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REVIEW

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Current and emerging biologics for the treatment of hereditary angioedema

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ABSTRACT

Introduction: Hereditary angioedema due to C1-INH deficiency (C1-INH-HAE) is a rare disease with unpredictable, self-limiting and localized swelling episodes involving the cutaneous and subcutaneous tissues. In the last decade, the spectrum of the possibilities to control the disease has considerably changed with the development of biologic therapies making necessary a careful evaluation of the differences among current and emerging treatments to properly optimize the management of patients.
Areas covered: This review serves to summarize the literature regarding the use of biologics for the treatment of C1-INH-HAE. Medications already available on the market and new drugs in different phases of development are addressed.
Expert opinion: the advent of biologic therapies dramatically improved the lives of patients with C1-INH-HAE although further improvement is still needed. Whether this is cost/effective will be answered in the next years when we will see if these major advances will benefit the majority of the patients.

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1. Introduction

Increasing knowledge on disease pathophysiology allows developing specific 'biologic therapies'. More or less restrictive definitions of biotherapeutics can be found. Here we consider as biologic therapies those treatments that specifically target a biologic function. These types of biologics can be extracted from living organisms as plasma-derived products, produced from specifically modified organisms, as recombinant products and monoclonal antibodies, but also synthetized to interfere with enzymatic function as well as to modify protein synthesis.

1.1. Biologic therapies

C1 inhibitor deficiency (C1-INH-HAE) is characterized by episodes of angioedema that last 2–5 days and resolves spontaneously. Outside from these episodes, clinical abnormalities are not apparent. Thus, treatment of HAE patients can be addressed to revert attacks (on-demand treatment, ODT) or to prevent recurrences (long-term prophylaxis treatment, LTP). Prophylaxis can also be used to prevent symptoms in conditions at high risk as surgical procedures (short-term prophylaxis, STP). Several drugs are already on the market for these purposes and others are under investigation. Available treatments prevent disease mortality and reduce disease burden. However, the high variability of the disease calls for further development to treat affected subjects safely and precisely.

In 1963, Donaldson et al. [1] discovered C1 inhibitor deficiency as genetic defect causing HAE and shortly thereafter, this protein, extracted from human plasma, became the first therapeutic options for these patients. Evolving from the original plasma product C1-INH has been adapted for subcutaneous administration to facilitate replacement therapy for attack prophylaxis. The same protein is now available as recombinant product from transgenic rabbits.

When it became clear that bradykinin was the principal mediator of angioedema symptoms in C1-INH deficiency, therapies started to be designed to targeted bradykinin production/activity. This category of pharmaceuticals now includes the antagonist of the bradykinin B2 receptor (BK B2R) icatibant; ecallantide, a recombinant selective inhibitor of the bradykinin releasing enzyme plasma kallikrein (pK); the anti-pK monoclonal antibody lanadelumab; the small pK inhibitory molecule, BCX 7353.

It is also clear, now, that Factor XII (FXII or Hageman factor) has a central role in activating the kallikrein-kinin system, which produces bradykinin [2,3]. This prompted the development of monoclonal antibodies to block activated Factor XII (FXIIa).

A number of therapeutic options targeted to block bradykinin are now available or under development for HAE (Tables 1 and 2). The availability of the treatment is different by country according to the local regulation [4]. These products reach the target using different mechanisms (Figure 1). The variety of interventions let envisage a future optimal tailoring of the treatments to different phenotypes and personal needs [5]. Here we will review the characteristics of these therapeutics.

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Article highlights

- The spectrum of biologic therapies has dramatically widened over the last decades, paralleling the progress of biotherapeutics in other fields, such as autoimmune and neoplastic diseases.
- Current biologic treatment options for hereditary angioedema include plasma-derived and recombinant C1-INH, recombinant new proteins and monoclonal antibodies (as ecallantide, lanadelumab and monoclonal antibodies blocking FXIIa) as well as synthetic peptides and small molecules (as icatibant, BCX 7353 and KVD900).
- The therapeutic options for children have recently widened and include not only pdC1-INH but also icatibant.
- Among emerging promising treatments is also gene therapy, namely SERPING1 replacement and antisense oligonucleotide inhibiting prekallikrein.
- Possible limitations to the use of biologic therapies are due to the risk of immunogenicity (even though rare) and to direct-indirect costs (which might be dampened in the long term, also thanks to self-administration).

This box summarizes key points contained in the article.

2. Plasma-derived and recombinant C1 inhibitors

2.1. Plasma-derived C1-INH

The first C1-inhibitor concentrate purified from pooled human plasma dates back to 1974, prepared by the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (now Sanquin Blood Supply Foundation) [6]. Marketing authorizations in Europe started in 1985, while in the U.S., it became available only in 2008.

