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Current and Emerging Management Options for Hereditary Angioedema in the US

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Abstract

Hereditary angioedema (HAE) is a rare disorder characterized by recurrent attacks of swelling that may involve multiple anatomical locations. In the majority of patients, it is caused by a functional or quantitative defect in the C1 inhibitor (C1-INH), which is an important regulator of the complement, fibrinolytic, kallikrein-kinin and coagulation systems. Standard treatments used for other types of angioedema are ineffective for HAE. Traditional therapies for HAE, including fresh frozen plasma, ε-aminocaproic acid and danazol, may be well tolerated and effective in some patients; however, there are limitations both in their safety and efficacy.

Several novel therapies have completed phase III trials in the US, including: (i) plasma-derived C1-INH replacement therapies (Berinert P® and Cinryze®); (ii) a recombinant C1-INH replacement therapy (conestat alfa; Rhucin®); (iii) a kallikrein inhibitor (ecallantide [DX-88]); and (iv) a bradykinin-2-receptor antagonist (icatibant). Both Berinert P® and Cinryze® are reported to have excellent efficacy and safety data from phase III trials. Currently, only Cinryze® has been approved for prophylactic use in the US. US FDA approval for other novel agents to treat HAE and for the use of Cinryze® in the treatment of acute attacks is pending.

Hereditary angioedema (HAE) is a rare disorder characterized by recurrent attacks of swelling that may involve the peripheral extremities, abdomen, genitalia, face, oropharynx or larynx. Prevalence of the disease is reported to be from 1 : 10 000 to 1 : 50 000.[1] Originally described in the late 1800s, the pathogenesis of HAE remained a mystery until the mid-20th century.[2] Most patients have either a quantitative (type I) or a functional (type II) defect in the C1 inhibitor (C1-INH), which is an important regulator of the complement, fibrinolytic, kallikrein-kinin and coagulation systems.[3,4] While in the majority of patients HAE results from autosomal dominant inheritance, 25% represent *de novo* mutations.[5] There is also a third type of HAE characterized by normal C1-INH levels.[6] Most cases of type III HAE are estrogen dependent, with a significant number possessing missense mutations in Hagemann factor (Factor XII).[7] The frequency of attacks can vary greatly, with some individuals experiencing attacks as often as several times a week.

Standard treatments for other types of angioedema, including epinephrine (adrenaline), corticosteroids and histamine H_1 or H_2 receptor antagonists, are ineffective for HAE. [8] Traditional therapies for HAE, including fresh frozen plasma (FFP), ε-aminocaproic acid and danazol, either have limited efficacy or a negative safety profile.[9] Several novel

therapies have completed or are completing phase III trials in the US; however, to date, only Cinryze® [1] has been approved for prophylactic use for HAE in the US. The purpose of this review is to summarize the current state of HAE treatment in the US and to highlight the exciting new therapies that are currently under investigation. The pathogenesis of this complex disease is discussed elsewhere.[10] However, figure 1 provides a brief synopsis of potential pathophysiological mechanisms involved and the target sites for investigational therapies.[10]

1. Current Treatment

Treatment of HAE is best subdivided into the following three areas: (i) long-term prophylaxis; (ii) short-term prophylaxis; and (iii) management of acute attacks. In Europe and Canada, the availability of C1-INH concentrate for many years has altered traditional treatment algorithms for HAE in terms of acute treatment, short-term prophylaxis and, in some cases, long-term prophylaxis.[1] In this article, we restrict discussion to treatment paradigms applicable to the US.

1.1 Long-Term Prophylaxis

1.1.1 Avoidance of Triggers

While it is not entirely clear what precipitates HAE attacks in many patients, it is important that patients be educated regarding avoidance of known triggers.[9] Trauma, even as minor as that associated with dental procedures, is a well known cause of attacks.[1,12] Stress can also be a precipitating factor and should be minimized when possible.[12] While it has been proposed that infections may also provoke some episodes, this association has yet to be definitively established.[12,13] Contraindicated medications include ACE inhibitors, because they have a propensity to increase bradykinin levels, and estrogens, including oral contraceptives and hormone replacement therapy.[12,14] Many women also report attacks that are linked to their menstrual cycle.[15]

1.1.2 Attenuated Androgens

In patients with frequent attacks (greater than once every 3 months) or with a history of life-threatening laryngeal attacks, long-term prophylaxis should be considered.[9] The only medications available for long-term prophylaxis in the US include attenuated androgens and antifibrinolytics. Careful attention to the benefit-risk ratio must be given when selecting these therapies.[9]

