

Currently available treatments and future treatment options for hereditary angioedema

KONRAD BORK

Department of Dermatology, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Key words

C1-esterase inhibitor – hereditary angioedema – kallikrein-kinin system – on-demand treatment – prophylaxis

Summary

Hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) is characterized by recurrent skin swellings, abdominal pain attacks, and – more rarely – potentially life-threatening laryngeal attacks. Thus, HAE-C1-INH may be associated with a significant morbidity and mortality. Over the last years, the field of research in the pathogenesis of HAE-C1-INH has greatly expanded. This has led to new clinical trials with new therapeutic options. Strategies for managing HAE-C1-INH are aimed at treating acute attacks or preventing attacks through the use of prophylactic treatment. Agents available for treating acute attacks include plasma-derived C1-INH concentrates, a bradykinin B2 receptor antagonist, and a recombinant

human C1-INH. In the USA, a plasma kallikrein inhibitor has additionally been approved. Long-term prophylactic treatments include attenuated androgens, a plasma-derived C1-INH concentrate, and antifibrinolytics. Plasma-derived C1-INH and a bradykinin B2-receptor antagonist are approved for self-administration at home. The number of management options for HAE-C1-INH has increased considerably within the last few years, thus helping to alleviate the burden of disease.

Cite this as Bork K. Currently available treatments and future treatment options for hereditary angioedema. *Allergo J Int* 2015;24:122–8

DOI: 10.1007/s40629-015-0062-4

Hereditary angioedema

Recurrent angioedema is clinically characterized by episodes of marked edema (“attacks”) involving the skin, the gastrointestinal tract, and other organs including potentially fatal upper airway obstruction [1]. Various forms of acquired and hereditary angioedema (HAE) share this clinical presentation. “Classic” HAE (HAE-C1-INH) is associated with a quantitative (type I) or qualitative (type II) deficiency of C1 esterase inhibitor (C1-INH) caused by mutations of the *SERPINC1* gene.

In 2000, a new type of HAE has been described without a deficiency of C1-INH. It was termed “HAE with normal C1-INH” (HAEnCI) or “HAE type III” [2]. Between 2006 and 2013, four different mutations in the gene coding for the coagulation factor XII (*F12* gene) in patients affected by HAEnCI have been identified [3, 4, 5, 6]. These mutations cause a change in the amino acid sequence in the proline-rich region of the FXII protein and were exclusively observed in patients with a subtype of

HAEnCI and unaffected carriers in their families, which was termed “HAEnCI and mutations in the *F12* gene” or “HAE-FXII” [3, 6, 7]. In other families with two or more patients per family, the genetic background is still unknown (“HAEnCI without mutations in the *F12* gene” or “HAE-unknown”) [7]. In HAE-FXII and in HAE-unknown no controlled

Abbreviations

BW	Body weight
B2R	Bradykinin B2-receptor
C1-INH	C1 inhibitor
HAE-C1-INH	Hereditary angioedema due to C1-INH deficiency
HAE	Hereditary angioedema
HAEnCI	HAE with normal C1-INH
KKS	Kallikrein-kinin system

Submitted
February 10, 2015

Accepted
March 16, 2015

Online version
www.springer-medizin.de/
allergo-journal

treatment studies have been performed up to now. However, treatment has been reported in case reports and small patient series [8].

HAE-C1-INH

HAE-C1-INH is a rare disease. The number of attacks varies considerably in patients. The burden of disease is high, especially in patients with frequent attacks.

Pathophysiology of HAE-C1-INH

C1-INH is a serine protease inhibitor and inhibits not only C1r and C1s in the complement system but also FXIIa, kallikrein, and FXIa in the kallikrein-kinin system (KKS) and in the coagulation system. HAE-C1-INH is associated with a deficiency of C1-INH caused by mutations of the *SERPING1* gene. The pathogenesis of HAE-C1-INH involves activation of KKS leading to the release of bradykinin. The mechanism of KKS activation, however, is still unknown. During an acute attack the activation of FXII and plasma prekallikrein and the formation of the serine proteases FXIIa and kallikrein are uncontrolled. Plasma kallikrein cleaves high-molecular weight kininogen resulting in the formation of the nonapeptide bradykinin, a potent vasodilator. Bradykinin activates the bradykinin B2-receptor (B2R) located on endothelial cells. The activation of the B2R is followed by relaxation of the smooth muscle cells of the vessels due to the production of nitric oxide by endothelial cells. In case of angioedema, this

leads to a vasodilation, increased vascular permeability, and localized fluid extravasation [9].