In Italy, between 1979 and 1985, a C1-INH preparation from Immuno Vienna was available, for compassionate use to treat severe life-threatening attacks in HAE patients. No virucidal measures were available at that time for plasma products, and wide transmission of hepatitis C virus (86% of exposed subjects), but no HIV, was associated to this preparation [6]. Starting from the eighties, policies for donors' selection and the introduction of specific manufacturing processes, drastically reduced the risk of viral infection from blood products. Since 1985, different plasma-derived C1-INH (pdC1-INH) preparations were registered in Europe for acute treatment of HAE attacks, and no further evidence of infection related to these preparations has ever been reported [6–9]. Despite the extended use of pdC1-INH, the first registrative study was published in 2009 [7]. It was a randomized, placebo-controlled, double-blind study that compared the efficacy of pasteurized C1 esterase inhibitor concentrate (Berinert®, CSL Behring) with placebo in the treatment of single, acute abdominal or facial attacks in patients with HAE. This trial demonstrated that the median time to onset of symptom relief was significantly shorter with C1-INH 20 U/kg (0.5 h) than with placebo (1.5 h; $p < .005$). Moreover, safety and tolerability of pdC1-INH were confirmed and no seroconversions were observed for HIV, hepatitis virus or human B19 virus. According to the results of the above-mentioned trial, the posology of pdC1-INH concentrate is based upon weight, with 20 units/kg body weight given as slow injection (5–10 min) through a peripheral vein. Most patients undergo resolution of the attack after the first ODT and fewer than 5% of the attacks require a second administration [10]. Pharmacokinetic parameters were calculated in HAE patients receiving intravenous injections of C1-INH concentrate in an

Table 1. Treatment options for hereditary angioedema due to C1-INH deficiency.

Drug category	Name	Therapeutic indication	Route of administration	Level of development
Replacement therapy				
Plasma-derived C1 INH	Berinert®, Cinryze®	ODT- STP- LTP	Intravenous	On the market
Recombinant C1 INH	Ruconest®	ODT-STP	Intravenous	On the market
Plasma-derivedPlasma derived C1 INH, low volume	Haegarda®	LTP	Subcutaneous	On the market U.S. only
Synthetic peptides				
Bradykinin B2 receptor antagonist	Firazyr®	ODT	Subcutaneous	On the market
Recombinant new protein				
pKallikrein inhibitor	Kalbitor®	ODT	Subcutaneous	On the market U.S. only
Small molecule				
pKallikrein inhibitor	BCX 7353	ODT-LTP	Oral	Phase III LTP/Phase 2 ODT
pKallikrein inhibitor	KVD 900	ODT	Oral	Phase I study
ASO to reduce prekallikrein production	IONIS-PKK$_{Rx}$	LTP	Subcutaneous	Phase I healthy volunteers
Generation 2 + ligand-conjugated ASO to reduce prekallikrein production	IONIS-PKK-L$_{Rx}$	LTP	Subcutaneous	Phase I healthy volunteers
Monoclonal antibodies				
Fully human mAb targeting pKallikrein	Lanadelumab (Takhzyro)	LTP	Subcutaneous	On the market U.S. only
Fully human mAb targeting FXIIa	CSL 312	LTP	Subcutaneous	Phase II study
Gene therapy				
SERPING1	ADVM-053	LTP	Intracellular delivery of virus vectors	Preclinical

Legend: C1 INH: C1 inhibitor; HAE hereditary angioedema; ODT: on-demand treatment; STP: short-term prophylaxis; LTP: long-term prophylaxis; pKallicrein: plasma kallikrein; mAb: monoclonal antibody; ADVM: adeno-associated virus vectors; ASO Antisense oligonucleotide

Table 2. HAE-specific treatments.

Drug (molecule), route of administration	Commercial name	Subjects and therapeutic regimen for prophylaxis	Subjects and therapeutic regimen for acute attacks
pdC1-INH, I.V.	Berinert 500 and 1500 IU, CSL Behring	Adults, adolescents, and children; pregnancy [b] 20 IU/kg, twice weekly	Adults, adolescents, and children; Pregnancy [b] 20 IU/kg
pdC1-INH, I.V.	Cinryze, Shire	Adults and adolescents; 1000 IU, twice weekly (up to 2500 IU, but no more than 100 IU/kg)	Adults and adolescents; 1000 IU, (additional 1000 U at discretion of physician)
Low-volume pdC1-INH, S.C.	Haegarda, CSL Behring	Adults and adolescents; 60 IU/kg, twice weekly	–
rhC1-INH Conestat alfa I.V.	Ruconest Pharming	–	Adults and adolescents; 50 IU/kg up to 4200 U (if≥84 Kg)
Rh mAb targeting plasma kallikrein, S.C.	Lanadelumab Shire	Adults and adolescents; 300 mg, twice or once monthly	–
Bradykinin B2 receptor antagonist Icatibant, S.C.	Firazyr Shire	–	Pre-filled syringe 30 mg prefilled
Ecallantide, Kallikrein antagonist, S.C.	Kalbitor Dyax Corp.	–	Vial 10 mg; 30 mg (3 mL) administered in 3 separate 10 mg (1 mL) injections
Oral molecule targeting plasma kallikrein, P.O.	BCX7353 [a] Avorlastat, Biocryst	Adults 110–150 mg daily	Adults 750 mg

