) is a disease characterized by recurrent self-limiting episodes of oedema without urticaria localized at the extremities, face, genitals, gastrointestinal and upper airway mucosa. Laryngeal involvement may cause fatal asphyxiation. HAE prevalence is uncertain, with estimates ranging between 1 in 10 000 and 1 in 150 000 persons worldwide [1-5]. It is most commonly due to genetic complement C1-inhibitor deficiency (C1-INH-HAE) even if, recently, other new mutations on different genes have been recognized [6-8].

In the pathophysiology of the acute attacks C1-INH plays a central role in the control of the activity of contact system enzymes, factor XIIa and plasma kallikrein. C1-INH deficiency facilitates contact system activation and local release of the vasoactive peptide bradykinin, responsible for oedema formation [9]. There are several types of HAE (Fig. 1). Two forms of the disorder arise from deficiency or dysfunction of C1-INH (types I and II, respectively), and can be detected by abnormal complement protein levels [10]. The other types of familial angioedema are characterised by normal C1-INH (nC1-INH-HAE) and normal complement studies. A small but growing number of suspected pathogenic variants in genes addressed to other protein synthesis have been identified to explain the disease in some families. In 2006 the first associated coagulation factor XII mutation was identified [6], and in 2018 the angiotensin-converting enzyme 1 and plasminogen genes were discovered [7, 8]. The pathogenesis in other families with unidentified gene mutation nowadays remains unclear. C1-INH-HAE depends on heterozygous SERPING1 variants that cause deficient production of the protein. Its immunological diagnosis is based on antigenic and/or functional plasma C1-INH levels below 50% of normal. The clinical penetrance of this defect approaches 100%, and angioedema stands out clearly in affected subjects.

BODY OF THE ARTICLE

Frequency and severity of angioedema recurrences are highly variable and represent the main drivers of disease burden. Different choices in the management of therapies should be considered according to the number and severity of the attacks, the impact on quality of life, and the availability of the treatment that is different in different countries. The treatment efficacy is different being dependent on the underlying hereditary defect. There is not a complete agreement concerning the on demand treatment (ODT) versus prophylactic treatment (PT) therapeutic strategies. While drugs that are effective on demand represent the solely approach to avoid mortality related to life-threatening attacks, both ODT and PT can reduce disease burden reducing severity and duration of attacks. PT has the additional advantage on reducing also attack frequency. Thus, complementary use of ODT and PT should be addressed from clinical standpoint and also for economics considerations. Indeed, the impact of direct and indirect costs on the society is relevant, the recurrences of the attacks cause significant disability with a consistent humanistic and economic impact of the disease due to reduced performances at school or work for patients and their caregivers [11-14].

Healthcare payers and healthcare systems worldwide raise major concerns about the financial impact of the already available and newly approved therapies on healthcare payment systems. The amount of the expenses leads to barriers and limitation of access to these life changing/saving therapies. This review will describe the differences of availability and access to therapies for the ODT and PT in Poland, Bulgaria and Italy, as an example for future consideration and development of sustainable and fair treatment policy of this rare disease.