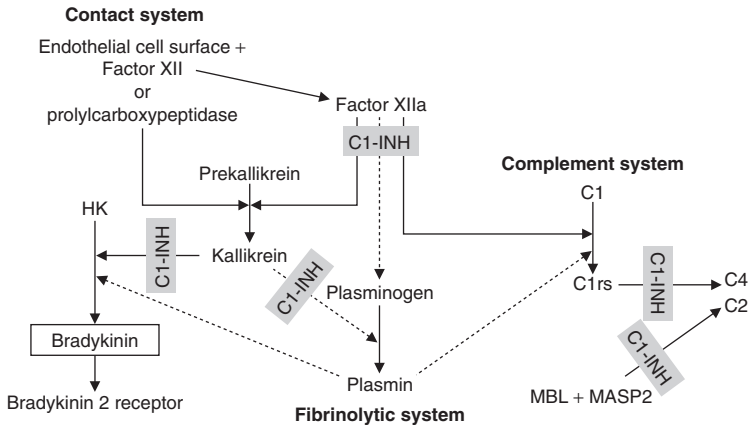

Fig. 1. The contact, complement and fibrinolytic systems (reproduced from Bernstein,[11] with permission). **C1-INH** = C1 inhibitor; **HK** = high molecular weight kininogen; **MASP** = MBL-associated serine protease; **MBL** = mannose-binding lectin; dashed lines indicate possible pathways of action.

1 The use of trade names is for identification purposes only and does not imply endorsement.

The most frequently used anabolic steroids for HAE in the US include danazol, stanozolol and oxandrolone. These drugs are synthetic 17-α-alkylated androgens and are preferred over older agents such as methyltestosterone because they are associated with fewer adverse effects.[16,17] Attenuated androgens are thought to exert their effects in HAE by increasing hepatic synthesis of C1-INH.[18,19] Nevertheless, this explanation has been challenged by the fact that patients with type II (normal quantitative but abnormal functional C1-INH levels) and type III (normal quantitative and functional C1-INH levels) HAE may also benefit from danazol.[20,21]

Multiple studies support the efficacy of danazol as long-term prophylaxis for preventing HAE attacks.[18,20,22,23] The first of these studies, published in 1976, was a small, double-blind, placebo controlled trial in which only one attack occurred in over 46 courses of treatment versus 44 attacks over 47 courses of placebo.[18] The largest retrospective trial, which included 118 patients treated for a duration of 2 months to 30 years (11 years on average), reported that 111 patients had some response to danazol.[20] Nevertheless, 17 patients continued to have 11 or more attacks per year despite taking the drug.

While some patients may experience significant clinical benefit from attenuated androgens, the adverse effects of these medications greatly limit their use. For example, in the retrospective study by Bork et al.,[20] 93 of 118 patients (78.8%) reported at least one adverse event. Fifty patients experienced weight gain, with one patient experiencing a 45 lb (20.5 kg) increase during the first year on danazol. Other frequent adverse effects included menstrual irregularities, virilization, headache, myalgia, depression and acne. Less frequent but serious adverse events included myocardial infarction, stroke, acute pancreatitis, biliary hamartoma and liver cell adenoma. The most frequently observed laboratory abnormalities were elevated liver function tests and cholesterol.[20] These results are, for the most part, in accordance with other published reports.[16,23,24] Some series have also reported hypertension as a frequent adverse effect at higher doses.[24] The association between danazol and the development of liver cell adenoma, and possibly hepatocellular carcinoma, has prompted many authors to recommend yearly ultrasonic examination of the liver for patients taking this medication.[20] Liver function tests and cholesterol levels should also be monitored regularly.[16]

Lower doses of danazol (<200 mg/day) are associated with significantly fewer adverse effects.[20,23] It is therefore recommended that physicians titrate down to the lowest effective dose to prevent attacks. Danazol and other androgens are relatively contraindicated during pregnancy and childhood.[25,26] Stanozolol is generally considered to have similar efficacy and safety to danazol, although some reports suggest it may be less effective.[26-28] Oxandrolone may be considered in children requiring attenuated androgen therapy, given that it is reported to cause less virilization and may have a better safety profile than either danazol or stanazolol.[26,29]

1.1.3 Antifibrinolytics

The antifibrinolytics include ε-aminocaproic acid and tranexamic acid, both of which are available in the US. These drugs have shown some efficacy in randomized controlled trials; however, they are considered to be less effective for long-term prophylaxis than attenuated androgens.[9,30,31] It is not well understood how antifibrinolytics act to prevent HAE attacks. They are primarily used in situations where the adverse effects of attenuated androgens preclude their use and, in particular, may be considered in children.[26] Typical adult dosage is 1–1.5 g three to four times per day.[32] Paediatric dosage is generally 0.17–0.43 g/kg/day.[26] Major adverse effects include an increased risk of thrombosis and increased muscle enzyme levels leading, in some cases, to rhabdomyolysis.[33,34] ε-Aminocaproic acid is listed as pregnancy class C.