Treatment of HAE-C1-INH

Treatment goals in HAE-C1-INH comprise the avoidance of asphyxiation and the reduction of the attack frequency and severity. Besides drug treatment, numerous other measures are necessary to reach these goals [10, 11]. There are two treatment strategies for HAE-C1-INH. The first is to treat acute swellings (on-demand treatment) and the second is to prevent attacks (short-term or long-term prophylaxis). A range of targeted and non-targeted treatments are available (**Tab. 1**). The approval status of medications for HAE-C1-INH in Europe and the USA is shown in **Tab. 2**.

Drugs targeted specifically to the disease have become available for treatment of acute angioedema attacks (**Tab. 1**). They are highly effective and include C1-inhibitors, either plasma-derived or recombinant, the kallikrein-inhibitor ecallantide, and the bradykinin B2-receptor antagonist Icatibant. Treatment for long-term prophylaxis include C1-INH (highly effective), attenuated androgens (highly effective), progestins (moderately effective), and tranexamic acid (less effective).

Treatment of Acute Attacks

During acute HAE-C1-INH attacks, the first therapeutic objective is to attenuate or stop the process of KKS activation. This can be achieved by administration of a protease inhibitor that binds plasma

Tab. 1: Target, currently available treatments, and future treatment options for hereditary angioedema due to C1-INH deficiency

Targets	Available treatments	Potential future treatment options
Coagulation factor XIIIa	Plasma-derived human C1-INH (replacement of the lacking protein); recombinant C1-INH	— Antibody against FXIIa — Subcutaneously applied C1-INH
Kallikrein	Plasma-derived human C1-INH (replacement of the lacking protein); recombinant C1-INH; Ecallantide*	— Subcutaneously applied C1-INH — Oral small molecule, directed against kallikrein — Subcutaneous long-acting antibody, directed against kallikrein
Prekallikrein	0	Antisense drug to inhibit the production of prekallikrein
Bradykinin-B2-receptor	Bradykinin-B2-receptor antagonist, icatibant	Further bradykinin-B2-receptor antagonists (currently not pursued)
Plasminogen	Tranexamic acid	0
<i>SERPING1</i>	0	Gene therapy (currently not pursued)
Target unknown	Attenuated androgens	0
Target unknown	Progestins	0

*Currently available in the USA, but not in Europe

Tab. 2: Approval of treatment options for hereditary angioedema due to C1-INH deficiency in Europe

	Approved in Germany/ Europe since	Approved in the USA since	Approved for
Plasma-derived C1-INH			
Beriner [®]	1979 (for treatment of HAE attacks)	2009 (for treatment of HAE attacks)	Adults and children
Cinryze [®]	2011 (for treatment and prevention of HAE attacks)	2008 (for prevention of HAE attacks)	Adults and adolescents
Bradykinin B2 receptor agonist			
Icatibant (Firazyr [®])	2008	2011	Adults (18 years old and older)
Recombinant C1-INH			
Conestat alfa (Ruconest [®])	2010	2014	Adults
Plasma kallikrein inhibitor			
Ecallantide (Kalbitor [®])	Currently not approved	2009	USA: 16 years old and older
Non-protein therapies			
Danazol	Approved in a few countries only	Approved	Adults
Tranexamic acid	Approved in a few countries only	Not approved for HAE	Europe: Adults and children

kallikrein and factor XIIa. It has been shown that replacement therapy with C1-INH (which inhibits both factor XIIa and kallikrein) can abort acute attacks of HAE-C1-INH. Similar results have been shown using various substances that inhibit kallikrein alone.

A second objective of therapy for acute HAE-C1-INH attacks is to inhibit bradykinin action by blocking the bradykinin B2-receptor on endothelial cells. For this purpose a synthetic molecule similar to bradykinin – but without causing vasodilation and vasopermeability – has been developed.