[a] – under phase III investigation
[b] – not registered for LTP but historically and often used in clinical practice.
Legend: i.v. intra venous; S.C.: subcutaneous; P.O.: oral administration.

attack-free interval: the elimination half-life (t½) was 33.3 ± 19.8 h. Another preparation of plasma-derived, nanofiltered C1-INH has also been shown to be effective for acute treatment of HAE [11]. This study also tested efficacy in preventing attacks and showed that 1000 U given i.v. every three to four days resulted in 50% reduction of attack rate and significant decrease in severity and duration of breakthrough attacks. An open-label multicenter extension study enrolling 146 C1-INH-HAE subjects confirmed initial data showing that treatment optimization needs individual dose adjustment [12]. A study evaluating escalating doses of Cinryze® prophylaxis revealed that up to 2500 U this product was well tolerated and reduced attack frequency in the majority of patients [13].

It is largely documented that efficacy of all ODTs is maximized by early administration [14–16]. Thus, patient is encouraged and educated to self-administer on-demand therapy at attack onset.

For STP 1000 U Cinryze® should be given within 24 h of the procedure and 1000 U Berinert® within 6 h of the procedure, being administration close to or immediately before the procedure a reasonable choice.

PdC1-INH is treatment of choice for ODT, STP, and LTP for pregnant women [17].

Before the recent phase 3 multicenter trial demonstrating the efficacy and safety of icatibant also for the pediatric population [18–20], pdC1-INH was the only available drug for treatment of acute attacks and STP (and seldom LTP) in children with C1-INH-HAE [10,21].

Cumulative experience in clinical trials and in practice, makes evident that pdC1-INH has an excellent safety profile. Reported adverse effects are rare and mild, including headache and fever, together with unusual allergic reactions characterized by edema, urticaria, itching and, in a very few circumstances, anaphylactic shock [22].

During the first 3 years in the U.S. market, 10 serious thrombotic events were reported as associated to i.v. Cinryze® given for LTP [23]. Those thrombotic events were ascribed to indwelling devices, as port-a-cath, for i.v. delivery and not to the drug itself.

So far, there is no evidence that repeated use of pdC1-INH can induce a resistance towards the drug.

In 2014 a prospective, randomized, open-label, crossover study was conducted by Martinez-Saguer et al. to evaluate the pharmacokinetics of the i.v. formulation of pdC1-INH after subcutaneous versus intravenous administration in subjects with mild or moderate HAE during an attack-free interval [24]. The study demonstrated that the mean relative bioavailability of functional C1-INH after subcutaneous administration was almost 39.7% and C1-INH antigen as well as C4 antigen levels were comparable to C1-INH activity levels in terms of relationship between the two routes of administration.

A formulation of pdC1-INH (CSL830), volume-reduced (500 U/mL) for subcutaneous use, was tested in the COMPACT phase II trial, demonstrating to be well tolerated and able to provide a dose-dependent increase in physiologically relevant functional C1-INH plasma levels [25].

The subsequent phase III study, evaluated twice-weekly s.c. administration of either 40 IU/kg or 60 IU/kg in leading. Along with the endpoints of clinical efficacy, the trial tested the

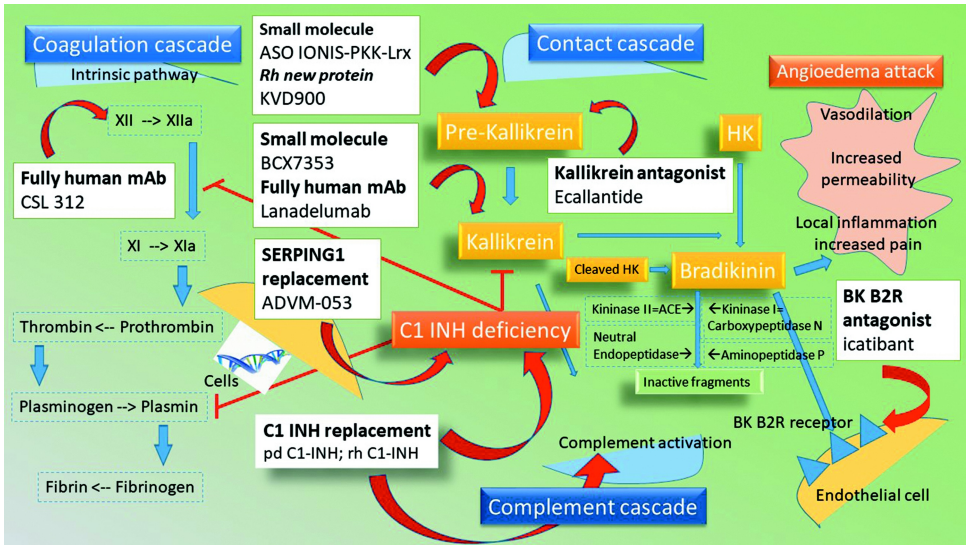

Figure 1. Site of action of current and emerging biologics for the treatment of hereditary angioedema.

