

Human pasteurized C1-inhibitor concentrate for the treatment of hereditary angioedema due to C1-inhibitor deficiency

Expert Rev. Clin. Immunol. 7(6), 723–733 (2011)

Konrad Bork

Department of Dermatology,
Johannes Gutenberg University,
Langenbeckstr. 1,
55131 Mainz, Germany
Tel.: +49 6131 177 290
Fax: +49 6131 176 614
bork@hautklinik.klinik.uni-mainz.de

Hereditary angioedema is a relatively rare genetic disorder affecting between one in 10,000 and one in 50,000 individuals worldwide. The most common clinical symptoms observed are relapsing swelling of the skin and abdominal pain attacks. However, more serious and potentially fatal laryngeal attacks can also occur. Hereditary angioedema is most frequently caused by a deficiency of C1-inhibitor. Replacement therapy with Berinert®, an intravenous pasteurized C1-inhibitor concentrate derived from human plasma, is a recommended treatment for rapid resolution of acute attacks of hereditary angioedema due to C1-inhibitor deficiency. Prophylactic therapy with C1-inhibitor is also available. Future advances may improve morbidity and mortality associated with hereditary angioedema.

KEYWORDS: angioedema • Berinert P • C1-inhibitor deficiency • hereditary angioedema • pasteurized C1-inhibitor concentrate

Hereditary angioedema (HAE) is a genetic disorder (Mendelian Inheritance in Man #106100) that is most commonly caused by a deficiency of functionally active C1-inhibitor (C1-INH); it is inherited in an autosomal dominant fashion [1–7]. To date, over 200 mutations in the C1-INH gene have been characterized [5,6]. Spontaneous mutations are frequent and account for around 20% of HAE cases [7]. The low plasma concentrations of functionally active C1-INH permit activation of the kallikrein-kinin system, the classical complement pathway, the fibrinolytic system and the coagulation system. As a result, vasoactive peptides are released, among which bradykinin is considered to be the most important mediator. In July 2000, a new type of dominantly inherited HAE, not associated with C1-INH deficiency, was described in ten families and termed 'HAE with normal C1-INH' or 'HAE type III' [8]. Two unique missense mutations in exon 9 of the coagulation factor XII were identified in six out of 20 unrelated families [9,10]. The focus of the present article, however, is HAE caused by C1-INH deficiency (HAE-C1-INH).

An estimated one in 10,000 to one in 50,000 individuals have C1-INH deficiency worldwide, although this may underestimate the true prevalence of the disease due to under-reporting and misdiagnosis [11]. Symptoms of HAE-C1-INH include skin swellings (including edema of the extremities, facial edema and edema of the genitals), abdominal pain attacks and, in rare cases, episodes of life-threatening upper airway obstruction [7,12]. Uncommon sites of edema include the uvula, tongue and soft pharynx [13]. CNS, pericardiac, renal and pleural involvement have all been observed. Erythema marginatum may be a prodromal sign and is described as a nonpruritic erythematous rash that may have a serpentine shape. Patients with HAE-C1-INH do not know in advance when a forthcoming attack will occur and whether an attack will affect the skin, gastrointestinal tract, larynx or some other site. Occasionally, precipitating events such as emotional stress, mechanical trauma, infectious diseases or the intake of estrogens or angiotensin-converting enzyme inhibitors,

can be identified. Attacks generally last for 1–7 days, followed by disease-free intervals that vary in length. Suffocation due to an untreated laryngeal attack is the most frequent cause of mortality [14]. Such attacks may follow trauma of the oral cavity (e.g., dental surgery) [11,15].

Treatment of HAE due to C1-INH deficiency

For convenience, the treatment of HAE-C1-INH can be distinguished between acute attacks, short-term prophylaxis and long-term prophylaxis [16].