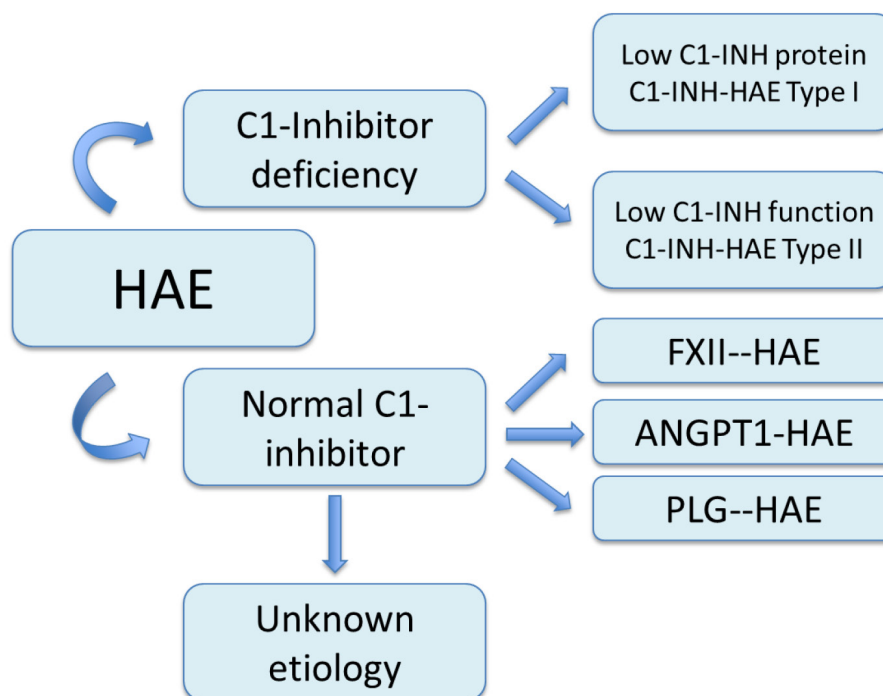


Fig. 1. Classification of the different form of hereditary angioedema

Legend: HAE - hereditary angioedema; C1-INH - C1 inhibitor; FXII - factor twelve; ANGPT1 - angiotensin-converting enzyme 1; PLG - plasminogen

Diagnosis: practical suggestions

In synthesis, the diagnosis of HAE should be considered in patients who demonstrate recurrent self-limited episodes of angioedema without urticaria or pruritus, lasting for two to five days (without treatment); when colicky, abdominal pain are recurrent and unexplained; when even a single laryngeal edema attack occurs, and when other known acquired forms of angioedema are excluded according to the consensus report from the Hereditary Angioedema International Working Group [10]. The presence of a positive family history of angioedema is suggestive but in some cases is absent. The type of angioedema is assessed by C1-INH and C4 measurements.

Treatment strategies in HAE

Acute treatment reduces severity and duration of attack for most patients, whose quality of life has improved since such treatments became available [15]. C1 inhibitor (plasma-derived or recombinant), ecallantide, or icatibant are effective acute treatments (details and table in the next chapter).

However, the assessment and protection of the upper airway is the first and most important management issue in the patient presenting with an acute attack involving any part of the airways, as none of the available therapies is universally effective. The maintenance of the airway patency must be carefully and promptly evaluated and maintained since the efficacy of the action of these agents requires time.

Every patient should have an acute care plan, the best acute treatment should be decided on an individual basis considering the specific environment of the patient, his/her compliance and possibility of self-administration and the presence of a care-giver. Best acute treatment may vary between attacks and should be re-evaluated over time for a given patient since the recurrence and severity of the attacks is likely to be different during the whole life.

Acute treatment of attacks in C1-INH-HAE

Acute treatment of hereditary angioedema due to C1 inhibitor deficiency has become available in the last 10 years and has greatly improved patients' quality of life. Two plasma-derived C1 inhibitors (Berinert® and Cinryze®), a recombinant C1 inhibitor (Conestat alpha/ Ruconest®), a kallikrein inhibitor (Ecallantide/Kalbitor®), and a bradykinin B2 receptor antagonist (Icatibant/Firazyr®) are all effective [16-21]. The relative efficacy of the drugs has not been compared in head-to-head trials. Sustainable good response is maintained over repeated treatments and several years. All currently available prophylactic agents are associated with breakthrough attacks; therefore, an acute treatment plan is essential for every patient, irrespectively to the presence of PT. The efficacy of human plasma in treating acute attacks has been suggested by case reports. No controlled trials have been ever performed [22].

In Italy, two plasma derived and one recombinant C1-INH (Berinert®, Cinryze®, Ruconest®), and the bradykinin receptor antagonist icatibant (Firazyr®) are registered for ODT. However, Ruconest is not always reimbursed by the Italian National Healthcare System, and its use remains marginal. Icatibant is delivered as prefilled syringe to be administered subcutaneously at a fixed dose of 30 mg, where-

as plasma-derived C1-INH (pdC1-INH) is delivered in vials of 500 IU for a weight-based dose of 20 IU/Kg. In Poland authorized and reimbursed treatment for ODT are recombinant C1-INH, plasma derived C1-INH and icatibant, while in Bulgaria only plasma derived and recombinant C1-INH are available (Table III). The use of ecallantide is approved by the Food and Drug Administration, only in the US. For children and pregnant women, plasma-derived C1 inhibitor has the best evidence for safety and currently remains first-line treatment.

The main characteristics of HAE medications are summarized in Table I.

Other new small molecules are under investigation for future use in the acute and prophylactic treatment of the attacks. BCX7353 is a novel oral plasma kallikrein inhibitor with promising results (preliminary data from the ZENITH-1, trial-unpublished) [25] showing that a single 750 mg oral dose of BCX7353 was well tolerated and superior to placebo for the treatment of acute attacks in HAE patients.

