
Hereditary angioedema: a current state-of-the-art review, VIII: current status of emerging therapies

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Objective: To provide an overview on the current status of emerging therapies for hereditary angioedema (HAE) in the United States.

Data Sources: Summary statements were obtained from each pharmaceutical company regarding their agent.

Study Selection: Each agent is undergoing or has completed phase 3, double-blind, placebo-controlled trials.

Results: Berinert P, a purified, virus-inactivated, human plasma-derived C1 inhibitor (C1-INH) concentrate, is being investigated in 2 international, multicenter, prospective trials. Experience with this agent in Europe and Canada indicates it is effective and safe. Cinryze is a nanofiltered C1-INH replacement therapy demonstrated to be effective and safe in acute and prophylactic arms of a phase 3, double-blind, placebo-controlled study. Rhucin, a recombinant human C1-INH replacement therapy from transgenic rabbits, has been shown to be effective and safe in phase 2 and phase 2/3 studies, with an additional phase 3 study ongoing. DX-88 or ecallantide, a potent and specific inhibitor of plasma kallikrein, achieved all primary and secondary efficacy end points in a placebo-controlled, double-blind, phase 3 study, with a second phase 3 study ongoing. Icatibant, a potent and specific peptidomimetic bradykinin 2 receptor antagonist, was studied in 2 phase 3 trials: FAST 1 (For Angioedema Subcutaneous Treatment) did not achieve statistical significance for the primary end point but did so for secondary end points, whereas FAST 2 achieved statistical significance for primary and secondary end points.

Conclusions: The future treatment of HAE in the United States appears promising based on progress being made in drug development for this orphan disease.

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INTRODUCTION

Hereditary angioedema (HAE) is a relatively rare (1:10,000 to 1:50,000 prevalence) genetic disorder that is most commonly caused by either a deficiency of functionally active C1 inhibitor (C1-INH) or having functionally inactive C1-INH. It presents as acute recurrent attacks of soft tissue skin swellings, abdominal pain, and, occasionally, episodes of life-threatening upper airway obstruction.^{1–5} The major genetic deficiency in the disorder is either an absent or nonfunctional C1-INH, which regulates the complement, fibrinolytic, kallikrein, and plasmin pathways (Fig 1). This article is intended to update the reader about the current status of emerging drugs currently being studied in the United States for the treatment of HAE. Summary statements were obtained from each pharmaceutical company regarding their agent. Each agent is undergoing or has completed phase 3, double-blind, placebo-controlled trials. These drugs can be classified as C1-INH replacement therapies or kallikrein pathway modulators. Much of the data herein, yet to be published, are intended to familiarize the reader with these agents so they will be more knowledgeable about these treatments as they

become available in the United States. Table 1 summarizes different characteristics of these agents, which, along with Figure 1, should be referred to throughout this article.

C1 ESTERASE INHIBITORS

Berinert P

Replacement therapy with an intravenous pasteurized C1-INH concentrate is the recommended treatment in regions around the world approved for acute attacks of HAE. Berinert P (CSL Behring, Marburg, Germany) is a purified, virus-inactivated, human plasma-derived C1-INH concentrate that replaces the missing physiologic protein and, as such, is recommended as first-line therapy for the treatment of acute attacks of HAE and for short-term prophylaxis in several guidelines.^{6,7}

Berinert P is administered by slow intravenous infusion. One unit of C1-INH in Berinert P is equivalent to 270 mg or 2.5 μ M per liter of plasma.⁸ The usual dose for the treatment of an acute attack is 1 vial of Berinert P (containing 500 U); this can be increased to 1,000 U if required, which is often the case in patients with a body weight of more than 80 kg.⁹ Berinert P can be stored at room temperature; therefore, it can be kept with patients at all times. The median half-life of C1-INH in Berinert P is approximately 46 hours after infusion in C1-INH-deficient patients with mild HAE and 32 hours in patients with severe HAE.¹⁰ No relapse or rebound of attacks has been reported because of this long half-life.