C1-INH concentrates

Since 1973, C1-INH concentrates derived from human plasma have been shown to be effective in treating and preventing all kinds of HAE-C1-INH attacks. Three licensed C1-INH concentrates are currently available.

Beriner[®]

Beriner[®] is a pasteurized and nanofiltered C1-INH concentrate, which was first licensed in Germany in 1979. The randomized, double-blind, placebo-controlled Trial 1 (IMPACT1) study evaluated the efficacy of Beriner[®] in 125 patients with HAE-C1-INH [12]. Patients were randomized to either 10 or 20 U/kg body weight (BW) Beriner[®] given in abdominal attacks and facial swellings. The median time to onset of relief of symptoms was significantly

shorter with 20 U/kg of Beriner[®] than with placebo (0.5 vs. 1.5 hours). At a dose of 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 vs. 1.5 hours) and the difference did not reach statistical significance. The conclusion was that Beriner[®] given intravenously at a dose of 20 U/kg is an effective treatment for abdominal and facial attacks in patients with HAE-C1-INH [12].

Three large uncontrolled clinical studies, which included thousands of attacks, found that a fixed dose of 500 U was highly effective in the majority of patients (98 %, 81 %, and 68.6 %, respectively) [13, 14, 15].

The potentially life-threatening nature of laryngeal attacks and facial attacks, which can evolve into laryngeal edema, require a body weight-adjusted dose of 20 U/kg to be used. In attacks that are not potentially life-threatening (i.e. those with swellings of the extremities and abdominal attacks), the dose can be adjusted to the patient's individual requirements; administration of a lower, fixed dose of 500 or 1,000 U per attack may be sufficient [11]. Beriner[®] is licensed for self-administration at home [16, 17]. In a few patients receiving Beriner[®] for a long period of time a slow increase in attack frequency (i.e. disease activity) has been observed [18, 19, 20].

Cinryze[®]

Cinryze[®] is a nanofiltered plasma-derived C1-INH. Two randomized double-blind placebo-controlled trials have been performed in patients with acute

attacks and showed high efficacy. Self-administration of Cinryze® significantly decreased attack duration, pain medication use, and graded attack severity [21].

Icatibant (Firazyr®)

Firazyr® is a novel, competitive and selective B2-receptor antagonist for subcutaneous injection in patients with HAE-C1-INH [22, 23]. In an initial phase II open-label study, 15 patients with 20 HAE attacks were treated with icatibant either intravenously or subcutaneously [24]. This was the first study to demonstrate the clinical usefulness of antagonizing the binding of bradykinin to bradykinin receptor-2 in HAE-C1-INH.

The safety and efficacy of icatibant have been further assessed in three randomized, double-blind, controlled prospective multicenter phase III studies: two were placebo-controlled and the third used oral tranexamic acid as comparator [25, 26].

An observational study showed that acute attacks of HAE-C1-INH resolve faster following early treatment with icatibant compared to late treatment [27]. Icatibant is licensed for self-administration.

Ecallantide (Kalbitor®)

Ecallantide, previously termed DX-88, is a 7.054 kDa recombinant protein comprised of 60 amino acids, produced in the yeast *Pichia pastoris*. It is a potent and selective inhibitor of kallikrein and acts by blocking its binding site. The plasma half-life is approximately 70 minutes when administered intravenously and 2 hours when administered subcutaneously.

The safety and efficacy of ecallantide were evaluated in the randomized, double-blind, placebo-controlled Evaluation of DX-88's Effect in Mitigating Angioedema (EDEMA3 and EDEMA4) trials [28, 29]. The results showed that ecallantide is highly effective. Side effects included hypersensitivity and, in a few patients, anaphylaxis.

Recombinant C1-INH

A recombinant human C1-INH has been developed for the treatment of HAE attacks. It is obtained from the milk of transgenic rabbits. The cloned human *C1-INH* gene was inserted into a mammary gland-specific expression vector under the control of an S1 casein promoter. The construct was introduced into fertilized New Zealand white rabbit oocytes by microinjection in order to generate a line expressing high levels (12 mg/mL) of secreted rhC1-INH. Rabbits have a short reproductive cycle and can produce sufficient quantities of rhC1-INH.