Another treatment under investigation in a Phase I trial for acute AE attacks modulates the inhibition of plasma kallikrein (PK). KVD 900 (KalVista) is a novel small molecule, selective and orally available PK inhibitor that is protective against PK-mediated high molecular weight kininogen (HK) cleavage in undiluted HAE and control plasma in an *ex vivo* assay [26].

Prophylaxis of C1-INH-HAE

The clinical considerations for long-term prophylaxis (LTP) therapy of C1-INH-HAE have significantly changed in recent years from pre-defined criteria of numbers of attacks or days of disability, to an individualized approach, taking multiple factors into account [27]. The contemporary state of mind is that C1-INH-HAE is a multi-factorial condition that affects each patient's life differently and with various burden even in the same patient over time [28].

Disease severity should be evaluated in the context of impact on quality of life and ability to conduct daily activities, and/or leisure [29]. Attack numbers, days of disability, or hospitalizations are controversial and might not necessarily be best indicative for the impact of the disease over the individual patient [30]. The first effective prophylactic drugs were oral androgens. Efficacy was found almost serendipity in 1960 before C1-INH deficiency was known to underlying HAE [31]. Ten years later, in absence of strong pathophysiologic rationale, antifibrinolytic agents were started in HAE prophylaxis. Efficacy has never clearly been proved and their use remained marginal. Thus, for 40 years, attenuated androgens remained the milestone of HAE prophylaxis. Their easy availability and low cost allowed patients around the world to access this treatment. Need for alternative comes from obvious side effects of such an approach. During that time, the first studies of intravenous plasma-derived C1-INH (pdC1-INH) for acute attacks showed promising clinical outcomes, with proper dose-selection being among the main unknowns. Viral-safety at that time was to be substantially improved overtime, yet with historical insecurity in patients and physicians with the early formulations [32-34]. Since then, the first studies with intravenous pdC1-INH for long-term prophylaxis provided evidence for the efficacy, safety and effect on quality of life, and many patients have benefited from this therapy. Nowadays, viral safety of C1-INH

Table I. HAE-specific treatment for treatment of acute attacks

| Drug (molecule), Route of administration | Commercial name | Subjects and therapeutic regimen for prophylaxis | Adverse events | Warnings and precautions | References |
|---|---------------------------------------|--|--|---|------------|
| pdC1-INH, I.V. | Berinert 500 and 1500 IU, CSL Behring | Adults, adolescents, and children; 20 IU/kg I.V. | Headache, nausea, rash, vomiting and fever | Theoretical infectious agents' transmission. Thrombotic and thromboembolic events. Allergic reactions. Potential immunogenicity. | [15-17] |
| pdC1-INH, I.V. | Cinryze, Shire | Adults and adolescents; 1000 IU, I.V. (additional 1000 U at discretion of physician) | Headache, nausea, rash, vomiting and fever | Theoretical infectious agents' transmission. Thrombotic and thromboembolic events. Allergic reactions. Potential immunogenicity. | [23] |
| rhC1-INH Conestat alfa I.V. | Ruconest Pharming | Adults and adolescents; 50 IU/kg up to 4200 U (if ≥ 84 Kg) S.C. | Headache, nausea, diarrhea, sneezing, skin burning sensation or rash, back pain, changes in taste, and spinning sensation (vertigo) | Allergic hypersensitivity reactions. | [20] |
| Bradykinin B2 receptor antagonist Icatibant S.C. | Firazyr Shire | Pre-filled syringe 30 mg prefilled S.C. | Local injection site reactions | Avoid in acute thrombosis. | [19] |
| Ecallantide Kallikrein antagonist S.C. | Kalbitor Dyax Corp. | Vial 10 mg 30 mg (3 mL) S.C. administered in 3 separate 10 mg (1 mL) injections; Allowed an additional dose of 30 mg within 24 hours | >10% headache, nausea, fatigue, diarrhea | Self-administration not allowed. Anaphylactoid events. | [21] |
| Oral molecule targeting plasma kallikrein #, P.O. | BCX7353, Avorlastat, Biocryst | Adults 750 mg P.O. | Gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain), skin rash, elevated liver enzymes, fatigue, headache, nasopharyngitis. | Higher doses associated with higher frequency of gastrointestinal AEs. Theoretical precaution for cardiovascular accidents. Expected drug interactions with medications interfering with CYP2 family. | [24] |

exploratory trial, results expected in the first quarter of 2019

pdC1-INH: plasma derived C1 inhibitor; rhC1-INH: recombinant human C1 inhibitor; Bradykinin B2 receptor: bradykinin beta two receptor; I.V.: intra venous route; S.C.: subcutaneous; P.O.: oral route of administration

products is nearly fully secured by means of modern biotechnologies and strict monitoring production processes [35].