1.2 Short-Term Prophylaxis

Short-term prophylaxis for HAE should be instituted prior to any planned invasive procedure, including dental procedures. Administration of FFP as a means to provide the patient with C1-INH prior to trauma has been shown to decrease the risk of precipitating an attack in several case series.[35,36] On the basis of expert opinion, the recommended dose is 2 units given 1 hour prior to the planned procedure.[1] Danazol can also be given for short-term prophylaxis, typically at a dosage of 600 mg/day for

4–7 days before the procedure and for several days afterwards.[9,37]

1.3 Acute Treatment

Outside of clinical trials, acute therapy for HAE in the US consists of FFP, antifibrinolytics or high-dose androgens. The use of FFP as acute therapy is supported by case reports and case series in the literature. There is a reported risk of worsening acute symptoms by administering FFP, although it appears to be relatively small.[9,38,39] On the basis of anecdotal evidence, ε-aminocaproic acid is also routinely given intravenously for acute attacks, although clinical trials to support its use in this manner are lacking. High doses (usually double the normal dose) of attenuated androgens can be administered to help modify the course of an acute attack, but their effects are delayed for at least 1–2 days after they are started.[1,9]

2. Emerging Therapies for Hereditary Angioedema (HAE) in the US

Break-through angioedema attacks do occur in a significant number of patients despite administration of preventive therapy. Moreover, while laryngeal attacks are relatively rare compared with attacks at other organ sites, the prevalence of these life-threatening attacks over the life-time of an individual is fairly high. In addition, the significant adverse effects of existing therapies greatly limit their use.[40] Therefore, consistently reliable and safe treatments for acute attacks of HAE represent a major unmet need in the US. For the remainder of this review, we discuss the current status of emerging therapies in the US.

Clinical trials investigating these therapies have been designed initially as double-blinded, placebo-controlled studies focused on acute intervention of HAE attacks followed by open-label use in many cases. A few trials have also investigated the use of these agents as prophylactic therapy to prevent attacks.

Drugs that are currently under investigation for the treatment of HAE in the US can be divided into the following three categories: (i) C1-INH replacement therapies; (ii) a kallikrein inhibitor; and (iii) a bradykinin receptor antagonist. The C1-INH replacement therapies can be further subdivided into plasma-derived products, including Berinert P® and Cinryze®, and a recombinant human C1-INH, conestat alfa (Rhucin®). Ecallantide (DX-88) is a kallikrein inhibitor and icatibant is a bradykinin-2-receptor (BK2R) antagonist. All of these drugs have already completed or are nearing completion of phase III trials presently. An overview of their properties and current status is provided in sections 2.1–2.3 and summarized in table I. It may be helpful to refer to figure 1 regarding the site of action for each of these therapies as they are discussed.

2.1 C1 Inhibitor Replacement Therapies

Plasma-derived C1-INH has been used to treat acute attacks of HAE since the 1970s. Since their introduction, plasma-derived products have dramatically improved the outcome of laryngeal attacks in HAE patients in countries where they are available.[41,42] The first double-blind, placebo-controlled trial documenting the efficacy of C1-INH replacement in the acute setting was published in 1996.[43] The time to onset of symptom improvement was 55 minutes in the treatment group versus 563 minutes for those receiving placebo. A second, randomized, controlled trial published in the same article also demonstrated efficacy for C1-INH given every third day as prophylactic therapy to prevent attacks. Prior to 1986, transmission of hepatitis C virus from plasma-derived C1-INH was a major problem. However, since the introduction of a heat-treatment step in the manufacturing process, the risk of viral transmission has been substantially reduced.[41] Currently, there are two plasma-derived C1-INH agents and one recombinant C1-INH agent being investigated in the US, which are discussed in the following sections.

2.1.1 Berinert P®

Berinert P® is purified human C1-INH, prepared by a European company (CSL Behring, Marburg, Germany) from the pooled plasma of US donors. It has been commercially available in Europe and Canada for two decades, and has excellent post-marketing efficacy and safety data. It is recommended as first-line therapy for acute attacks and short-term prophylaxis in several international guidelines, and is currently licensed for use in Germany, Austria,

Table I. Summary of emerging therapies for the treatment of hereditary angioedema (HAE) [reproduced from Bernstein,[11] with permission]

