Hereditary Angioedema: New Hopes for an Orphan Disease

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Abstract

Hereditary angioedema is a rare genetic disorder, manifested by recurrent edema leading to disfigurement, organ dysfunction and life-threatening respiratory impairment that may become fatal. The hallmark of HAE is C1 esterase inhibitor deficiency, but recent evidence points at bradykinin as the main mediator that causes hyperpermeability of small vasculature, leading to accumulation of edema fluid. Current therapeutic options for HAE are limited, and consist of drugs, replacement therapy, and supportive treatment. In view of many disadvantages of the current therapeutic modalities, new approaches to the treatment of HAE are now being offered. This review summarizes our experience with a new line of medications developed for the treatment of acute exacerbations and prophylaxis of HAE – icatibant: bradykinin receptor antagonist, ecallantide: kallikrein inhibitor, and two C1 INH preparations: Berinert-P, human plasma-derived concentrate, and Rhucin: novel recombinant C1-INH produced in transgenic rabbits. Preliminary results of these studies are encouraging and may bring new hope to the patients with this distressing condition. The exact number of HAE patients in Israel is unknown and because patients are treated individually and comprehensive laboratory assessment is partial, many cases might be missed or not treated according to accepted guidelines. We offer a new specialty center for HAE patients, addressing the medical and psychosocial needs of patients and their families.

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Hereditary angioedema is a rare genetic disorder (OMIM #106100), affecting 1:10,000 to 1:50,000 in the general population. HAE is inherited as an autosomal dominant trait, but its gene is highly variable and more than 150 new mutations have already been recorded [1-4]. The biochemical basis leading to HAE manifestations is either a quantitative (decreased production) or qualitative (decreased activity) deficiency in plasma C1 esterase inhibitor [5]. This factor is a soluble, single-chain glycoprotein (molecular weight 105, 478 amino acids) synthesized in the liver [3,6,7]. The majority of patients are heterozygous, but in most cases production of plasma C1-INH reaches only 5–30% of the normal plasma level (far less than the expected 50%) (2,3). At the present time only one family with two affected alleles has been described [8]. C1-INH belongs to the SERPIN superfamily of enzymes (**ser**in **p**rotease **in**hibitors) and is encoded on chromosome 11q12-13.1 [2]. Its proposed physiological role is to regulate vascular permeability by inhibiting certain steps in the complement system (mainly C1 and C-kinins), coagulation system (factor XIIa and kallikrein) and the fibrinolytic system (thrombin and tissue plasminogen activator) [2,3]. Recent evidence implies that bradykinin, a ubiquitous vascular mediator, is the main mediator of HAE [10]. Brakykinin is generated from plasma kinins by kallikrein or kallidin and is rapidly degraded by kininase (endopeptidases: angiotensin-converting enzyme, neutral endopeptidase, carboxypeptidase N, etc.). It binds to specific vascular receptors (BK R1&2) and causes local generation of nitric oxide, prostacycline (PGI2) and endothelium-derived hyperpolarization factor, thus causing vasodilatation and hyperpermeability [9,10]. The movement of fluids into the interstitial spaces leads to non-pruritic edema. As high molecular weight kininogen is exhausted and bradykinin is degraded, the episode may subside and accumulating fluids are gradually absorbed [3,10].

Although clinically indistinguishable, two biochemical types of HAE have been described: type I (85% of affected patients) is characterized by reduced production, loss of function of total plasma C1-INH and low C4, and type II (15%) by dysfunctional C1-INH (low function but normal levels of antigen) and low levels of C4 [3,11,12].

Bradykinin, a ubiquitous vascular mediator, is the main mediator of hereditary angioedema

Recently a non-histaminergic angioedema, similar to HAE but with normal levels of C1-INH and complement, was described in several families in Europe. This new type is entitled familial angioedema (or hormone-dependent, "type III"). A gain-of-function mutation in factor XII (that may explain resistance to C1-INH inhibition) was described in about a third of these families [13]. Acquired angioedema is another rare disease, affecting mostly patients with lymphoproliferative disorders, benign monoclonal gammopathy (monoclonal gammopathy of unknown significance) and autoimmune disorders (anti-C1-INH antibody formation) [14-16]. Additionally, many patients treated with ACE inhibitors are at increased risk to develop angioedema, since ACE is the

HAE = hereditary angioedema
C1-INH = C1 esterase inhibitor
ACE = angiotensin-converting enzyme

main endopeptidase responsible for the degradation of bradykinin to its inactive metabolites [11,17].