However, there is a treatment burden associated with any intravenously administered medication. Often, patients are unable or unwilling to access their veins for drug administration. Patients with venous access problems used subcutaneous ports, which are associated with risks of infection and thrombosis [36, 37]. Recently, new prophylactic therapies have improved efficacy, a more favourable benefit-risk profile, and a reduced treatment burden aiming to change the considerations for prophylaxis therapy among patients and physicians [38, 39]. Subcutaneous therapies avoid the need for venous access and likely reduce the treatment burden compared to intravenous administration. Development of a safe and effective oral therapy would meet the major unmet need by terms of ease of treatment administration. With these improvements in therapeutic options, prophylaxis therapy will likely start to be used more often in HAE patients, leading to individual patient-tailored treatment to diminish disease burden.

A promising and completely different approach to provide long-term protection from angioedema attacks in affected individuals is under investigation in a C1 Heterozygote C1-INH deficient mouse model. A single treatment intravenous administration of an adeno-associated virus (AAV) gene transfer vector expressing the genetic sequence of the normal human C1 esterase-inhibitor (AAVrh.10hC1EI) is effective in providing sustained circulating C1-INH levels sufficient to prevent angioedema episodes [40]. At present the program of using this vector in HAE is on hold since most recent data from the study in alpha1 anti-thrypsin failed to observe a clinically meaningful level of protein expression [41].

Patients with HAE with normal C1-INH tend not to respond to epinephrine, antihistamines, or glucocorticoids, similar to those with C1-INH-HAE. However, in absence of knowledge on this heterogeneous condition these therapies remain first choice approach until inefficacy is clearly assessed.

Treatment options for HAE with normal C1-INH are not defined. It is assumed that their pathogenesis goes through kallikrein mediated release of bradykinin. Based on this assumption bradykinin targeted approach as for C1-INH-HAE has been attempted. However, treatment experience is limited and results anecdotal in absence of controlled clinical trials. Several novel field of investigation to reduce production of bradykinin are in the preclinical phase such as 2 RNA interference drugs affecting factor XII production, ALNF12 and ARC-F12; a monoclonal antibody antifactor XIIa, CSL 312; and gene therapy.

The drugs currently used for LTP of C1-INH-HAE are summarized in Table II.

Treatment availability in Poland, Bulgaria and Italy

Treatment availability in Italy, Poland and Bulgaria are summarized in the Table III.

Italy

The story of HAE in Italy began in 1971 when the first C1-INH-HAE patient was diagnosed. For the diagnosis Professor Angelo Agostoni sent a sample of serum to Virgin-

ia Donaldson, who showed the lack of C1-INH antigen by immune-electroforetic technique using an anti-C1-INH specific antiserum. By that time, therapy was limited to some initial experience with fresh frozen plasma to reverse acute attacks. For the same purpose the Italian group used with some success the anti-proteasac compound Trasylol [55]. Interestingly, Trasylol was made of aprotinin extracted from bovine lungs. The aminoacid sequence of the reactive site of aprotinin was used derive ecallantide, the recombinant anti kallikrein registered in U.S. for on demand treatment of HAE. By 1974 two additional families had been diagnosed in Milan and at the Netherland Red Cross (now Sanquin) the first C1-INH concentrate from plasma had been prepared for human use [56]. Dr Brummelhuis made available samples of this preparation to Prof. Agostoni, who used it in two HAE patients at two different doses (12,000 and 36,000 U) to reach significant post infusion increase of the deficient protein (Marco Cicardi, Doctorate thesis 1975). In the same time other companies engaged in plasma derived product (Immuno Vienna, Berhing Marburg and the American Red Cross) worked on C1-INH preparations that reached the European market around 1985. In U.S. development of new plasma products was stopped when the HIV epidemic became apparent. The C1-INH preparation that just started to be tested was placed on hold and until 2008 no plasma derived C1-INH has been registered in U.S. [57].

Since 1983, Immuno's C1-INH was the first marketed preparation to become generally available for treatment of severe acute HAE attacks for Italian C1-INH-HAE patients. In 1976 the group of Frank provided clear evidence for the capacity of the attenuated androgen danazol, not only to dramatically reduce angioedema attacks, but also to revert C1-INH deficiency in HAE patient. For 35 years plasma derived C1-INH as ODT and danazol as PT covered the therapeutic needs of Italian HAE patients. Year 2010 represents the start of the new era of the HAE treatment that now sees two plasma derived C1-INH, one recombinant C1-INH, one bradykinin B2 receptor antagonist, one inhibitor of plasma kallikrein and one recombinant monoclonal antibody targeting plasma kallikrein available for OD and/or LTP.