Company	Agent	Action	Route	Half-life (h)	Safety	Study phase	US FDA status
CSL Behring	Berinert P®	Plasma-derived C1-INH	Intravenous	36–48	No serious adverse effects reported	Completed phase III	NDA submission pending for acute HAE
Lev Pharmaceuticals	Cinryze®	Plasma-derived C1-INH	Intravenous	36–48	No serious adverse effects reported	Completed phase III	Approved for prophylactic use in the US
Pharming	Rhucin®	Recombinant C1-INH	Intravenous	3	Very safe; contraindicated if rabbit allergy	Completed phase III	Open-label trial
Dyax	Ecallantide	Kallikrien inhibitor	Subcutaneous	2–4	Very safe; no evidence of anaphylaxis in phase III trials	Completed phase III	NDA submission pending; open-label trials
Jerini	Icatibant	Bradykinin-2-receptor antagonist	Subcutaneous	2–4	Local injection site reactions; no serious adverse effects reported	Completed phase III	New phase III trial likely to start after negative opinion by FDA

C1-INH = C1 inhibitor; **NDA** = new drug application.

Switzerland, Hungary, Japan and Argentina. It is also available commercially in France, Canada and Australia.[1,11,41]

The efficacy of Berinert P® has been well documented in the literature. While double-blinded studies of patients with laryngeal attacks are difficult to conduct, there is good evidence from retrospective and open-label trials that the drug performs very well when utilized for this purpose.[42,44,45] One study found that the time to onset of action ranged from 10 minutes to 4 hours, with a mean duration of laryngeal symptoms of approximately 15 hours versus 100 hours for those who did not receive the drug.[42] Studies have shown similar efficacy for abdominal attacks and skin swellings.[46] There are no published incidences of patients who did not respond to treatment, although repeat administration of Berinert P® has been required in some patients for complete resolution of symptoms.[11]

Although its use as long-term prophylaxis is off-label even in countries where it is commercially available, there are published reports documenting that the drug is effective when used in this fashion.[43] Administration of one vial (500 units, where one unit represents the amount of C1-INH activity in 1 mL of plasma) every 4–5 days has been shown to prevent attacks.[47]

Berinert P® is administered at room temperature by slow intravenous infusion. One vial (500 units) is often sufficient, although patients over 80 kg frequently require two vials (1000 units).[46,48,49] The median half-life of the drug for a mild and severe attack of HAE is 46 and 32 hours, respectively.[50] This long half-life may account for the absence of reported relapse or rebound attacks with this medication.[11,48,51] Berinert P® has a very good safety profile based on extensive post-marketing data and information provided by the Global Pharmacovigilance Department.[11] There are only ten reported adverse effects deemed directly related to the drug for over 100 million units administered.[48] These have included anaphylactoid reactions, formation of C1-INH antibodies, localized redness at the injection site, fevers, chills and headaches. Anaphylactoid reactions have been attributed to rapid infusion rates and not allowing the drug to warm to room temperature before administration.[46,48]

Preparation of Berinert P® includes multiple steps to decrease the risk of viral transmission. Donors for pooled plasma are carefully screened and individual donations are analysed for hepatitis A, B and C, HIV and parvovirus 19. After separation of the C1-INH from cryo-depleted human plasma by adsorption and precipitation, the purified material is pasteurized by heat treatment for 10 hours at 60°C, then further purified by precipitation and chromatography, sterile filtration and lyophilization without preservatives.[48] Since its introduction over 20 years ago, there have been no reported incidences of viral transmission from Berinert P®.[52]

Barring unforeseen new developments, there is good reason to believe that Berinert P® will soon be commercially available in the US. Data from IMPACT (International, Multicenter, Prospective, Angioedema, C1-INH trials) 1 and 2 supported the use Berinert P® for acute HAE attacks involving multiple locations, including laryngeal and abdominal attacks.[53] IMPACT 1 was a double-blind, randomized, three-arm trial designed to assess the efficacy and safety of Berinert P® at doses of 10 and 20 U/kg versus placebo in 125 patients with moderate to severe abdominal and facial HAE attacks. The study met its primary endpoint of showing that Berinert P® provided a significant difference in time to onset of symptom relief relative to placebo. At a dose of 20 U/kg, the time to symptom relief was 30 minutes, compared with 90 minutes for placebo ($p = 0.0025$). The drug was effective for both moderate and severe attacks, irrespective of body location.[53] IMPACT 2 was a prospective, open-label study, which allowed for treatment with Berinert P® for attacks involving multiple potential body locations (peripheral, facial, abdominal, laryngeal). Treatment of 355 attacks in 39 patients with HAE revealed similar results to IMPACT 1, with patients experiencing improvement in HAE-related symptoms irrespective of body site.[11] Consistent with post-marketing surveys, safety data from the IMPACT trials were reassuring in that there were no drug-related serious adverse events and no reports of viral transmission from Berinert P®.[11,53] As of October 2008, submission of a new drug application to the US FDA is pending for Berinert P® to be used for the treatment of acute HAE attacks.[11]