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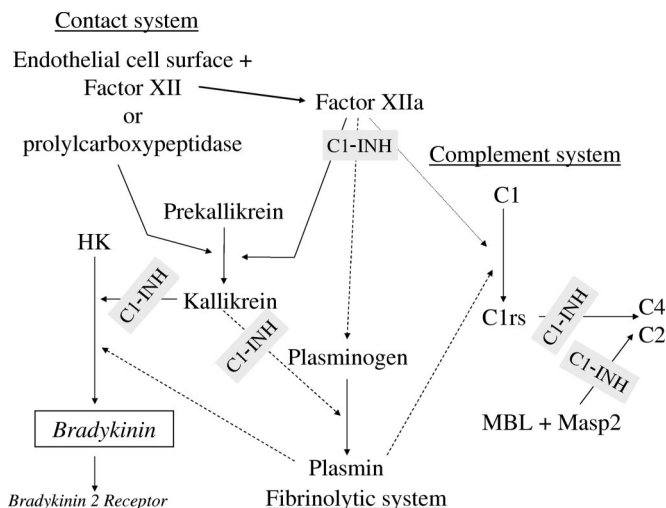


Figure 1. The contact, complement, and fibrinolytic systems. C1-INH indicates C1 inhibitor.

Beriner P is produced from pooled human plasma from US sources. The manufacturing process of Beriner P includes steps for elimination and inactivation of possible viral contaminants, which includes separating the C1-INH from cryodepleted human plasma by adsorption and precipitation steps; the purified material is then pasteurized by heat treatment for 10 hours at 60°C and then further purified by precipitation and chromatography, sterile filtrated, and lyophilized without preservatives. Furthermore, the pooled human plasma from which Beriner P is derived is subject to rigorous donor selection to exclude hepatitis A, B, and C, human immunodeficiency virus 1, and parvovirus 19. Examination of these processes has revealed high overall virus reduction factors for these manufacturing steps.^{8,11}

Beriner P has been shown to be effective in treating and preventing laryngeal edema, abdominal pain, and skin swellings of HAE due to C1-INH deficiency in a number of clinical studies and case reports.^{9,12–15} In all studies, all patients responded to treatment; a few patients required repeat administration of Beriner P to achieve complete resolution of symptoms. Relief from symptoms can occur from as early as 10 minutes after administration of Beriner P, and complete resolution of symptoms has been reported from approximately 1 hour after treatment, especially when treated early.^{9,14} Furthermore, a reduced duration of attacks is commonly observed after treatment with Beriner P.^{12,14} Beriner P is also effective for long-term prophylaxis of HAE, although this is outside its current license in Europe and Canada.¹⁶ Within this setting, administration of 500 U of Beriner P every 4 to 5 days results in patients remaining free of symptoms of HAE.¹⁶

Beriner P has been used in Europe and Canada for more than 20 years; therefore, a lot of postmarketing surveillance data are available. According to the Global Pharmacovigilance Department, Beriner P has demonstrated a good record

Table 1. Summary of Emerging Therapies for the Treatment of Hereditary Angioedema

Sponsor	Drug	Action	Route	Half-life, h	Safety	Study Phase	FDA status
CSL Behring	Beriner P	C1 esterase inhibitor	Intravenous	36–48	No serious adverse effects reported	Completed phase 3	NDA submission pending
Lev	Cinryze	C1 esterase inhibitor	Intravenous	36–48	No serious adverse effects reported	Completed phase 3	NDA submission pending
Pharming	Rhucin	Recombinant C1 esterase inhibitor	Intravenous	3	Very safe; theoretical concern for sensitization to rabbit proteins and anaphylaxis	Completed phase 3	Open label trial
Dyax	Ecallentide	Kallikrein inhibitor	Subcutaneous	2–4	Very safe; no evidence of anaphylaxis observed in phase 3 studies	Phase 3 study ongoing	Pending completion of trials
Jerini	Icatibant	Bradykinin 2 receptor antagonist	Subcutaneous	2–4	Local reactions at injection site; no serious adverse effects reported	Completed phase 3	NDA Submitted

Abbreviations: FDA, Food and Drug Administration; NDA, New Drug Application.