Poland

The first Polish family with members affected by C1-INH-HAE was reported by Dr. Korzeniewska at a local allergists' session in 1984. A year after, Prof. Krystyna Obtulowicz diagnosed in Krakow the next patient with a severe, and life threatening clinical course of the disease. In response to the request of Prof. Obtulowicz's, Berhing company donated a certain amount of human plasma derived C1-INH to the hospital in Krakow. This "stock" served as a rescue treatment for quite a long time for that exact patient, who still remains under care in the same center, as well as for other newly diagnosed in the meantime patients [58]. Unfortunately, except the situation described above, the early beginnings of HAE management in Poland were much more difficult. The only licensed drug, Berinert, could be obtained by means of direct import for a particular patient. This procedure was challenging and long-lasting, therefore a real access to rescue treatment was very limited. Over the years, attenuated androgens (mostly danazol) were widely utilized, both for long-term prophylaxis and for HAE attacks, despite of many reported side effects. Children and pregnant women were treated with the anti-fibrinolytic agent - tranexamid acid, which is inexpensive and widely available,

Table II. HAE-specific treatments for prophylaxis of attacks




| Drug (molecule), Route of administration | Commercial name | Subjects and therapeutic regimen for prophylaxis | Adverse events | Warnings and precautions | References |
|--|--|---|--|---|---|
| Androgens, P.O. | Danazol | Adults, Lowest therapeutically relevant dose (50-200 mg/d P.O.) | Hepatotoxicity, virilization, hepatocellular carcinoma, lipid abnormalities, weight gain, mood effects | Preferably not to use in females and pre-puberty children. Potential virilization of the fetus. Dose more than 200 mg/d not advised for LTP use. Do not use in subjects with malignant tumors (breast and prostate cancer). | [42-46] |
| Tranexamic acid, P.O. | Tranex | Adults and adolescents 500-3000 mg/d P.O. | Diarrhoea, nausea, vomiting, pruritus, headache, myalgia | No plain efficacy proofs. Beware of thrombotic complications in predisposed patients | [47, 48] |
| pdC1-INH, I.V. | Berineret ¥ 500 and 1500 IU, CSL Behring | Adults, adolescents, and children; 20 IU/kg, twice weekly, I.V. | Headache, nausea, rash, vomiting and fever | Theoretical infectious agents' transmission. Thrombotic and thromboembolic events. Allergic reactions. Potential immunogenicity. | [49-52] SPC of the product |
| pdC1-INH, I.V. | Cinryze, Shire | Adults and adolescents; 1000 IU, twice weekly, I.V. (up to 2500 IU, but no more than 100 IU/kg) | Headache, nausea, rash, vomiting and fever | Theoretical infectious agents' transmission. Thrombotic and thromboembolic events. Allergic reactions. Potential immunogenicity. | [17, 32, 53, 54] SPC of the product |
| Low-volume pdC1-INH*, S.C. | HAEGARDA, CSL Behring | Adults and adolescents; 60 IU/kg, twice weekly, S.C. | Injection site reactions, hypersensitivity, nasopharyngitis, and dizziness | Theoretical infectious agents' transmission. Potential thrombotic events. Potential tachyphylaxis. | [38] SPC of the product NCT01576523 NCT01912456 NCT02316353 |
| Rh mAb targeting plasma kallikrein, S.C. | Lanadelimab * Shire | Adults and adolescents; 300 mg, twice or once monthly, S.C. | Injection site reactions, hypersensitivity, nasopharyngitis, rash, and dizziness | Potential immunogenicity. Theoretical precaution for cardiovascular accidents, bleeding, and autoimmune disorders. | [39] SPC of the product NCT02586805 |
| Oral molecule targeting plasma kallikrein, P.O. | BCX7353 # Avorlastat, Biocryst | Adults 110-150 mg daily P.O. | Gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain), skin rash, elevated liver enzymes, fatigue, headache, nasopharyngitis. | Higher dose associated with higher frequency of gastrointestinal AEs. Theoretical precaution for cardiovascular accidents. Expected drug interactions with medications interfering with CYP2 family. | [24] |