Clinical manifestations

Manifestations of HAE vary from one patient to another in severity, occurrence and frequency, ranging from 14% asymptomatic patients to life-threatening episodes. They include edema of the extremities, face, tongue, larynx and genitalia, and edema of the intestinal wall leading to severe abdominal pain, nausea, vomiting, diarrhea and intestinal obstruction [18,19]. A typical attack may last for 24–72 hours, and in most cases will resolve spontaneously. However, swelling of the tongue and larynx are life threatening, and laryngeal edema with imminent respiratory impairment and fatal outcome has been described. Estimated risk of death from asphyxiation if the attack is left untreated is fairly high (15–33%) [12,13].

HAE is a chronic disease, with exacerbations precipitated primarily by mechanical forces or tissue trauma in one-third of the patients. Other factors are hormones (mainly estrogens), inflammation, infections, and emotional and stressful situations [12,13,18,19]. The quality of life of HAE patients is profoundly affected by the unpredicted and debilitating attacks, fear of disease consequences, dependence on medications and side effects. New quality of life parameters have recently being developed to assist patients and their families, in addition to the formation of patient support groups in several countries [20].

Treatment

Current therapeutic options for HAE are limited, comprising medications, replacement therapy, and supportive treatment [21]. In contrast to acute allergic-anaphylactic angioedema, agents such as adrenalin, antihistamines and corticosteroids are ineffective in HAE [12]. Current treatment modalities during acute attack include fresh frozen plasma, trenexamic acid (Hexacapron®), and human plasma-derived C1-INH concentrates. Long-term prophylaxis includes danazol (attenuated androgen that increases hepatic C1-INH production), tranexamic acid and repeated administrations of C1-INH concentrates, on a weekly or biweekly protocol [12,13,21,22].

The last option has been successfully implemented in several HAE specialty centers, providing outpatient and home treatment programs (including self-administration) [23]. Although very effective as a maintenance therapy, attenuated androgens were shown to be associated with various side effects, including virilization in women, elevation of hepatic enzymes, increase in total cholesterol and low density lipoprotein and, rarely, hepatic tumors [12,13,19].

New clinical guidelines addressing the management and treatment of HAE were recently developed, including management of acute attacks, on-demand treatment, and maintenance (prophylaxis) [13,24-26].

New treatment modalities

In view of many disadvantages of the current therapeutic modalities (availability, price, side effects, potential long-term risks, etc.), new approaches to the treatment of HAE are now being offered [27-29]. Two novel molecules were designed to target bradykinin, either by inhibiting its generation from plasma kininogens [30], or by direct inhibition of its specific receptors on blood vessels [31]. The first, ecallantide (Dyax, USA), is a specific kallikrein inhibitor synthesized by employing a phage-display library technology. The second, icatibant (Jerini, Germany), is a novel molecule with specific bradykinin receptor (BK B2) binding activity on blood vessels. Other treatments that were studied globally in multicenter studies over the last few years include C1-INH replacement therapy for both acute and prophylactic treatment: a) pasteurized C1-INH concentrate (Berinert-P®, CSL-Behring, Germany), b) nano-filtrated human plasma-derived C1-INH (Cinryze®, Lev pharmaceuticals, USA) and, c) genetically engineered recombinant C1-INH, produced in transgenic rabbits (Rhucin®, Pharming, Netherlands).