2.1.2 Cinryze®

The second plasma-derived C1-INH replacement product, Cinryze®, is produced by Lev Pharmaceuticals (New York, USA) in partnership with the Sanquin Blood Supply Foundation. Sanguin, formerly the Central Laboratory of the Dutch Red Cross, produces a similar product known as Cetor®, which has been on the market in the Netherlands for 11 years. As with Berinert P®, Cinryze® is derived from pooled plasma of US donors. However, additional steps in the purification process are undertaken with Cinryze® to provide added safety. Specifically, Cinryze® undergoes nanofiltration by two serial 15-nm filters, which offers protection against non-enveloped viruses and prions.[54] This process is estimated to provide prion reduction capabilities >9 $\log_{10}$.[55]

Lev Pharmaceuticals reports that more than 180 patients with HAE have participated in their studies, with over 60 000 doses of Cinryze® administered. The company has completed two double-blind, placebo-controlled, phase III, multicentre trials in the US, known as the CHANGE (C1 inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating efficacy) trials. These trials investigated outcomes of treatment with Cinryze® for both acute attacks of HAE and for long-term prophylaxis. Cinryze® is currently available through ongoing open-label trials for acute and prophylactic indications.[56]

Based on current dose recommendations in Europe and results from pharmacokinetic studies, the dose of Cinryze® administered in the CHANGE trials was 1000 units, given as a one time dose with the possibility of repeat administration if necessary for acute treatment, or twice weekly for long-term prophylaxis. The studies were open to patients aged ≥6 years, and permitted treatment for attacks involving the face, larynx, gastrointestinal tract and genitourinary system. An open-label rescue dose was available at any time in the acute treatment trial for severe laryngeal symptoms or after 4 hours if subjects did not respond to the initial blinded dose. Those who did not respond to the initial rescue dose within 1 hour were eligible for a second open-label dose. The acute treatment trial met its primary endpoint, the median time to unequivocal onset of relief, with a significant p-value to 0.026.[56]

Patients who completed the acute treatment CHANGE trial and had at least two attacks per month were eligible for the prophylactic trial. This was a randomized, double-blind, placebo-controlled, crossover, multicentre study in which subjects received 12 weeks of study drug or placebo for a total of 24 weeks. Patients could receive open-label rescue dose administration for acute attacks as necessary. Twenty patients completed the entire 24-week study. The study successfully met its primary endpoint, which was defined as the normalized number of attacks of angioedema per day during each treatment period using subjects as their own controls. The mean number of attacks over a 12-week period on placebo was 12.7, while those receiving Cinryze® experienced a mean of 6.3 attacks (a 51% reduction; $p < 0.0001$). Secondary endpoints of the trial were also all statistically and clinically significant. These included the severity of attacks, mean number of open-label injections administered for acute attacks, duration of attacks and number of days of swelling.[56]

The safety profile of Cinryze® based on the US phase III studies, ongoing open-label studies and post-marketing data in Europe appears to be very good. The most common adverse events in the randomized and open-label trials were upper respiratory infections and sinusitis. No drug-related serious adverse events were reported and there were no clinically significant changes in laboratory testing or viral surveillance studies. An unexpectedly high number of patients were found to have antibodies to C1-INH at screening and treatment in the CHANGE trials. However, confirmatory tests did not support these results in all but two patients, both of whom had positive tests at screening. Lev Pharmaceuticals is testing participants in ongoing open-label trials and will report their findings to the FDA.[56]

While randomized trials regarding the use of Cinryze® and other C1-INH replacement therapies for short-term prophylaxis have not been conducted, there are case reports documenting the efficacy of its use in this setting. One recently reported case involved a 51-year-old man with HAE who received 1000 units of Cinryze® 1 hour prior to mitral valve reconstruction surgery requiring a cardiopulmonary bypass pump. There were no complications during the surgery, which lasted for over 4 hours. The patient did develop some mild swelling of his lower back and lips on postoperative day 2, but these symptoms quickly resolved with administration of a second dose of 1000 units of Cinryze®. The remainder of his postoperative course was unremarkable and he did not experience any clinically relevant laboratory changes. This represented the first successful use of C1-INH prophylactically and acutely in a patient undergoing cardiac surgery requiring a cardiopulmonary bypass pump.[57]

In May 2008, Lev Pharmaceuticals announced that the Blood Products Advisory Committee to the FDA voted unanimously that there is sufficient safety and efficacy data for the approval of Cinryze® for the prophylactic treatment of HAE. As of October 2008, the FDA has approved Cinryze® for prophylactic treatment of HAE in the US. Data regarding the acute treatment of HAE attacks with Cinryze® has not yet been presented to the Blood Products Advisory Committee. Publication of the results of the CHANGE trials and commercial availability of Cinryze® in the US are anticipated by late 2008 to early 2009.[11,58]