* - under registration process in Europe

- under phase III investigation

¥ - not registered for LTP but historically and often used in clinical practice

Table III. Treatment availability in Italy, Poland and Bulgaria

| Drug | | Italy  | Poland  | Bulgaria  |
|------|-------------------------|---|--|--|
| OD | pdC1-INH Berinert® 500 | Yes | Yes | Yes |
| | pdC1-INH Berinert® 1500 | Yes | Yes | Not available |
| | pdC1-INH Cinryze® | Yes | Not available | Not available |
| | rhC1-INH Ruconest® | Yes (# not all regions) | Yes | Yes |
| | Icatibant Firazyr® | Yes | Yes | No (expected in 2019) |
| | Ecallantide Kalbitor® | Not available | Not available | Not available |
| STP | C1-INH iv | Yes | Yes | Yes |
| | Androgens | Yes | # off-label and not reimbursed | Not available |
| LTP | Tranexamic acid | Yes | # off-label and not reimbursed | Not available |
| | Androgens | Yes | # off-label and not reimbursed | Not available |
| | C1-INH iv | Yes | # not reimbursed | # off-label |
| | scC1-INH Berinert | Off-label | # not reimbursed | Not available |
| | Lanadelumab* | Yes | Not available | Not available |
| | BCX7353* | Yes | Not available | Not available |

OD - on demand therapy; STP - short-term prophylaxis; LTP - long-term prophylaxis; pd - plasma-derived; rh - recombinant human; sc - subcutaneous; iv - intravenous

*clinical trials - extensions

but far less effective than first-choice treatments. Due to shortages of Berinert, fresh frozen human plasma was the main therapy for most severe edema attacks in emergency situations.

These "early therapies" have been substituted gradually by disease-specific drugs, which received regulatory approval for C1-INH-HAE patients in the European Union, US, and other countries. In Poland, a major breakthrough in treatment of acute attacks took place between March 2013 and June 2015. Within this period, the national public health authorities decided to reimburse the costs of on demand treatment with Ruconest, followed by Berinert, and Firazyr. This made the drugs available for Polish C1-INH-HAE patients. Moreover, Berinert is also available for short-term prophylaxis. Training courses among patients for self-administration were another important step towards better management of the disease. Drugs targeting the contact system cascade, such as aprotinin in the past or ecallantide at present, have never been used in Polish HAE patients. Other new molecules or technologies, which have been recently investigated, for instance lanadelumab targeting plasma kallikrein in order to prevent angioedema attacks, or shifting C1-INH delivery from intravenous to subcutaneous route for prophylaxis of attacks, wait to be introduced into everyday practice in Poland.

Bulgaria

The first C1-INH-HAE family in Bulgaria was diagnosed in 1972 by Prof. Bozhko Bozhkov who sent serum samples for complement investigations to Prof. Sir Peter Lachmann in the UK [59]. More families were recognized in the following years in the Clinic of Allergy in Sofia. Still, there was a long period of "dark ages" by terms of treatment availability and disease awareness for patients in Bulgaria. In the beginning, fresh frozen human plasma (FFP) was the only available (in theory) treatment for acute attacks. Nevertheless, this was an option considered only in medical facilities where physicians were aware about the diagnosis (1-2 centers throughout the country).

After 1990, attenuated androgens began to be used for treatment of the disease, with a price not affordable for patients, and a possible state reimbursement after a bulky protocol procedure only for selected cases of very severe course of the disease. "Lucky" patients only received the drug for several years until in 1998 the drug definitively disappeared from the pharmaceutical market of the country. This caused an unresolved problem also for other patients with indication to receive continuous androgen therapy (e.g. endometriosis).

For a very short period Trasylol was available for acute HAE attacks but treated cases were less than 2% of all C1-INH-HAE patients. The risk and fear for acute anaphylactic reactions actually expelled the drug from use, consistent with its faith in other countries.

During the years 2000-2012, patients were followed with the only possibility to advise the severe cases seek

prophylaxis options in fitness websites where vague stanozolol-containing aimed for body-building food supplements were marketed online. FFP remained the only possibility for acute HAE attacks, again with very low percentage of the attacks being actually treated.

Many HAE patients were forced to seek better healthcare conditions, and decided to immigrate to other European