INH: inhibitor; pd-: plasma derived; rh: recombinant; mAb: monoclonal antibody; ADVM: adeno-associated virus vectors; ASO IONIS-PKK Antisense oligonucleotide: ASO inhibiting Pre-kallikrein; BK B2R: bradykinin beta2 receptor; ACE: angiotensin-converting enzyme. The white squares contain the treatment options. The red arrows indicate the site of action of each medication.

capacity of this treatment to maintain patients on C1-INH functional plasma levels of 40% of normal value, a level predicted to be protective from angioedema attacks. The number of attacks per month was 1.2 in the 40 U/Kg group, 0.5 in the 60 U/Kg and 4.0 in the placebo. C1-INH plasma levels reached a steady state after three weeks of treatment. At 60 U/Kg mean C1-INH function in plasma was 48% (range 38–60) with dose-dependent reduction in attack risk [26–28]. FDA approved 60 U/Kg of subcutaneous C1-INH (Haegarda®) twice per week for prophylaxis of attacks in patients with HAE due to C1-INH deficiency.

2.2. Recombinant human C1-INH

Recombinant human C1 inhibitor (rhC1-INH, Conestat alpha, Ruconest®, Pharming Technologies B.V., Leiden, The Netherlands) is obtained through a purification process of transgenic New Zealand white rabbits' milk. The drug has been evaluated for its efficacy for treatment of C1-INH-HAE patients during acute angioedema attacks in several studies, including three double-blind, placebo-controlled efficacy studies [29,30] and five open-label studies [31–35]. Treatment resulted in rapid attack resolution and no relapses or rebound suggesting, that despite a shorter half-life (approximately 2 h), rhC1-INH has an activity comparable to that of the plasma products. A meta-analysis of trials using pd- or rhC1-INH showed that efficacy mainly relays on the infused amounts and not on the pharmacokinetic characteristics.

Accordingly, one open-label and one double-blind, randomized, placebo-controlled study showed that rhC1-INH is effective in preventing attacks when given intravenously once or twice per week [35,36]. The mean number of attacks of HAE over 4 weeks was significantly reduced with rhC1-INH twice weekly, and once weekly, versus placebo, with mean differences of – 4.4 attacks and – 2.8 attacks, respectively [36]. In addition, small case report series confirmed efficacy in LTP and in STP before deemed invasive medical procedures [37].

The development plan of the company indicates new approaches for subcutaneous, intramuscular and transdermal patch delivery [https://www.pharming.com/release-annual-report-2017/]. The safety data analyses about rhC1-INH demonstrate that the drug is generally safe and well tolerated when administered for treatment and prevention of HAE attacks. The adverse event profile found in the randomized, placebo-controlled studies was similar for patients treated in the rhC1-INH and placebo treatment groups. There was no increase in the incidence of treatment-emergent adverse events with higher rhC1-INH dose (50 and 100 IU/kg), administration of additional rhC1-INH doses for an attack, or with repeated treatment of subsequent attacks [31]. The most common adverse reactions (≥2%) reported in all clinical trials were headache, nausea, and diarrhea.

Although the drug is considered generally safe, important for clinical practice is to avoid its use in patients who have rabbit allergy due to potentially serious allergic reactions, which has happened within 3 min after administration of rhC1-INH in a single healthy volunteer with a pre-existent (retrospectively known), non-disclosed rabbit dander allergy [38].

Immunogenicity of rhC1-INH was extensively tested throughout the clinical development programs, supporting that rhC1-INH has low potential to induce anti-C1-INH antibodies or anti-host-related impurities (HRI) response. Confirmed antibodies against C1-INH or HRI were observed infrequently and were not associated with clinical symptoms indicating hypersensitivity or changes in rhC1-INH efficacy [39]. There was no association between treatment-emergent adverse events or new acute HAE attacks and the presence of any confirmed anti-C1-INH or anti-HRI antibodies.

No anti-rabbit IgE antibodies were reported elevated with treatment with rhC1-INH, and no severe hypersensitivity reactions

were reported beyond the single case in the phase 1 study, and in the post-approval phase.

3. Recombinant new protein and monoclonal antibodies

3.1. Ecallantide for ODT

Ecallantide (Kalbitor®, Dyax, Cambridge, MA) is a potent and specific inhibitor of plasma kallikrein. It is a recombinant 60-amino acid long protein synthesized in the yeast *Pichia pastoris* [40–43]. Development studies (EDEMA0, EDEMA1, EDEMA2, EDEMA3 – double-blind and repeat dosing, EDEMA4, and DX-88/19) investigated the use of ecallantide in patients with hereditary angioedema [40,41,44]. The results for 30 mg subcutaneous injection of ecallantide were superior to placebo and provided sustained relief up to 24 h after treatment [40,41] when administered within 8 h of onset of a moderate to severe HAE attack in patients ≥10 years of age. It is now registered in U.S. for acute HAE manifestations in patients 12 years of age, or older, with a dose of 30 mg (3 separate vials of 10 mg, 1 ml) for subcutaneous administration [Kalbitor (ecallantide) – short product characteristic of the drug]. The use of the drug is associated with hypersensitivity reactions in up to 10.8% of the cases (8.7% when administered subcutaneously and 17.9% intravenously). These hypersensitivity reactions fulfill the criteria for systemic hypersensitivity (type 1 anaphylactic or anaphylactoid reactions), in up to 4.4% of the cases symptoms began within 1 h of drug exposure. Due to hypersensitivity reactions in the development studies, the drug is to be administered by a health-care professional experienced to treat both anaphylaxis and HAE.