2.1.3 Conestat Alfa

In order to address the need for a readily available supply of C1-INH that was not dependent on plasma donations, the Dutch company Pharming (Leiden, the Netherlands) developed conestat alfa (Rhucin®), a recombinant human C1-INH made from the milk of transgenic rabbits. Clinical trials have been completed in Europe and the US; however, approval for commercial use is still pending.[11]

The production techniques utilized to make conestat alfa have resulted in a highly purified, functionally active product with extremely low risk of pathogen transmission. The drug is reported to have purity levels of 99.98%, with less than 20 ppm of contaminants. Liquid chromatography and mass spectrometry has demonstrated 70% similarity in the amino acid sequence between plasma-derived C1-INH and conestat alfa. Conestat alfa has shown similar functional effectiveness to plasma-derived C1-INH in terms of inhibiting C1, plasma kallikrein, Factor XIa and Factor XIIa. However, differential glycosylation of conestat alfa relative to the human protein has been found to decrease the half-life to approxi-

mately 3 hours.[52,59] Nevertheless, the clinical relevance of this shortened half-life relative to plasma-derived C1-INH has not been demonstrated in clinical trials.[11]

Initial data on the use of conestat alfa in humans was published in 2005. In this phase I study, 12 asymptomatic patients with HAE received conestat alfa 100 U/kg on two separate occasions. No drug-related adverse events or clinically relevant vital sign changes, ECG findings or laboratory abnormalities were reported. Pharmacokinetic analysis revealed that C1-INH levels were elevated to twice normal levels for 2 hours and remained greater than 0.4 U/ml for approximately 9 hours. Measurement of C4 levels, which reflect biological activity of conestat alfa, showed similar results to those seen with plasma-derived C1-INH. In this trial, which excluded patients with a history of hypersensitivity to rabbits, none of the participants experienced hypersensitivity reactions. However, there has been at least one report of a hypersensitivity reaction to conestat alfa involving hives and wheezing in a healthy volunteer who did not reveal a previous history of allergy to rabbits.[11,59] Administration of conestat alfa to patients with a history of rabbit allergy is not recommended by the manufacturer.[11]

The efficacy of conestat alfa in treating acute HAE attacks has been demonstrated in several small, open-label, phase II studies. In one study of nine patients with 13 severe attacks who received conestat alfa 100 U/kg, all patients reported significant relief of symptoms, with 80% reporting relief within 2 hours and minimal symptoms by 12 hours.[60] In another brief report on the findings from exploratory, open-label, phase II and phase III, randomized, double-blind, placebo-controlled studies in Europe, both patients and physicians found treatment with conestat alfa 100 U/kg to be favourable compared with untreated previous attacks. Median time to onset of symptom improvement was approximately 1 hour, time to symptom relief was approximately 4 hours and no relapses occurred. There were no clinically relevant adverse responses or antibodies found to C1-INH or rabbit proteins.[61]

Pharming recently completed separate, randomized, placebo-controlled, double-blind, multicentre studies in Europe and North America, and an open-label phase is ongoing in both studies. Interim analysis of the European study found that both the primary endpoint of time to beginning of relief of symptoms (median of 60 minutes vs 8.5 hours for placebo; $p = 0.0009$) and the secondary endpoint of time to symptom resolution (6.1 hours vs 20.2 hours for placebo; $p = 0.0038$) were fulfilled.[61] Publication of their complete data are pending; however, 100% response rates in the treatment arm versus 36% in the placebo group have been reported.[62] Data from the North American study is also pending publication, although Pharming reports similar positive results to the European trial. In this trial, which involved 39 individuals in the US and Canada randomized to receive either conestat alfa 100 or 50 U/kg versus placebo, there were clinically and statistically significant differences ($p < 0.01$) between conestat alfa and placebo for both primary and secondary endpoints. There were no statistically significant differences in endpoints between the 100 and the 50 U/kg doses.[63] Safety data from the European and North American randomized trials and the open-label phase are reported to be reassuring.[11,63] While Pharming initially received a negative review by the European Medicines Agency (EMEA), they plan to re-file their marketing application in 2009 for approval of conestat alfa in the European market now that additional data are available. They plan to file for FDA approval in the US in late 2008.[63]