HAE specialty centers offer better treatment and address the needs of patients and their families

HAE in Israel

The exact number of HAE patients in Israel is unknown since no central registry exists. Patients are being seen by different clinics and physicians, and comprehensive laboratory assessment is lacking. The present laboratory data in Israel are based on three parameters – complement components C3 and C4, and levels of antigenic C1-INH – but functional assay (C1-INH plasma activity) was not performed locally until recently. Due to the rarity of this condition, the delayed diagnosis (estimated as more than 20 years by some authors) and possible misdiagnoses (i.e., recurrent unexplained abdominal pain, familial Mediterranean fever, etc), we speculate that only a few patients in Israel are being treated according to the current treatment guidelines.

Figure 1 presents a simplified drug regimen algorithm recommended for acute, on-demand and prophylaxis of HAE in Israel. This summary will describe our recent experience with new treatments offered for acute HAE attacks. Patients from the Sheba Medical Center Angioedema Center were invited to participate in any of the abovementioned new treatment protocols. They were treated during acute exacerbations of peripheral edema (swelling of extremities, genitals, face, tongue and larynx), and acute abdominal attacks.

Clinical studies with new drugs for HAE

Through the Sheba Medical Center allergy-immunology clinics and laboratories we obtained a database of almost 100 patients suffering from recurrent angioedema. Patients whose history, clinical symptoms and baseline laboratory results confirmed

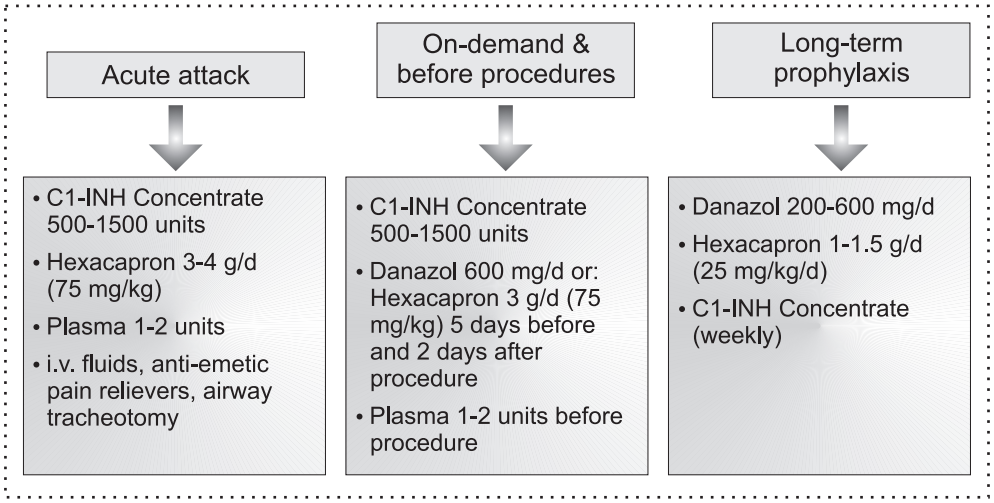

Figure 1. Recommended treatment algorithms for HAE using the currently available drugs in Israel

Table 1. Acute HAE treatments and new drugs in four clinical trials at Sheba Medical Center, 2005-2008*

Drug	Route	Recruited	Included	Double-blind study: treated patients	Open-label study: treated patients	Total treated patients	HAE attacks
Icatibant (Firazyr)	s.c.	27 (M11, F16)	18 (M8, F10)	5	2	7	65
Berinert-P	i.v.	15 (M5, F10)	11 (M4, F7)	5	–	5	5
Ecallantide (DX88)	s.c.	7 (M4, F4)	6 (M4, F2)	–	2	2	2
rC1INH (Rhucin)	i.v.	17 (M7, F10)	13 (M4, F2)	–	9	9	14
Total		66	48	10	13	23	86

Conducted in the Angioedema Center of Sheba Medical Center, Tel Hashomer.
M = male, F = female

the diagnosis of HAE were invited to participate in any of four clinical studies, performed in parallel in centers in Europe, the United States and South America. The studies were sponsored by the manufacturers and designed either as double blind, placebo controlled (in one case as a double-blind/double-dummy study) or as open label. All study protocols were approved by the local ethics review board (Helsinki Committee) of our institution, and written informed consent was obtained from each patient or, in the case of a minor, from a legally acceptable representative. An independent data and safety monitoring board scrutinized the management and safety of the study. Table 1 shows the investigational drug protocols, participating HAE patients and number of treatments given in the last 3 years.