Two separate randomized, double-blind, placebo-controlled clinical trials were conducted in Europe and North America. In Europe, a randomized,

double-blind, placebo-controlled phase III study was conducted with 32 patients [30]. All instances of treatment with rhC1-INH were successful, with no relapses.

Mode of application, rebounds

All mentioned medications for acute attacks of HAE-C1-INH are highly effective. Plasma-derived C1-INH concentrates and recombinant C1-INH have to be administered intravenously. The rate of attack recurrences if treated with C1-INH concentrate is very low. Icatibant and ecallantide are administered subcutaneously; however, in about 10% of treated attacks a second injection is necessary to control the attack [31, 32]. Currently, only plasma-derived C1-INH and icatibant are licensed for home-based self-administration. Most of the agents are not licensed for use in children or in pregnancy.

Prevention of Attacks

There are two treatment strategies in HAE-C1-INH. The first is to treat an acute swelling attack (on-demand therapy) and the second is to prevent swelling attacks (short-term or long-term prophylaxis). A partial or complete prevention of clinical symptoms of HAE-C1-INH can be achieved by direct replacement of the deficient C1-INH. There are other long-term prophylaxis regimens for HAE-C1-INH, such as attenuated androgens and the plasminogen inhibitor tranexamic acid. In both kinds of treatment the exact mode of action is not fully understood. Tranexamic acid may be less effective than attenuated androgens.

Attenuated androgens

Attenuated androgens have been used since 1976, and so there is extensive understanding of their efficacy and safety. Attenuated androgens are highly effective in preventing HAE attacks [33, 34]; however, their long-term use may be associated with numerous side effects, and close monitoring of patients is mandatory [33].

C1-INH concentrates

The C1-INH concentrates Cinryze® and Berinert® have been used for prevention of HAE-C1-INH attacks, but only Cinryze® is currently approved for this indication. The efficacy and safety of Cinryze® has been evaluated in a multicenter, double-blind, placebo-controlled, crossover study [35]. The mean number of HAE attacks in each 12-week treatment period was significantly lower for patients receiving Cinryze® than for those treated with placebo. The recommended prophylactic dose of Cinryze® is 1,000 U every 3–4 days. In an open-label study, patients showed a 94% reduction in the number of monthly attacks [36]. Some patients are not

adequately controlled with this dose, however. It was shown in a recent study with escalating doses of Cinryze® that a dose escalation up to 2,500 U every 3–4 days reduced the attack frequency and was well tolerated [37].

Beriner® is currently not licensed for long-term prophylactic use. Beriner®'s high efficacy in long-term prophylaxis has been reported in case reports and small case series since 1989 [38, 39]. A series of 14 patients received one or more weekly intravenous injections of Beriner® for an average of 9 years [20]. The most important benefit of this treatment was a reduction in symptom intensity: the vast majority of attacks were only mild or very mild. The percentage of attacks that were severe was 93.3 % without prophylaxis and 3.8 % with prophylaxis. In some patients an increased amount of Beriner® was required to prevent attacks. Some patients reported rapidly developing attacks and skin swellings at multiple locations, reflecting increased HAE-C1-INH activity [20]. However, none of the patients reported any loss of effectiveness during the treatment with Beriner®.

Recombinant C1-INH

In an open-label observational study 25 patients with HAE-C1-INH received 50 U/kg rhC1-INH once weekly [40]. The study revealed that the attack frequency appeared to be reduced. The half-life of rhC1-INH is 1.6 h. Although this finding cannot be considered definitive, one possible explanation for the efficacy of rh-C1-INH in long-term prophylaxis despite its short half-life might be that even short and transient restoration of C1-INH plasma level can be sufficient for stabilizing the kallikrein-kinin system for some time.

Costs of HAE-Specific Treatments

The HAE-specific treatments with plasma-derived or recombinant C1-INH, icatibant or ecallantide are expensive. In some patients with many attacks the annual per patient medication can exceed 100,000 Euro. Home-based self-administration may reduce the treatment costs associated with HAE-C1-INH.