Treatment of acute attacks

Preparations of C1-INH concentrate from human plasma were first used to treat HAE-C1-INH in 1973, and have since been shown to be effective in treating and preventing laryngeal and abdominal pain attacks [17–24]. In 1996, a double-blind, randomized study in patients with HAE-C1-INH compared the efficacy of Baxter/Immuno vapor-heated C1-INH concentrate with placebo; the average time to relief was 55 min in 11 patients receiving C1-INH concentrate and 563 min in 11 patients receiving placebo [19]. Despite its proven efficacy [19,20], the Baxter/Immuno C1-INH concentrate was withdrawn from the market in 2003. Intravenous human pasteurized C1-INH concentrate has been shown to be very effective in the treatment of all HAE attacks requiring treatment, including laryngeal attacks [16,22,23,25]. Mild skin swellings and mild abdominal pain attacks, however, require no treatment or possibly treatment with spasmolytics in the case of abdominal attacks. Side effects of human pasteurized C1-INH concentrate are extremely rare. However, some anaphylactic reactions have occurred, possibly due to a too-rapid infusion speed or use of a preparation that had not attained room temperature before infusing [16,23].

In July 2008, icatibant (Firazyr®; Shire, Basingstoke, UK), a bradykinin B2-receptor antagonist, received marketing authorization in Europe for the symptomatic treatment of HAE attacks in adults. Clinical studies showed that the drug is effective and that it has a favorable safety profile [26,27]. Firazyr is injected subcutaneously. In approximately 10% of attacks, the swellings reoccurred at either the same or a different site (rebound phenomenon) and a second (9%) or a third (1%) injection became necessary. Local side effects at the injection site were common and included erythema, urticarial wheal and burning pain.

Recently, conestat alfa, a recombinant human (rh) C1-INH (Ruconest®/Rhucin®, Pharming Group NV, Leiden, The Netherlands) has been developed for the treatment of HAE attacks and received marketing authorization in Europe in October 2010. rhC1-INH is expressed in the mammary gland of rabbits. In clinical studies, rhC1-INH given intravenously was highly effective in the treatment of HAE attacks [28]. Subtle differences in post-translational glycosylation result in a shorter half-life compared with the human C1-INH concentrate. Since a healthy volunteer with an undisclosed rabbit allergy experienced an anaphylactic reaction after administration of rhC1-INH, the EMA decided that Ruconest is contra-indicated in all patients

with known or suspected rabbit allergy, or with positive serum IgE antibodies against rabbit dander due to the risk of major allergic reactions. Before initiating treatment, patients should be tested for the presence of IgE antibodies against rabbit allergens. Antibody testing should be repeated once a year or after ten treatments, whichever occurs first.

In December 2009, ecallantide (Kalbitor®; Dyax Corp., Cambridge, MA, USA), a recombinant kallikrein inhibitor, received marketing authorization in the USA for the symptomatic treatment of HAE attacks in adults. Ecallantide is a potent and selective inhibitor of plasma kallikrein, thus also inhibiting the formation of bradykinin. Clinical studies showed that the drug is highly effective [29]. Ecallantide is given subcutaneously by healthcare professionals with appropriate medical support to manage HAE-C1-INH and anaphylaxis because in some patients the administration of ecallantide was followed by hypersensitivity reactions, including anaphylactic reactions.

An alternative to C1-INH replacement therapy during an HAE attack is fresh frozen plasma (FFP). Besides the concern about virus safety, other problems of FFP are due to the presence of the enzymatic substrates that sustain angioedema and the need to infuse larger volumes. Therefore, FFP is only recommended for use when C1-INH concentrate or icatibant are not available.

Because laryngeal attacks are potentially life-threatening, and because the relative rarity of the disease means that there is a general lack of knowledge in the medical community about HAE-C1-INH, guidelines recommend that patients maintain a supply of C1-INH concentrate or icatibant at home and with them when traveling [16].