3.2. Lanadelumab for LTP

Lanadelumab (DX-2930) is a recombinant, Chinese hamster ovary cell-expressed, fully human IgG1, kelight-chain, monoclonal antibody that was discovered by screening an antibody phage display library21 against purified pK [45,46].

It is a potent (Ki ¼ 125 pM) and specific inhibitor of pK. As for other monoclonal antibodies, the pharmacokinetic profile allows one subcutaneous injection of lanaldelumab to inhibit pK for at least two weeks. Lanadelumab was first evaluated in a single-center, double-blinded study in 32 healthy subjects randomized to receive a single subcutaneous administration of the drugs [45]. In this first evaluation, no dose-limiting toxicity was registered. Major and commonly reported adverse events were headache. At different doses (0.1-, 0.3-, 1.0-, and 3.0-mg/kg dose groups) mean elimination half-lives were 20.6, 16.8, 17.6, and 21.2 days, respectively. Dose- and time-dependent inhibition of pK was evident.

After this preliminary data a phase 1b, multicenter, double-blind, placebo-controlled, multiple-ascending-dose trial was conducted [47]. Thirty-seven patients with HAE due to C1-INH deficiency were randomly assigned in a 2:1 ratio to receive either lanadelumab (24 patients) or placebo (13 patients), in two administrations 14 days apart and in different dose groups (30 mg, 100 mg, 300 mg or 400 mg). The efficacy measure was the rate of attacks of angioedema within the period of 8–50 days after administration of the treatment compared with the placebo group.

Most common adverse events, after injection site pain, were headache, the mean elimination half-life was 2 weeks. Lanadelumab was completely effective in resetting the number of attacks in the totality of patients in the 300-mg dose group and in 82% of the 400-mg dose group compared to placebo. The pivotal phase III, multicenter, randomized, double-blind, placebo-controlled study [HELP Study ClinicalTrials.gov. Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE. https://clinicaltrials.gov/ct2/show/NCT02586805. Accessed 10 February 2017] enrolled up to 120 patients to further assess the safety and efficacy of lanadelumab to prevent acute angioedema attacks and now it has been published [48]. Patients were treated for 26 weeks with subcutaneous lanadelumab at 4 different regimens: 150 mg every 4 weeks, 300 mg every 4 weeks, 300 mg every 2 weeks, or placebo. All patients received injections every 2 weeks, the primary efficacy end point was the number of attacks. Compared with placebo, the most effective treatment regimen was 300 mg every 2 weeks with a difference in the attack rate per month of −1.71 (P < 001) compared with placebo.

Patients who completed the double-blind study were continued into the long-term open-label extension that enrolled additional 100 new patients [HELP Study Extension ClinicalTrials.gov. Long-term Safety and Efficacy Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE. https://clinicaltrials.gov/ct2/show/NCT02741596. Accessed 10 February 2017] [49]. Lanadelumab is now approved in U.S. E.U. for HAE LPT at doses of 300 mg every two weeks.

3.3. Monoclonal antibodies blocking factor XIIa

The fully human anti-FXIIa monoclonal antibodies (mAb) 3F7 is a potent and highly specific inhibitor of the proteolytic activity of FXIIa. 3F7 binds to rabbit, mouse and human activated FXII. Administration of 3F7 abrogated skin edema induced by contact activation triggered by mast-cell released heparin in mice. 3F7 was also shown to abolish bradykinin-mediated increase of vascular permeability induced by the angiotensin-converting enzyme (ACE) inhibitor captopril in C1-inhibitor-deficient mice. Comparison of 3F7 with current HAE therapeutics in these murine edema models revealed that 3F7 has potent and prolonged efficacy. CSL312, a variant of 3F7 with improved affinity and potency, effectively inhibited dextran sulfate triggered FXII contact activation and bradykinin formation in plasma of healthy donors and HAE patients. FXIIa, besides cleaving FXI and inducing fibrin production, cleaves plasma prekallikrein to pK, which in turn cleaves high molecular weight kininogen to release bradykinin [Zhihui (Helen) Cao, Biondo M, Rayzman V et al. Development and Characterization of an Anti-FXIIa Monoclonal Antibody for the Treatment of Hereditary Angioedema. J Allergy Clin Immunol Feb 2015 135 (2S), Page AB194 Abstract].

A Multicenter, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in subjects with HAE will start recruitment soon [https://www.clinicaltrials.gov/ct2/show/NCT03712228?term=csl312&rank=1].