2.2 Ecallantide

Ecallantide (DX-88) exerts its beneficial effects in HAE by specifically inhibiting plasma kallikrein, a serine protease involved in the production of bradykinin (see figure 1). The drug is manufactured exclusively by the US company Dyax (Cambridge, Massachusetts, USA). Ecallantide is a recombinant protein identified using phage display technology and produced in *Pichia pastoris* yeast. It was selected based on its strong affinity and specificity for plasma kallikrein. In fact, ecallantide is an even more potent and selective inhibitor of kallikrein than C1-INH.[64]

To date, efficacy and safety data for ecallantide have been promising. The drug has been administered for at least 300 moderate to severe attacks in 175 patients with HAE and two patients with acquired angioedema.[11] It is a recombinant product

and, as such, is free of human or animal contaminants. Given that bioavailability of the drug was found to be similar for both intravenous and subcutaneous routes of administration, it is now exclusively administered by subcutaneous injections.[65] This should have obvious advantages in terms of home administration. Ecallantide has been extensively studied in clinical trials, including four phase I trials, three phase II trials and two phase III trials that included patients aged ≥10 years.[65,66] Early trials suggested that significant improvement in symptoms occurred within 4 hours of receiving the drug and that the median time to initial improvement was less than 30 minutes. The 30-mg subcutaneous dose was found to be the most suitable and has been the dose utilized in subsequent studies.[67] Acute reactions at dose administration were observed in at least eight patients who participated in some of the early studies investigating ecallantide.[11] These have included rhinitis, flushing and gastrointestinal symptoms, as well as at least one reaction that was classified as either anaphylactic or anaphylactoid.[68] Specific IgG and IgE antibodies to ecallantide have been found in some patients; however, elevated tryptase levels have not been described. The aetiology of these reactions is still under investigation.[69] While serious reactions have not occurred in larger, more recent trials, current recommendations by the manufacturer are that adrenaline (epinephrine) and benadryl be immediately available when the drug is administered. There have yet to be any published reports of rebound or relapse attacks in patients receiving ecallantide, despite the short half-life of the drug (2–4 hours). Results from ongoing trials should shed further light on this important issue.

The first phase III trial for ecallantide, known as EDEMA (Effect in Mitigating Angioedema)-3, was a randomized, double-blind, placebo-controlled, multicentre trial evaluating the efficacy of subcutaneous ecallantide 30 mg for acute HAE. There was also an open-label arm for those who completed the randomized phase. The primary endpoint was the "treatment outcome score", which was a measure of patient reported symptom relief. Of the 71 patients included in the final analysis, the mean "treatment outcome score" was significantly higher for those who received ecallantide than placebo (58.5 vs 18.5; $p = 0.021$). For the secondary outcome of change in mean symptom complex severity score at 4 hours after drug administration, there was also a statistically significant difference in favour of ecallantide over placebo (−0.96 vs −0.48; $p = 0.024$). A significantly greater number of patients in the treatment group reported overall improvement within the first 4 hours of drug administration compared with placebo (19 of 35 [54.3%] for active drug vs 11 of 36 [30.6%] for placebo). Mean time to significant improvement was also much shorter in the treated versus placebo group (149 minutes vs 240 minutes; $p = 0.044$). Safety data from EDEMA-3 was very encouraging, with similar adverse event rates reported in the placebo and treatment groups (13.9% vs 11.1%) and no serious treatment-related adverse effects.[11]

Dyax Corporation has recently completed enrolling patients into a second phase III trial known as EDEMA-4. This second, randomized, double-blind, placebo-controlled, multicentre trial is evaluating the efficacy and safety of ecallantide 30 mg for acute HAE attacks. Pending results from this trial, and given the favourable results of EDEMA-3, the company anticipates that FDA approval for this novel therapeutic agent may be granted in late 2008 or early 2009.[11]

2.3 Icatibant

Icatibant is a synthetic decapeptide, similar in structure to bradykinin, which functions as a highly specific and extremely potent antagonist of the BK2R (see figure 1). Given that the BK2R is thought to mediate most of the key activities of bradykinin, including the vasodilation associated with HAE, inhibition of this receptor should antagonize these effects.[70] Icatibant is stable and resistant to the proteolytic effects of carboxypeptidase-N and angiotensin converting enzyme, which degrade bradykinin.[71] The drug is manufactured by the German company Jerini (Berlin, Germany). It was originally developed as an intravenous preparation and subsequently reformulated in a subcutaneous form, which has been used in all clinical trials in the US.[72]

Studies investigating the BK2R and the antagonistic effects of icatibant have recently provided further insight into the pathophysiology of HAE. Studies using C1-INH double-knockout mice dem-

onstrated increased vascular permeability when bradykinin was able to bind to the BK2R, but normal vascular permeability when icatibant blocked binding of bradykinin to the receptor.[73] The effects of bradykinin were also inhibited when the kallikrein inhibitor ecallantide was administered. Antagonism of the BK2R by icatibant with resulting inhibition of bradykinin-mediated vasodilation has also been demonstrated in humans.[74]