- **Icatibant (FAST 2 study)**

Icatibant is a synthetic decapeptide containing five non-proteinogenic amino acids. It is stable and not degradable by bradykinin-cleaving enzymes (ACE and CPN). Icatibant was shown as an extremely potent BK-B2 receptor antagonist with the same affinity as BK itself. Both animal (C1-INH-deficient mice) and human Phase I and IIa safety, tolerability, pharmacokinetic and pharmacodynamic studies have been conducted with various formulations of icatibant. Phase III multicenter studies were initiated, and by the end of 2007 over 1200 healthy subjects and HAE patients had been exposed to one or more doses of icatibant in controlled clinical studies [32,33]. In the initial phase icatibant was administered by subcutaneous injection (30 mg) and was compared to tranexamic acid (1000 mg 3 times a day) in a double-blind/double-dummy fashion. Patients above age 18 with both type I and II HAE were eligible to participate. Multicenter Phase III studies (double-blind and open-label extension) were recently concluded (March 2008). In Israel, 54 patients (27 at Sheba Medical Center) were screened for the trial. Fifteen patients (7 from Sheba) were treated during the course of both controlled phase and open-label extension phases. A total of five double-blind and 60 open-label acute HAE treatments were administered at Sheba [Table 1]. Preliminary results of these studies are depicted in Figures 2–4.

To summarize, during the open-label phase 60 individual doses of icatibant were administered: 28 times to one patient, 15 times to one patient, 9 times to one patient, 3 times to two patients and only once to two patients. Icatibant was found highly effective in abrogating acute attacks in various organs. Mean time to first symptom improvement was 40.6 minutes (SE 18.3) for abdominal pain (N=25), and 57.7 minutes (SE 26.4) for cutaneous attacks (N=38). Apart from local pain, burning sensation and erythema at the injection site, no significant adverse reactions were noted during the study. Results of the multicenter studies (FAST1+2) have been described elsewhere. These studies show significant shortening of time to first improvement (i.e., 0.8 hours vs. 16.9 hours with placebo and 7.9 hours with tranexamic acid), and good safety profile. Lately, the European Commission approved the new product (Firazyr®) and it is awaiting approval by the U.S. Food and Drug Administration.

ACE = angiotensin-converting enzyme
CPN = carboxypeptidase N
BK = bradykinin

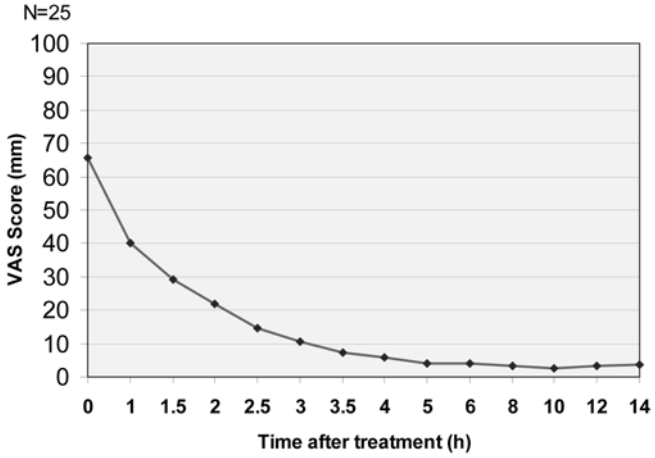

Figure 2. Abdominal pain score. Mean patient VAS score (Visual Analog Scale of 1-100 mm) in response to icatibant treatment during acute abdominal attack.