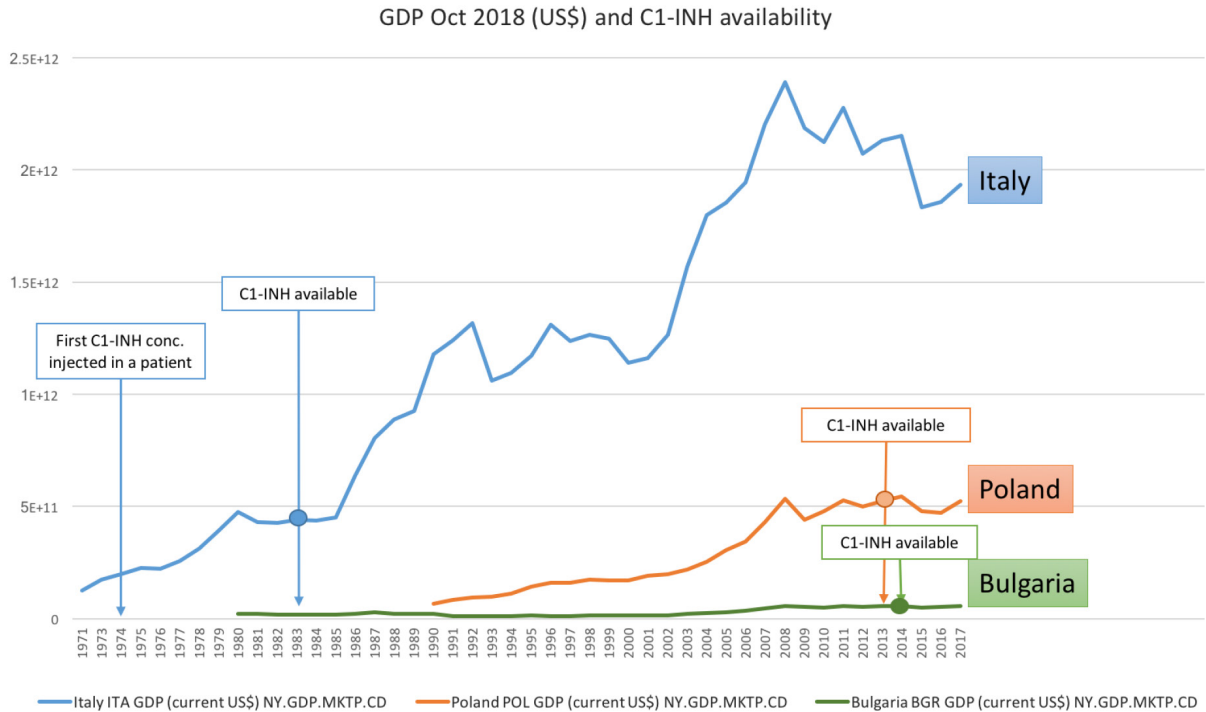


Fig. 2. GDP and C1-INH availability

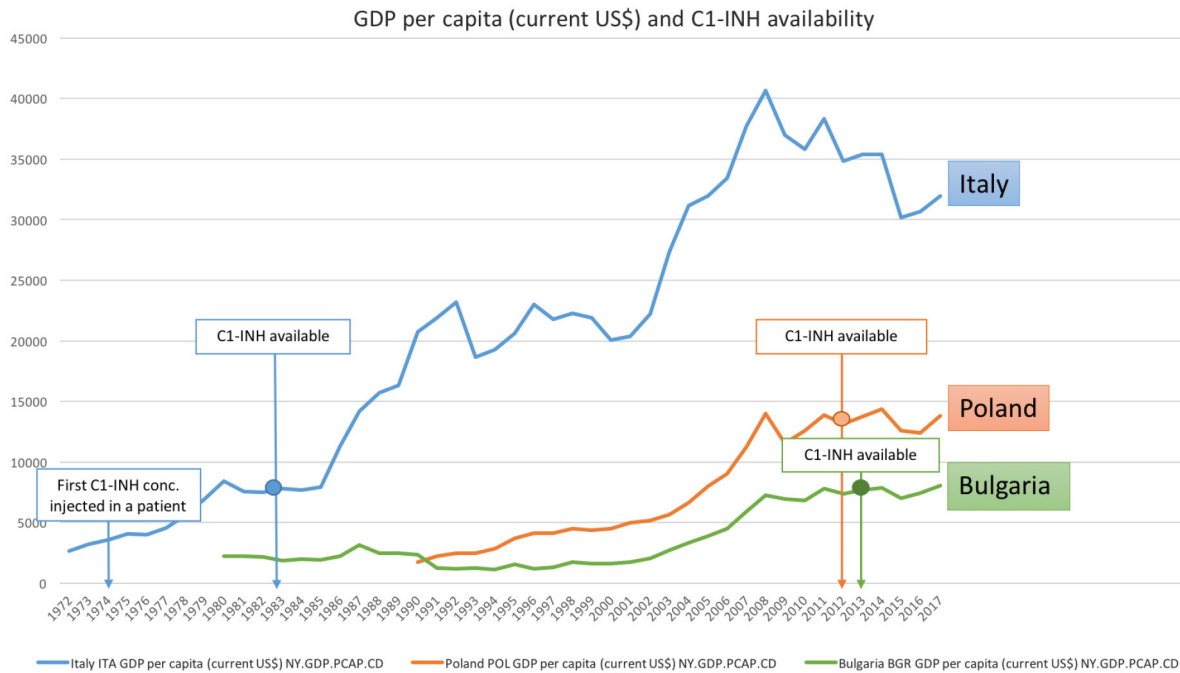


Fig. 3. GDP per capita (current US\$) and C1-INH availability (source data.worldbank.org)