of efficacy and safety during this period. There have been no reports of viral transmission with the use of Berinert P, and adverse effects are uncommon, with fewer than 30 events reported, of which only 10 were thought to be directly related to treatment of 100 million units dispensed.⁸ Adverse effects that may be associated with Berinert P include anaphylactoid reactions (most thought to be related to too fast of an infusion rate or not allowing Berinert to come to room temperature before administration), the formation of inhibitory antibodies, localized redness at the injection site, and general reactions such as fever, chills, and headaches.^{8,9}

Clinical trials to evaluate the efficacy and safety of Berinert P are ongoing worldwide. The 2 International, Multi-center, Prospective, Angioedema, C1-INH Trials (IMPACT) have recently been completed in a large number of centers across Europe, the United States, and the rest of world. Both IMPACT 1 and IMPACT 2 trials demonstrated that Berinert P was effective and safe for treatment of HAE attacks in many locations including the abdomen and larynx (data on file). Berinert P is currently licensed for use in Germany, Austria, Switzerland, Hungary, Japan, and Argentina and on temporary use authorization in France. Furthermore, Berinert P can be used under the Special Access Programs in Canada and Australia.¹⁷

Cinryze

Lev Pharmaceuticals (New York, New York) is developing a nanofiltered C1-INH replacement therapy for the treatment and management of HAE. Building on more than 30 years of successful use of C1-INH in Europe, Lev has partnered with the Sanquin Blood Supply Foundation to develop C1-INH for the United States. The Lev product, a fourth-generation C1-INH, is being investigated in the United States for both the treatment of acute attacks of HAE and prophylaxis against HAE attacks.

Nanofiltration of plasma products provides additional safety margins and is particularly effective against nonenveloped viruses. The Lev product uses 2 serial 15-nm filters in the manufacturing process. Studies performed on this process showed mean log₁₀ reductions ranging from more than 8.7 to more than 19.1 log₁₀.¹⁸ Nanofiltration has also been shown to be effective in removing prions, further raising the safety profile of plasma proteins manufactured with this process.¹⁹

Lev has completed acute and prophylactic arms of a phase 3, double-blind, placebo-controlled study with nanofiltered C1-INH for the treatment of HAE and has ongoing open-label extension studies under way as well. End points of the short-term study include time to unequivocal relief and time to complete resolution of acute attack. End points for the prophylactic study include frequency of angioedema attacks and average severity of attacks. Both studies will investigate changes from baseline in serum C1-INH antigenic and functional levels. Lev anticipates publication of the combined results of this pivotal trial later this year.

Rhucin

Production of recombinant human C1-INH (rhC1-INH) (Rhucin; Pharming, Leiden, The Netherlands) with transgenic rabbits was started to improve the treatment options in patients with HAE. Major advantages of production of human C1-INH via recombinant DNA technology are that the recombinant material is not derived from a human source, that the production can more easily be controlled, and that the production can be scaled up to meet the requirements for the treatment of HAE and other potential indications.

A stable pharmaceutical product that contains highly purified rhC1-INH with less than 20 ppm of contaminants has been produced. rhC1-INH is highly similar to plasma-derived C1-INH because LC-MS peptide mapping data have revealed that there is approximately 70% recovery of the amino acid sequence of rhC1-INH and conformity to that of the expected amino acid sequence found with plasma-derived C1-INH. rhC1-INH is heavily glycosylated, which affects the half-life of this agent (approximately 3 hours). However, differential glycosylation does not affect the functional activity of rhC1-INH because the inhibitory potency of rhC1-INH toward target proteases C1s, kallikrein, factor XIa, factor XIIa, plasmin, and thrombin is not affected and has been shown to be comparable with that of plasma-derived C1-INH.^{20,21}