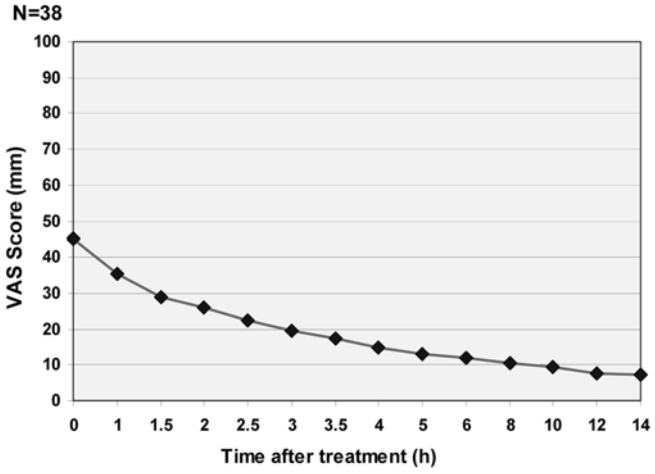

Figure 3. Cutaneous edema score. Mean patient VAS score in response to icatibant treatment during cutaneous attacks (extremities, face, genitalia).

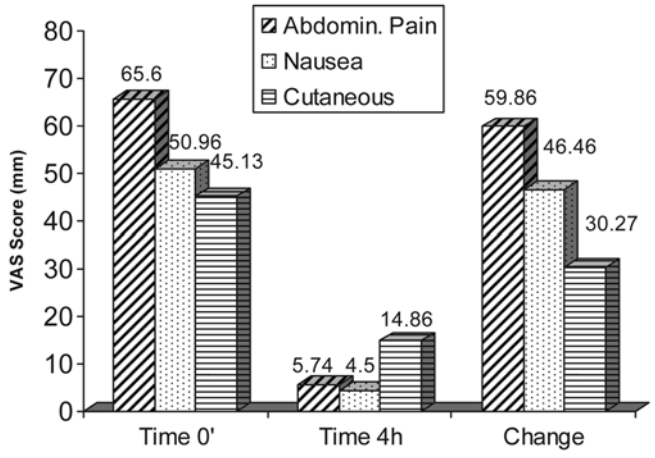

Figure 4. Response to treatment. Mean patient VAS score at the time of injection of icatibant and 4 hours later. Figures above the bars show the mean VAS score for each parameter: abdominal pain and nausea during 25 attacks, cutaneous symptoms during 38 attacks.

- **Ecallantide (EDEMA-3 study)**

Ecallantide (formarly DX-88) is a 60 amino acid recombinant protein expressed in P*ichia pastoris* yeasts. It was found in earlier studies to be a highly specific and effective inhibitor of the kallikrein cascade, thereby decreasing generation and accumulation of bradykinin during an acute attack [30]. Ecallantide 30 mg was administered subcutaneously to patients above age 10 for all types of attacks (severe upper airway compromise was treated as open label). Assessment of the effect was by a combined outcome score – a composite measure specific for HAE, patient-reported outcomes, mean symptom complex severity, and time to significant improvement on a scale of 1 to 4. Safety parameters included laboratory, electrocardiographic, adverse-event recordings and measurement of immunoglobulin E and non-IgE antibodies to ecallantide and P. *pastoris*.

We recruited seven HAE patients for this study, but only two (12 and 16 years old) were randomized during an acute attack, since the study in Israel and Europe was prematurely terminated earlier than scheduled. Results of the studies in the USA and Europe, including isolated reports on anaphylactic reactions (sensitization via anti-P*ichia* IgE antibodies?), has been published elsewhere [34,35].

- **Berinert-P (IMPACT study)**

Providing a human plasma-derived C1-INH is the mainstay of HAE treatment. Berinert-P is a highly purified, virus-inactivated C1-INH concentrate derived from human plasma and approved for the treatment of acute disease and for prophylaxis of HAE. Concentrates were used for more than 30 years in over 400,000 treatments with an excellent safety record [36-38].