New Potential Treatment Options for HAE-C1-INH

The continuing search for new therapies in HAE-C1-INH has resulted in a number of drug candidates, which are at various stages of clinical development (Tab. 1).

BCX4161 is an oral small molecule kallikrein inhibitor that is being developed by BioCryst Pharmaceuticals Ltd. (Durham, NC, USA). Preclinical studies showed that it is a potent and specific inhibitor of plasma kallikrein. A phase IIa proof of concept clinical trial (OPuS-1, Oral Prophylaxis-1) of BCX4161 in patients with HAE-C1-INH has been recently initiated.

Using a phage display technology, a long-acting inhibitor of plasma kallikrein has been developed by Dyax Corp. (Burlington, MA, USA). DX-2930 is a recombinant fully human monoclonal antibody inhibitor of plasma kallikrein. It is developed to be a long-acting, prophylactic agent that prevents HAE attacks.

A recent study has shown that a subcutaneous injection of 1,000 international units (IU) Beriner® is clinically feasible. The absolute bioavailability of the subcutaneously administered C1-INH concentrate was about 40 % [41]. Currently, an international phase III study of a volume-reduced formulation of Beriner® for subcutaneous injection to prevent attacks in patients with HAE-C1-INH is running.

ViroPharma Inc. completed a clinical phase II study to evaluate the safety, tolerability, and efficacy of subcutaneously administered Cinryze® with recombinant human hyaluronidase (rHuPH20) to prevent attacks in patients with hereditary angioedema due to C1-INH deficiency. It is a randomized, double-blind, cross-over study. In the study a recently developed low-volume subcutaneous formulation of Cinryze® is used. The primary objectives of the ongoing study are to evaluate the safety, tolerability, and efficacy of two doses of Cinryze® with recombinant human hyaluronidase (rHuPH20) administered by subcutaneous injection.

Recently a factor XIIa inhibitory antibody has been developed. It is a fully human function-neutralizing antibody that binds into the FXIIa enzymatic pocket. CSL Behring announced that a fully humanized monoclonal antibody against coagulation factor XIIa has been added to the company's research pipeline.

Furthermore, an antisense drug was designed to inhibit the production of prekallikrein [42]. Prekallikrein is involved in the activation of the kallikrein-kinin system during acute attacks of HAE-C1-INH. Inhibiting the production of prekallikrein might be a prophylactic approach to preventing attacks of HAE-C1-INH.

Conclusion

In the last few years, a number of drugs have been developed, either for treatment of acute attacks of HAE or for long-term prophylaxis of the disease. Hopefully these drugs will diminish the burden of hereditary angioedema by reducing the risk of asphyxiation and by reducing the number of severe attacks.

Prof. Dr. Konrad Bork

Department of Dermatology

University Mainz

Langenbeckstraße 1

55131 Mainz, Germany

E-Mail: bork@hautklinik.klinik.uni-mainz.de

Conflict of interest

The authors state that there are no conflicts of interest.

Cite this as

Bork K. Currently available treatments and future treatment options for hereditary angioedema. *Allergo J Int* 2015;24:122–8