A phase 1 study of rhC1-INH was conducted to evaluate the adverse effects, safety, and pharmacokinetics of rhC1-INH in asymptomatic patients with HAE.²¹ Exclusion criteria included sensitization to rabbit. No drug-related adverse events or clinically significant changes in electrocardiography results, vital signs, and laboratory parameters were observed. All patients were exposed to rhC1-INH on 2 occasions without evidence of allergic hypersensitivity reactions or clinically significant antibody responses to rhC1-INH. One healthy volunteer who failed to disclose sensitization to rabbits experienced hives and wheezing after receiving rhC1-INH, which resolved without incident (data on file). Infusion at the 100-U/kg dose led to functional C1-INH levels in plasma of at least twice the normal level for approximately 2 hours and greater than 0.4 U/mL for approximately 9 hours. rhC1-INH displayed dose-dependent biologic activity by increasing the C4 level, which was approximately 2-fold at 12 hours after rhC1-INH at 100 U/kg, and decreasing levels of cleaved C4. The manufacturer recommends that patients receiving rhC1-INH not be sensitized to rabbits; therefore, this was an exclusion criterion for all phase 2 and 3 studies.

Phase 2 and phase 2/3 studies have shown safety and efficacy of rhC1-INH for the treatment of acute HAE attacks.²² The latest results from these studies further demonstrate safety and efficacy of rhC1-INH.²³ rhC1-INH at 100 U/kg was used to treat 21 HAE attacks in 14 patients. No clinically significant adverse events, changes in vital signs, safety laboratory parameters, or antibody responses to C1-INH or rabbit milk protein were observed. Both patients and physicians evaluated treatment with rhC1-INH as favorable compared with previous untreated attacks. The median time

to the beginning of relief was 30 and 60 minutes, as reported by physicians and patients, respectively. The median time to minimal symptoms was 4 hours. All treated attacks resolved completely within the observed 4-hour time frame and no relapses occurred. No difference in response was observed on first and repeated treatments.

In all clinical studies, more than 100 administrations of rhC1-INH have occurred. These administrations have illustrated the safety of the product. Furthermore, treatment with rhC1-INH promptly reduced the symptoms of acute attacks of HAE.

The safety, efficacy, and tolerability of rhC1-INH at 100 U/kg in treating acute attacks of HAE were evaluated in this recently completed randomized, placebo-controlled, double-blind, European multicenter study. An interim analysis of this study demonstrated a statistically significant superiority of rhC1-INH over placebo for both the primary efficacy end point (time to beginning of relief; $P = .0009$) and the secondary efficacy end point (time to minimal symptoms; $P = .0038$). The median time to the beginning of relief and the median time to minimal symptoms after treatment with rhC1-INH were 60 and 368 minutes, whereas beginning of relief and minimal symptoms with placebo occurred at 508 and 1,209 minutes, respectively. Patients receiving rhC1-INH achieved a 100% response rate compared with those receiving placebo who achieved a 36% response rate. In addition, the data provide positive reassurance for the safety of rhC1-INH with no new or unexpected safety findings, such as anaphylactic or anaphylactoid reactions. The interim analysis was forwarded to the Independent Data Monitoring Committee for evaluation. The Independent Data Monitoring Committee considered a placebo-controlled continuation of the study not advisable for ethical reasons. Based on this consultation, the sponsor has decided to stop the randomized, placebo-controlled part of the trial. The trial will continue as an open-label study, allowing patients who have been enrolled to receive open-label treatments.

KININ PATHWAY MODULATORS

DX-88 (Ecallantide)

DX-88 (ecallantide; Dyax Corp, Cambridge, Massachusetts) is a small 60-amino acid protein identified through Dyax's proprietary phage display technology and produced as a recombinant protein in *Pichia pastoris* yeast. DX-88 is a highly potent and specific inhibitor of plasma kallikrein.²⁴ Through inhibition of plasma kallikrein in the kallikrein-kinin system, an HAE attack may be stopped by limiting further activation of plasma kallikrein and the subsequent production of bradykinin.^{24–27}

The safety and efficacy of DX-88 have been evaluated in 8 completed clinical trials: 4 phase 1 studies in healthy adult volunteers, 3 phase 2 studies, and 1 phase 3 study (which had a double-blind and an open-label, repeat-dosing phase) in patients 10 years and older with angioedema.^{26,27} More than 300 moderate to severe attacks of angioedema that involved

all anatomic sites (abdominal, peripheral, laryngeal, and combinations) have been treated in 175 patients with HAE and 2 with acquired angioedema. Early on, a few cases of allergic reactions to DX-88 have been reported, and in some instances specific IgG and IgE antibodies have been observed. However, the clinical explanation for these reactions remains unclear. Furthermore, there have been no reported cases of anaphylactic reactions in subsequent phase 3 clinical trials. In early clinical studies, DX-88 was administered to patients with HAE via intravenous or subcutaneous routes.²⁶ DX-88 is now administered to patients with HAE exclusively by subcutaneous injection.