The study we participated in was designed to assess the efficacy of Berinert-P at intravenous doses of 10 or 20 U/kg body weight compared to placebo, in the treatment of single, acute abdominal or facial HAE attacks. The IMPACT study was randomized, double blind and placebo controlled and was conducted between August 2005 and December 2007 in 36 centers in the USA, UK, Canada, Argentina, Europe and Israel. The main study end-point was to show that Berinert P is capable of shortening the time to onset of symptom relief in acute abdominal or facial HAE attacks compared to placebo, and to provide a statistically secure dosing recommendation for C1-INH (previous recommended initial dose was 500 units, < 10 units/kg in most cases). Patients were eligible if they were at least 6 years old, had laboratory-confirmed C1-INH deficiency (type I or II HAE), and were then treated intravenously within 5 hours of the beginning of the attack. We recruited 15 patients and treated 5 in a double-blind fashion (10 or 20 U/kg body weigh). Preliminary results of the IMPACT studies show a significant (P = 0.003) response to the 20 units/kg regimen, as compared to placebo (mean onset of symptom relief 30 minutes compared to 90 minutes). Phase III studies with Berinert-P were concluded at the end of 2007 [39], and Biologics License Application was submitted

Ig = immunoglobulin

to the FDA in March 2008. Berinert-P is already available in Israel. We provide it to our patients through form 29c, as an outpatient treatment, or delegate its use by physicians during acute attacks, or before procedures in emergency departments and community medical centers.

- **Recombinant C1-INH (Rhucin study)**

Recombinant C1-INH is produced in transgenic rabbits with expression levels exceeding 10 g/L. The human C1-INH gene is linked to bovine aS1-caseine promoter, which enhances its secretion in rabbit milk. rC1-INH is highly purified and is 98% homologous to the human product. Phase I and II studies were performed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of the product in both healthy subjects and symptomatic HAE patients. No allergic reactions and no tolerance or neutralizing anti-C1-INH antibodies have developed. Preliminary data with Rhucin [40] show that time to beginning of relief is 1 hour (vs. 8.5 hours with placebo) and time to minimal symptoms was 6.1 hours (compared to 20.2 hours for placebo).

New drugs were recently developed for HAE, capable of abrogating the acute attacks and prevent recurrent attacks by prophylactic treatment

We are currently participating in a phase III study aimed at demonstrating the efficacy and safety of intravenous rC1-INH (Rhucin) 100 units/kg in patients with acute HAE attacks in different body locations. Patients are asked to report immediately at the onset of a new attack, and to start the treatment not more than 5 hours later. We have so far treated 14 HAE attacks, including laryngeal edema. Response is quick: within 40–60 minutes, and no adverse events have been observed. Rhucin has a shorter half-life than human products and an additional dose is sometimes required. No increase in anti-Rhucin antibodies or the emergence of anti-rabbit antibodies has been observed, even after repeated doses. This study is still ongoing, with the intent to administer multiple treatments in order to assess efficacy and tolerability of the new product.

The concept of an HAE specialty center

Prolonged experience with HAE patients led us to establish a specialty Angiodema Center at the Sheba Medical Center. A protocol consisting of central management and treatment of HAE was recommended in recent clinical guidelines [13,23,25] and similar centers are already active in Germany, Holland, the UK, Hungary and other countries. Angioedema centers will be able to better address the medical and psychosocial needs of patients and their families. Sheba's Angioedema Center has a team of immunologists and nurses and is capable of providing a comprehensive laboratory assessment (levels of complement, quantitative and functional C1-INH assays, coagulation cascade, etc.). The role of the immunology-specialist nurse is pivotal in this setting, to provide advice, patient education, outlining of treatment protocols and communication with patients and their families. Patients are instructed to identify imminent attacks ("prodrome") and to avoid provoking triggers and medications that may precipitate attacks. Personal treatment plans, including emergency treatments, are employed and we communicate with physicians in the community and if necessary, the health maintenance organizations. Genetic counseling and new drug investigational protocols are being offered. Similar to other centers, we began using prophylactic treatment with C-INH concentrates, and self-administration programs are considered when conditions are appropriate.

FDA = Food and Drug Administration
rC1-INH = recombinant C1-INH

Conclusions

Much progress has been made since hereditary angioedema was first described more than 120 years ago by Quincke and Osler. Although still considered an "orphan" disease, the renewed interest in HAE and the development of new products open new horizons and offers hope to patients and their families. New drugs, patient organizations, and the establishment of HAE-dedicated specialty centers will likely reduce the burden of the disease and its grim prognosis in the future.

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