4. Synthetic peptides and small molecules

4.1. Icatibant

Icatibant, previously designated as HOE140, is a synthetic peptide highly specific antagonist for BK-B2R. It was shown to inhibit bradykinin-induced vasodilation in humans. Furthermore, increased vascular permeability in C1-INH knockout mice was reversed by using icatibant. A phase II study first demonstrated the clinical usefulness of antagonizing bradykinin binding to BK-B2R in HAE [50]. It is approved for treatment of attacks in HAE patients since 2008 in Europe and since 2011 in the U.S.

The efficacy (e.g. reduction in symptom severity, onset of primary symptom relief and complete relief) and safety of icatibant for treatment of acute angioedema attacks was demonstrated by three double-blind, randomized, multicenter trials, comparing icatibant versus either placebo or tranexamic acid [51–53]. A recent phase III, multicenter, open-label, non-randomized, single-arm study showed that icatibant is safe, effective and well tolerated as ODT in the pediatric population (children and adolescents aged 2 years to less than 18 years) [18,54].

Icatibant is dispensed in pre-filled syringes of 3 ml containing 30 mg of the medication, which must be administered by slow subcutaneous injection, preferably in the abdominal region. Icatibant is indicated only for on-demand therapy of acute HAE attacks in adults, adolescents, and children aged 2 years and older. The half-life is about 1–2 h.

Even though a single injection of icatibant is usually sufficient to achieve full recovery, a second injection can be administered after 6 h if needed (and a third injection may follow after 6 additional hours, without exceeding the dose of three injections per day).

In children and adolescents the recommended dose of icatibant is based on body weight (10 mg for children from 12 kg to 25 kg body weight, 15 mg from 26 kg to 40 kg, 20 mg from 41 kg to 50 kg, 25 mg from 51 kg to 65 kg, 30 mg over 65 kg). The safety and efficacy of icatibant have not been established yet in children under 2 years of age or weighing less than 12 kg. The subcutaneous route of administration facilitates home treatment preventing vein access problems, often present in pediatric age [55].

The most common adverse reaction to icatibant is mild transient erythema and pain at the injection site. Gastrointestinal complaints (abdominal pain, nausea), headache, fever, asthenia, dizziness, and increase in transaminases have been rarely reported in patients using icatibant without prove of being drug related. Icatibant is contraindicated during acute ischemic events to avoid inhibition of bradykinin vasodilatory effect.

4.2. BCX 7353

It is a potent synthetic small molecule designed to block the enzymatic site of human plasma kallikrein activity. BCX7353 potently inhibits kallikrein activity, cleavage of HK in normal and HAE plasma, and suppresses the release of bradykinin after contact system activation on endothelial cells. In vitro potency and specificity of BCX7353 for plasma kallikrein leads also to a reduction in potency of FXIIa relative to IC_{50} for pK interfering with the coagulation cascade due to its steric analogy between the two enzymes [Chen X, Kotian P, Wilson R. Preclinical Characterization of BCX7353, an Oral Plasma Kallikrein Inhibitor, for the Treatment of Hereditary Angioedema. AAAAI Congress 2017 Abstract]

The first phase I study [Cornpropst M, Dobo S, Collier J, et al. BCX7353, a potent inhibitor of plasma kallikrein, shows sustained maximal enzyme inhibition when dosed orally once daily: results from a phase 1 trial in healthy subjects. J Allergy Clin Immunol 2016; 137: AB401. abstract] conducted in 92 human healthy volunteers, evaluated the pharmacokinetics, pharmacodynamics, and safety of this pK inhibitor. Each healthy subjects received single (10, 30, 100, 250, 500 or 1000 mg) or multiple (125, 250, 500 mg x7 days or 350 mg x14 days), once-daily (QD) oral doses of BCX7353 or placebo. The half-life of BCX7353 was 50–60 h and, kallikrein inhibition was highly correlated to plasma concentrations. The adverse events reported were gastrointestinal and maculopapular rash demonstrating a good safety profile. The molecule was tested for its efficacy in the reduction of the number of angioedema attacks in an international, three-part, dose-ranging, placebo-controlled trial, where four doses of BCX7353 (62.5 mg, 125 mg, 250 mg, and 350 mg once daily) for the prevention of angioedema attacks over a 28-day period were evaluated [56]. In the 72 of the 77 patients who completed the trial the rate of confirmed angioedema attacks was significantly lower among patients who received BCX7353 at daily doses of 125 mg or more than among those who received placebo with confirmed mild gastrointestinal symptoms as the principal side effect. (Funded by BioCryst Pharmaceuticals; APeX-1 ClinicalTrials.gov number, NCT02870972.). A phase III randomized, double-blind, placebo-controlled, three-arm trial testing two doses of BCX7353 (110 mg and 150 mg) for prevention of angioedema attacks, started in march 2018 (APeX-2). The trial consider as a primary efficacy endpoint the rate of angioedema attacks over 24 weeks of study drug administration (ClinicalTrials.gov Identifier: NCT03485911)

The molecule was also tested for the treatment of acute attack at a dosage of 750 mg. Data from the preliminary phase of the study [https://www.epgonline.org/uk/news/initial-results-from-zenith-1-trial-of-bcx-7353-or-both-prophylactic-and-acute-treatment-of-hae-attacks—biocryst-pharma-.html Data from Pharmawand – Curated by EPG Health – Date added 6 September 2018] showed that patients who self-treated their HAE attacks on a blinded basis with oral BCX 7353 or oral placebo had improvement in symptoms and differences of the VAS scores as early as 1 h after oral BCX 7353 dosing, and were sustained through 24 h highlighting an attractive profile also for patients seeking an oral treatment for acute HAE attacks.