The first clinical trial of icatibant in humans was published in 2007. In this trial, 15 patients with 20 acute HAE attacks were treated with various doses of intravenous icatibant 1 mg/mL or subcutaneous icatibant 10 mg/mL concentrations, respectively. Attacks involving the face, extremities and abdomen were included. Patients completed visual analogue scale (VAS) scores and diaries to assess attack-related symptoms and adverse events. Each patient's historical pattern of HAE attacks was used as a reference for untreated attacks. Icatibant resulted in significant improvement in VAS scores at 4 hours in all participants (median difference of 4.11 cm [95% CI 1.72, 6.07]; $p < 0.01$). The mean time to onset of symptom relief was 1.16 hours (95% CI ±0.95 hours) for the intravenous and subcutaneous routes combined, although it appeared to be faster in the groups receiving drug subcutaneously (0.58 hours for intravenous vs 0.45 hours for subcutaneous). All patients receiving subcutaneous icatibant experienced injection site reactions lasting <24 hours. Moderate headache was reported in one patient more than 4 hours after drug administration. Two patients who received the intravenous formulation and two who received subcutaneous icatibant experienced either a relapse of symptoms or a new attack between 14 and 24 hours after initially responding well to the drug. These relapses may be related to the short half-life of icatibant, which is only 2–4 hours.[71]

Two phase III, double-blind, randomized, placebo-controlled studies, known as FAST (For Angioedema Subcutaneous Treatment)-1 and FAST-2 have been completed. FAST-1 enrolled 56 patients with acute HAE attacks in the US, Canada, Australia and South America. FAST-2 enrolled 74 patients with acute attacks in Europe and Israel. Both studies allowed for open-label treatment of laryngeal attacks and open-label administration after failure to respond to a randomized dose.[11]

In FAST-1, there was no statistically significant difference in median time to clinically significant symptom relief for icatibant versus placebo (2.5 vs 4.6 hours; $p = 0.142$). These findings may have been related to a high response to placebo for abdominal attacks. However, the difference in median time to relevant symptom relief was statistically significant in the FAST-2 trial for study drug versus tranexamic acid (2.0 vs 12.0 hours; $p < 0.001$). Both studies showed significant differences in time to first symptom improvement in favour of icatibant (FAST-1: 0.8 vs 16.9 hours; $p < 0.001$; FAST-2: 0.8 vs 7.9 hours; $p < 0.001$). Patients receiving open-label icatibant for laryngeal attacks reported a clinically relevant reduction in the time to first symptom improvement (FAST-1: 0.6 hours; FAST-2: 1.0 hours). Despite the short-half life of the drug, only 11.6% (FAST-1) and 8.6% (FAST-2) of the attacks required a second injection. The timepoint for relief of at least 90% was reached after 8.5 hours and 10 hours for icatibant in FAST-1 and FAST-2, respectively.[11]

In more than 580 administrations of icatibant, there have yet to be any drug-related serious adverse events. The most common adverse effects reported in FAST-1 and FAST-2 were mild local injection site reactions, which resolved spontaneously within a few hours. These reactions primarily consisted of erythema or swelling, with some cases of burning, itching or pain. Neither study found any clinically relevant adverse changes in laboratory parameters, vital signs, blood pressure, heart rate, ECG or physical examination findings.[11]

Both the FDA and the EMEA have granted orphan drug status to icatibant for the treatment of HAE and other forms of angioedema. In April 2008, icatibant received a favourable opinion from the Committee for Medical Products for Human Use of the EMEA. However, the new drug application to the FDA from Jerini for the use of icatibant as treatment for acute HAE failed to gain approval. The company has recently submitted a detailed response to the advisory panel of the FDA addressing concerns that led to an unfavourable letter.[75]

3. Novel Applications of Medications for HAE

A detailed discussion regarding potential applications of novel HAE therapies as treatments for other diseases is beyond the scope of this review. Briefly, plasma-derived C1-INH has been investigated as a therapy for sepsis, acute myocardial infarction and as a means to attenuate the pro-inflammatory effects of cardiopulmonary bypass surgery. While both animal and human studies have shown some promise in all of these areas, there is still a great deal of work to be done to establish the safety and efficacy of C1-INH for these conditions.[76-79] The use of recombinant C1-INH for these purposes has yet to be investigated. Bradykinin-mediated angioedema, including that induced by ACE inhibitors, is another condition for which C1-INH, kallikrein-antagonists and bradykinin-receptor blockers may prove useful.[70]

These agents may also be potentially useful in a number of clinical conditions yet to be realized.

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