Legend: GDP - gross domestic product;

Italy: C1-INH first injected in 1974; C1-INH generally available since 1983;

Poland: Rh Ruconest since 2013, pd Berinert 500 since 2014, icatibant since 2015;

Bulgaria: C1-INH (rh Ruconest and pd Berinert 500 registered in 2013 and reimbursed since 2014)

countries where modern treatment options for HAE were available (e.g. Italy, Austria, Germany, Spain, Portugal). As a result, a significant number of the diagnosed HAE families were lost for follow-up with no clear evidence up-to-date what was the fate of the family.

In 2013 registration of the first C1-INH concentrate was accomplished (rhC1-INH, Ruconest, and thereafter, pdC1-INH, Berinert 500), and started to be reimbursed during 2014. The drugs are indicated for acute episodes of HAE with no limit of localization, or severity of the attacks. Lives of C1-INH-HAE patients gradually improved with less hours with angioedema, better quality of life, and ameliorated possibility to maintain working and leisure activities. Future improvement would come when various treatment options by terms of route of administration, as well as, option for LTP for relevant cases are available.

Healthcare and economic specificities of HAE and future perspectives

In the last decade, the development of new, disease-specific therapies to treat HAE has revolutionized patient management. However, the cost of these treatments remains high and availability differs by country and region [60, 61]. The development of new specific drugs for treatment of HAE was made possible by researchers and pharmaceutical industry and via the orphan drug policies now available in the European Union and the United States. Nevertheless, countries differ by terms of economic indicators and healthcare status, and this is also demonstrated by HAE medication availability in regions throughout the European Union, as well. For example, Western economies helped sustained drug development and disease investigation to bring available treatment possibilities for HAE patients worldwide. As exemplified in Figure 2, the first injection of C1-INH concentrate extracted from human plasma for investigational purposes was conducted in Italy back in the beginning of 1974. Since then, HAE treatment significantly changed, together with knowledge about the pathomechanisms attributing to the disease. Another example is HAE specific drug availability in Poland and Bulgaria (Figure 2 and 3): introduced approximately when the countries' gross domestic product (GDP) and GDP per capita indicators became equal to that of Italy when HAE treatment was generally available back in 1983. Another point of view could be that HAE-specific treatments became generally available when rising C1-INH therapies started to be widely marketed in new regions around the world, as drug production could be sustainably maintained.

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Finally, return of granted investments and bringing HAE treatments to a more affordable price by modern technologies would help distribute treatment options further in regions where even nowadays the only life-saving option for C1-INH-HAE patients remains human plasma on demand.

COMMENTARY

Although, several new therapies for acute attacks of hereditary angioedema, and prophylaxis for patients with recurrent episodes have been introduced in the past decade, C1-INH-HAE remains a complex disease with a significant physical, psycho-social, and economic burden for both affected patients, their families, and the society in general. Not all treatments are appropriate for all patients, neither is the availability secured throughout different regions of the world, nor even throughout different parts of Europe.

Research is ongoing to improve HAE diagnosis and selection of individualized therapy for every patient in order to optimize clinical outcomes. Still, the disease has a serious economic impact with high direct and indirect costs, and high expenses related to the new therapies developed for patients to reduce symptoms and attack recurrence. As a result, treatment of HAE is often complicated by economic barriers and optimal management obstacles that must be overpassed to provide the best care for the patients with this rare disease.

KEY POINTS

- C1-INH-HAE is a multi-faceted disease that affects each patient's life differently and with various burden even in the same patient over the time of his life.
- Specific HAE treatments are nowadays effective and safe to treat both acute angioedema manifestations, as well as, prevent recurrence of attacks.
- C1-INH-HAE remains a complex disease with a significant physical, psycho-social, and economic burden to both affected patients, their families, and the society in general.
- Availability of HAE specific medications is not ubiquitously distributed across-the-borders, neither throughout European countries, nor worldwide.
- Effective disease management is often complicated by economic barriers and optimal treatment obstacles that must be overpassed to provide the best care for the patients with this rare disease.

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