4.3. KVD900

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. KVD900

protects HK from ex vivo pK mediated cleavage in plasma from patients with HAE [Feener EP, Murugesan N, Robson PA et al. Results from a semi-automated capillary-based immunoassay. EAACI 26 May 2018–30 Munich]. KVD900 is under investigation in a phase I trial in healthy volunteers to evaluate its safety and tolerability [https://www.clinical-trials.gov]. Preliminary data suggest that KVD900 prevented the breakdown of kininogen in a dose-dependent manner in both HAE patients and in healthy volunteers and it was shown to be generally well tolerated at doses as high as 600 mg. It exhibits high solubility and high permeability with rapid uptake into the plasma and high plasma concentrations, these characteristics suites for a new ODT of acute HAE attacks in the next future. A phase II clinical trial for KVD900 is currently planned to start in late 2018 and to be completed in mid-2019 [http://ir.kalvista.com/node/7656/html].

5. Gene therapy

5.1. SERPING1 supplementation

Preclinical studies on the use of gene supplementation therapy to cure C1-INH-HAE provided promising results in a C1-INH deficient murine model presenting characteristics associated with HAE in humans [57]. Single systemic administration of extrachromosomal copies of the human C1-INH gene (SERPING1) into the mice cells through a transfer vector resulted in persistent human C1-INH plasmatic function and protection against increased vascular permeability. The long-term gene expression coupled to leakage relief suggests that long-lasting protective effect and, that this delivery system could offer long-term protection to individuals affected by C1-INH-HAE following a single administration.

In patients, efficacy and safety of gene therapy with adeno-associated virus (AAV) vectors have been demonstrated for both hemophilia B [58,59] and hemophilia A [60], maintaining protective levels of FIX and FVIII, respectively.

The challenge that has to be addressed in HAE individuals is to restore C1-INH synthesis in cells that already produce an altered form of C1-INH, which could potentially impair the expression of the wild-type one. The phase I/II advanced clinical trial, has now been discontinued. Although ADMV-043 was safely administered and well tolerated, protein expression did not meet a clinically meaningful level [http://investors.adverum.com/news-releases/news-release-details/adverum-biotechnologies-provides-program-updates]. On the other hand, a new study [60] shows that in a patient-derived fibroblasts, C1-INH secretion has been restored by vector administration of C1-INH gene, suggesting that it feasible to overcome the dominant negative disease mechanisms by gene supplementation. Nevertheless, Adverum announced that will not submit an Investigational New Drug application to FDA for ADVM-053 for the treatment of HAE by the end of 2018.

5.2. Antisense oligonucleotide (ASO) inhibiting prekallikrein

Ionis Pharmaceuticals is developing IONIS-PKK-LRx, an antisense drug designed to reduce the production of prekallikrein (PKK), as a prophylactic treatment for patients with HAE. A Phase 1 study in healthy volunteers has been completed. In this study, subjects treated with IONIS-PKKRx achieved dose-dependent reductions of up to 95% in PKK. Safety and tolerability profile of IONIS-PKKRx supports continued development. [Available from: http://www.ionispharma. com/pipeline/; https://www.bioportfolio.com/resources/trial/187317/Safety-Tolerability-Pharmacokinetics-and-Pharmacodynamics-of-IONIS-PKK-LRx-Administered-Subcutaneously-to.html].

6. Costs

Chronically recurrent attacks of C1-INH-HAE cause a consistent humanistic and economic impact of the disease for patients and their caregivers. Long-term consequences for education attainment and careers have been reported in HAE patients [61–63]. On the other side, available for HAE are very expensive with costs per treated attack, in E.U. around 1500 euro and for prophylaxis up to 250,000 euro per patient per year. In U.S. costs are 4–5 fold higher.

The perception that cost of treatment of rare diseases is inappropriately high compared to the total pharmaceutical expenditures and health-care costs is not completely correct. Based on an analysis conducted in the U.S. and E.U., the impact on costs is in line with the prevalence of these diseases in the population that is around 10%. Expenditures on orphan drugs for orphan indications was approximately $33.5 billion roughly reflecting the same proportion of pharmaceutical expenditures and only 1% of the total health-care expenditures [64].

The direct costs of treatment are considerably different worldwide. In several incoming countries the availability of new effective on demand and attack preventing treatments is often limited, nonetheless costs of not treating HAE appropriately are also quite high and difficult to estimate. It is hopeful that as the number of newly approved therapies to treat HAE will increase, the cost of therapy will decrease at the same time making treatment more accessible.

Trying to define the burden of the disease in the past years, patients were recruited from the US Hereditary Angioedema Association (HAEA) database [65]. Total annual per-patient costs were estimated at $42,000 for the average HAE patient. The amount of indirect costs was estimated to be $16,000 annually for the average patient considering the rates of missed work and loss of productivity.