The primary and secondary efficacy end points for patients treated with DX-88 were achieved at 4 hours after treatment in the randomized, placebo-controlled, double-blind portion of the phase 3 study, Evaluation of DX-88's Effect in Mitigating Angioedema 3 (EDEMA3), which involved 72 patients with moderate to severe HAE attacks (pharmaceutical data on file). The trial end points were comprehensive measures of symptom outcomes and were not based on evaluation of single symptoms. The primary end point was the treatment outcome score, an evaluation of the change in all symptoms in which a positive score represents symptom improvement. The 2 secondary end points were the mean symptom complex severity score, an evaluation of total symptom burden in which a negative change from baseline indicates symptom improvement, and time to significant overall improvement (pharmaceutical data on file). Among 71 patients who completed their assessments, the mean treatment outcome score for those who received 30 mg of DX-88 subcutaneously was significantly higher than for those who received placebo (53.8 vs 18.5; $P = .021$), and the mean change from baseline in mean symptom complex severity score was significantly lower (-0.96 vs -0.48 ; $P = .024$). More patients who received DX-88 reported significant overall improvement within 4 hours than did those who received placebo (19 of 35 [54.3%] vs 11 of 36 [30.6%]). The median time to significant overall improvement was 149 minutes for patients who received DX-88 and more than 240 minutes for those who received placebo ($P = .044$). Improvement of patient symptoms within 4 hours in this study was consistent with results obtained from an earlier placebo-controlled study and previous open-label studies in patients with HAE treated with DX-88 (pharmaceutical data on file).

DX-88 was well tolerated by patients with HAE in the double-blind phase of the phase 3 study, and tolerability was consistent with previously completed studies. Most adverse events were mild to moderate.^{28,29} Anaphylactic or anaphylactoid reactions have not been observed in clinical trials. Treatment-related adverse events, based on the investigators' assessments, were experienced by 4 patients (11.1%) in the ecallantide group and 5 patients (13.9%) in the placebo group. No patients experienced treatment-related serious adverse events and none withdrew because of adverse events.

DX-88 was well tolerated by patients who received subcutaneous injections as treatment for acute HAE attacks. In

the phase 3 EDEMA3 study, all of the primary and secondary end points were achieved. More patients with HAE who received DX-88 reported significant overall improvement within 4 hours of treatment than did those who received placebo. Dyax is currently conducting a second phase 3 study of DX-88 and anticipates Food and Drug Administration approval at the end of 2008.

Icatibant

Icatibant (Jerini, Berlin, Germany) is a potent and specific peptidomimetic antagonist of the bradykinin B2 receptor (BK2R). It is a synthetic decapeptide that contains 5 nonproteinogenic amino acids with a similar structure to bradykinin. It is stable and not degraded by the 2 main bradykinin-cleaving enzymes, carboxypeptidase and angiotensin-converting enzyme. Icatibant is an extremely potent BK2R antagonist with the same affinity for BK2R as bradykinin itself, across species including humans. It is specific for BK2R and does not interact with bradykinin B1 receptors (BK1R) or with receptors of other peptides (eg, angiotensin II, substance P, and neurokinin A).³⁰

The BK2R is constitutively expressed in most normal tissues, whereas the BK1R is absent or expressed at low levels in most tissues. Both receptors are G protein coupled. Binding of bradykinin to the BK2R on endothelial cells causes vasodilation and acute pain.^{31,32}