DOI: 10.1007/s40629-015-0062-4

References

1. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012;130:692–7
2. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;356:213–7
3. Bork K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. *Clin Immunol* 2011;141:31–5
4. Kiss N, Barabas E, Varnai K, Halasz A, Varga LA, Prohaszka Z, et al. Novel duplication in the F12 gene in a patient with recurrent angioedema. *Clin Immunol* 2013;149:142–5
5. Bork K, Wulff K, Hardt J, Witzke G, Lohse P. Characterization of a partial exon 9/intron 9 deletion in the coagulation factor XII gene (F12) detected in two Turkish families with hereditary angioedema and normal C1 inhibitor. *Haemophilia* 2014;20:e372–5
6. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun* 2006;343:1286–9
7. Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 2009;124:129–34
8. Bork K. Hereditary angioedema with normal C1 inhibitor. *Immunol Allergy Clin North Am* 2013;33:457–70
9. Bork K. Angioedema. *Immunol Allergy Clin North Am* 2013;34:23–31
10. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012;67:147–57
11. Bork K MM, Bas M, Hartmann K, Biedermann T, Kreuz W, Aygören-Pürsün, Martinez-Saguer I, Ott H, Wedi B. Hereditäres Angioödem durch C1-Inhibitor-Mangel. *Allergo Journal* 2012;21:109–18
12. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009;124:801–8
13. Bork K, Meng G, Staubach P, Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 2005;45:1774–84
14. Farkas H, Jakab L, Temesszentandrási G, Visy B, Harmat G, Fust G, et al. Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy. *J Allergy Clin Immunol* 2007;120:941–7
15. Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 2008;63:751–7
16. Rizk C, Karsh J, Santucci S, Yang W. Self-administration of intravenous C1 esterase inhibitor in hereditary angioedema. *Cmaj* 2013;185:791–2
17. Bork K. Pasteurized and nanofiltered, plasma-derived C1 esterase inhibitor concentrate for the treatment of hereditary angioedema. *Immunotherapy* 2014;6:533–51
18. Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. *Am J Med* 2009;122:780–3
19. Kalfus I, Frank M. C1 inhibitor therapy and hereditary angioedema. *Am J Med* 2010; 123:e15; author reply e7
20. Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int Arch Allergy Immunol* 2011;154:81–8
21. Tourangeau LM, Castaldo AJ, Davis DK, Koziol J, Christiansen SC, Zuraw BL. Safety and efficacy of physician-supervised self-managed c1 inhibitor replacement therapy. *Int Arch Allergy Immunol* 2012;157:417–24
22. Hock FJ, Wirth K, Albus U, Linz W, Gerhards HJ, Wiemer G, et al. Hoe 140 a new potent and long acting bradykinin-antagonist: in vitro studies. *Br J Pharmacol* 1991;102:769–73.
23. Bork K, Yasothan U, P K. Icatibant. *Nat Rev Drug Discov* 2008;7:801–2
24. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 2007;119:1497–503
25. Cicardi M, Banerji A, Bracho F, Malbran A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; 363:532–41
26. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 2011;107:529–37
27. Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS One* 2013; 8:e53773
28. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 2010;363:523–31
29. Levy RJ, Lumry WR, McNeil DL, Li HH, Campion M, Horn PT, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol* 2010;104:523–9
30. Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010; 126:821–7 e14
31. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000899/human_med_000793.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124 . Product information. EPAR. Annex 1. Accessed March 13, 2015
32. Li HH, Campion M, Craig TJ, Soteres DF, Riedl M, Lumry WR, et al. Analysis of hereditary angioedema attacks requiring a second dose of ecallantide. *Ann Allergy Asthma Immunol* 2013;110:168–72
33. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol* 2008;100:153–61
34. Fust G, Farkas H, Csuka D, Varga L, Bork K. Long-term efficacy of danazol treatment in hereditary angioedema. *Eur J Clin Invest* 2011
35. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;363:513–22
36. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med* 2012;125:938 e1–7

37. Bernstein JA, Manning ME, Li H, White MV, Baker J, Lumry WR, et al. Escalating Doses of C1 Esterase Inhibitor (CIN-RYZE) for Prophylaxis in Patients With Hereditary Angioedema. *J Allergy Clin Immunol Pract* 2014;2:77–84 e1
38. Bork K, Witzke G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 1989;83:677–82
39. Martinez-Saguer I, Heller C, Fischer D, Ettingshausen CE, W. K. Prophylactic treatment with pasteurised C1 inhibitor in hereditary angioedema (HAE) – a prospective 32 months follow up. *Blood* 1999; 94(10), Sup 1, Abstract # 1032:2339
40. Reshef A, Moldovan D, Obtulowicz K, Leibovich I, Mihaly E, Visscher S, et al. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study. *Allergy* 2013;68:118–24
41. Martinez-Saguer I, Cicardi M, Suffritti C, Rusicke E, Aygoren-Pursun E, Stoll H, et al. Pharmacokinetics of plasma-derived C1-esterase inhibitor after subcutaneous versus intravenous administration in subjects with mild or moderate hereditary angioedema: the PASSION study. *Transfusion* 2014;54:1552–61
42. <http://isispharm.com/backup/Pipeline/Therapeutic-Areas/SevereandRare.htm#ISIS-PKRx>. Accessed March 13, 2012