A recent prospective observational study conducted in Italy over a period of one year in 2014 [66] reported total costs amounted to €1.58 million, equivalent to slightly more than €11 900 per patient per year. The average cost for a single attack was €1183 (SD €789) including drug costs, emergency department visits, and diagnostic tests. The differences in the costs reported are explained by the different reimbursement modalities, even if differences in prescription of the drugs cannot be directly compared. However, these data are meant to get over in the next few years since the numbers (and costs) of new treatment are remarkable and their cost-effectiveness is going to be evaluated as soon as possible based on real-life data.

Another important topic to be addressed regarding the evaluation of costs is the impact of health-care networking and organization. Spanò et al. [67] highlighted that an

alternative and innovative treatment strategy, i.e. self-administration, by focusing on treatment outcomes and costs, can create value for patients and health-care systems.

Despite cost savings, when the treatment is self-administered or given in the home setting, in many countries treatment of attacks is only available in hospital and clinic settings.

7. Unmet need for treatment of hereditary angioedema

Frequency, location, and severity of angioedema recurrences in HAE patients remain unpredictable due to incomplete understanding of initial events leading to attacks. Thus, variability of clinical phenotypes remains obscure and adapting available treatments to such variability far from being perfect.

Current treatments are effective in minimizing the risk of death, but cannot guarantee disease control to all patients. Side effects and intravenous route of administration limit the use of LTP treatments that are diffusely available.

ODTs are on average very effective in reducing the length of the attacks, but not all patients can learn i.v. self-administration and other present short-term relapse/recurrence of treated attacks.

High costs prevent access to treatment for several countries and question sustainability were available.

8. Expert opinion

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The term hereditary angioedema refers to genetic diseases primarily characterized by recurrent angioedema that create risk of death due to asphyxia and temporary disability resulting in poor quality of life. Variants in four different genes can lead to HAE. For one form, C1-INH-HAE, the pathogenetic mechanism and the mediator are identified. When the mechanism of disease is known, treatments can be specifically targeted to block such mechanism.Current biological treatment options for HAE include plasma derived and recombinant C1-INH, targeted therapies as icatibant and ecallantide but emerging treatment as monoclonal antibodies, small molecules and gene therapies are promising and near to be soon available.We prefer to consider 'biologic' not only therapies produced by living organisms, but also those that modify specific biologic conditions known to lead to a disease status. The era of recombinant DNA switched pharmacology from a biologic chemistry-based science to a biology-based science. The possibility to produce targeted antibodies demonstrated that it is possible to design a drug based on the action that we want to obtain. Thus, monoclonal antibody technique gave the first targeted biologic therapies and opened to the development of other biologic and non-biologic techniques to provide molecules with predetermined specific biologic activities.

In addition the development of gene therapy with SERPING1 supplementation is a new concept in the approach to the treatment of the disease. Nowadays, the treatment of C1-INH-HAE patients is based on an on-demand strategy, alone or in conjunction with long term prophylaxis. With the evolution of the gene therapy and, more generally biologic therapy, we can consider that the prophylaxis is extended to a very long period and, if effective, it is very close to reach a complete control of the disease and a great improvement in the quality of life of patients.

Looking at development of C1-INH-HAE, the disease mediator and the pathogenetic mechanism leading to its release was definitively proved in the 90s of the last century, the same time that was facing the expansion of biotecks aimed at developing techniques for drug designing. With this in mind, we can understand why a disease with a population prevalence around 1:50,000 has on the market 6 biologic products made with different techniques, a seventh one on phase 3 and additional ones on early clinical/preclinical development. Obvious question is: is this a virtuous example of how health care should progress? Such an obvious question has no obvious answer. We know the costs of drug development, and we know that society pays for health-care costs. We state the question, but we are not going to give an answer. As physicians treating HAE we can see that the advent of biologic therapies dramatically improved the lives of our patients and that we still need further improvement. Indeed current treatments are effective in minimizing the risk of death, but cannot guarantee disease control to all patients. Whether this is cost/effective will be answered in the next 10 years when we will see if these major advances will benefit the majority of the patients.

List of abbreviations

HAE:	hereditary angioedema
C1-INH:	C1 inhibitor
FXII:	Factor XII
HER2:	human epidermal growth factor receptor 2
ODT:	on demand treatment
LTP:	long term prophylaxis treatment
STP:	short term prophylaxis
BK B2R:	bradykinin B2 receptor
pK:	plasma kallikrein
FXIIa:	activated Factor XII
pd:	plasma derived
FDA:	food and drug administration
rh:	recombinant human
mAb:	monoclonal antibodies
ACE:	angiotensin-converting enzyme
HK:	high molecular weight kininogen
ADVM:	adeno-associated virus vectors
A1AT:	alpha-1 antitrypsin
ASO:	antisense oligonucleotide
PKK:	prekallikrein
U.S.:	United States
E.U.:	European Union
HAEA:	US Hereditary Angioedema Association

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