Plasma bradykinin levels are increased during HAE attacks.³³ Because microvascular leakage is mediated by bradykinin, this may explain the edema formation during HAE attacks.^{34,35} Further evidence for bradykinin being the key mediator in HAE is derived from animal studies. Using C1-INH knockout mice, it was demonstrated that blocking bradykinin at any level invariably resulted in reverting the increased vascular permeability characterizing these animals.³⁶ Icatibant has been shown to reverse increased vascular permeability in C1-INH knockout mice and to inhibit bradykinin-induced vasodilation in humans.³⁷

Icatibant has been investigated for the treatment of a variety of diseases, including asthma. Recently, clinical efficacy of Icatibant in the treatment of HAE was demonstrated in an early proof-of-concept, phase 2 clinical trial. Fifteen patients with 20 acute cutaneous or abdominal HAE attacks were treated with Icatibant. After intravenous and subcutaneous administration of Icatibant, symptom intensity decreased rapidly within 4 hours. The treatment considerably shortened the duration of attacks compared with similar untreated attacks in the same patients.³⁸ This study became the basis for advancing Icatibant into 2 phase 3 clinical trials (FAST 1 and FAST 2 [For Angioedema Subcutaneous Treatment]) for the subcutaneous treatment of HAE.

FAST 1 was a double-blind, randomized, placebo-controlled trial that enrolled 56 patients with moderate to severe cutaneous or abdominal HAE attacks from the United States, Canada, Australia, and South America, whereas FAST 2 was a double-blind, randomized, comparator-controlled (tranexamic acid) trial that enrolled 74 patients with acute HAE

attacks from 11 European countries and Israel. Patients with laryngeal attacks were treated open label with Icatibant. After completion of the double-blind treatment, patients of both studies could be treated open label with Icatibant in an open-label extension phase. The primary efficacy end point in both studies was the median time to clinically significant symptom relief and was referred to as *time point of relief of at least 30% (TOR30⁺)*. Secondary efficacy end points encompassed among others the time to first symptom improvement and the time to almost complete symptom relief, which was referred to as *time point of relief of at least 90% (TOR90⁺)*.

In FAST 1 the median time to clinically significant symptom relief was 2.5 hours for Icatibant and 4.6 hours for placebo ($P = .142$), whereas in FAST 2 it was 2.0 hours for Icatibant and 12.0 hours for tranexamic acid ($P < .001$). The lack of significance in FAST 1 for the primary end point was believed to be due to an unexpectedly high response to placebo in patients with abdominal pain. Efficacy of Icatibant was confirmed by the time to first symptom improvement, which was highly statistically significant in favor of Icatibant in both studies (FAST 1: 0.8 vs 16.9 hours, $P < .001$; FAST 2: 0.8 vs 7.9 hours, $P < .001$). TOR90⁺ was reached after 8.5 and 10 hours for Icatibant in FAST 1 and FAST 2, respectively.

Eleven patients with laryngeal attacks who were treated open label with Icatibant showed in both studies a clinically relevant reduction in the time to first symptom improvement (FAST 1: 0.6 hour; FAST 2: 1.0 hour). Despite the short elimination half-life (1.2 hours) of Icatibant compared with that of C1-INH (36.1 hours), 87.1% of the attacks in the open-label extension phase of FAST 1 and 91.0% of the attacks in FAST 2 required only 1 injection of Icatibant. Between 8.6% (FAST 2) and 11.6% (FAST 1) of the attacks required only a second injection.

Icatibant proved to be safe in both studies, with no drug-related serious adverse events and no clinically relevant changes in laboratory parameters, vital signs, blood pressure, heart rate, electrocardiographic results, or physical examination findings. Most common adverse effects were local reactions of mild intensity at the injection site with erythema and swelling or to a lesser percentage burning, itching, and pain. These symptoms resolved spontaneously within a few hours. To date, more than 580 HAE attacks have been treated with subcutaneous Icatibant without any drug-related serious adverse events, underlining the favorable safety profile of Icatibant.

Both the Food and Drug Administration and the European Medicines Agency have granted orphan drug status to Icatibant for the treatment of HAE and other forms of angioedema. A marketing authorization application was filed with the European Medicines Agency in August 2007. The filing of a New Drug Application for Icatibant in the treatment of hereditary angioedema to the Food and Drug Administration is planned for 2007.

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