Short-term prophylaxis

One hour prior to diagnostic and surgical intervention in the head and neck areas (including dental surgery and endotracheal narcosis), human pasteurized C1-INH concentrate can be administered prophylactically. Alternatively, short-term prophylaxis of HAE can be performed with attenuated androgens (e.g., danazol or stanozolol), starting 5 days before and ending 2–5 days postevent, or with FFP [15,16,30]. Mild attacks still occurred in a few cases despite pretreatment with C1-INH concentrate.

Long-term prophylaxis

Long-term prophylaxis can be achieved using androgens, anti-fibrinolytic agents, or human pasteurized C1-INH concentrates. Attenuated androgens, which increase plasma concentrations of C1-INH, are an effective treatment used worldwide in patients who have suffered numerous HAE attacks prior to commencing treatment [31–34]. Numerous side effects may be associated with attenuated androgens, including weight gain, menstrual irregularities, virilization, muscle pains, headaches, depression, fatigue and nausea [34–36]. Additionally, liver tumors have been observed in some cases [37] and plasma levels of liver enzymes and lipids may increase [38].

In acute attacks of HAE-C1-INH, there is an activation of the fibrinolytic system leading to the generation of plasmin. Therefore tranexamic acid, which is an antifibrinolytic agent, has

been used for long-term prophylaxis of HAE-C1-INH [39]. The side effects are generally fewer than with attenuated androgens, and can include nausea, vomiting, diarrhea and faintness. However, tranexamic acid may be less effective than attenuated androgens. Long-term prophylaxis with human pasteurized C1-INH concentrate has been performed in selected patients (see later).

Cinryze® (ViroPharma Inc., Exton, PA, USA) is a C1-INH concentrate derived from human plasma that is purified by nanofiltration and chromatographic procedures. Cinryze received marketing authorization in the USA in October 2008 for the prevention of HAE attacks. It is indicated for prophylaxis in adolescents and adults with a history of HAE attacks. Cinryze was evaluated for efficacy and safety in a multicenter, double-blind, placebo-controlled, crossover study [40]. Patients were enrolled if they had been experiencing two or more HAE attacks per month. A total of 20 patients completed the study. The mean number of HAE attacks in each treatment period of 12 weeks was significantly lower for patients receiving Cinryze than for those receiving placebo. Significant reductions were also noted in the mean severity and duration of HAE attacks. It was concluded that Cinryze, given intravenously at a dose of 1000 units (U), was effective in preventing or reducing the frequency of HAE attacks. Breakthrough attacks had to be treated by additional C1-INH injections. Two patients had more attacks during the treatment period than beforehand. The recommended dose of Cinryze is 1000 U every 3–4 days.

C1-INH concentrates

In Europe, three human pasteurized C1-INH concentrate preparations are currently authorized for the treatment of HAE attacks: Berinert® P (CSL Behring GmbH, Marburg, Germany), Ceter® nf (Sanquin, Amsterdam, The Netherlands) and Cinryze. This article will focus on results obtained with Berinert (licensed in some countries under the brand name of Berinert P).

Introduction to the compound

The predecessor human C1-INH concentrate to Berinert was first licensed in Germany in 1979. A series of developments subsequently improved the tolerability, and the first human pasteurized C1-INH concentrate (Berinert P) was licensed in Germany in 1985 [41]. The pooled human plasma used for manufacturing Berinert is obtained from rigorously selected healthy donors. The healthy individuals identified as potentially suitable donors have their plasma tested using licensed serological assays for antibodies against HIV-1 and 2 and hepatitis C virus (HCV) as well as for hepatitis B virus surface antigen (HBsAg). The plasma pools for fractionation are tested by a sensitive nucleic acid testing/PCR assay for hepatitis A virus RNA, hepatitis B virus DNA, HCV RNA, HIV-1 RNA, and high titers of human parvovirus B19 (B19V) DNA (<5 log₁₀ international units [IU] B19V DNA/ml). In-process controls demonstrate that discarding reactive donations and pooling only nonreactive donations is a successful approach. Validation studies involving the intentional addition of viruses have confirmed the extent to which the

manufacturing process of Berinert P was able to inactivate and eliminate the enveloped viruses HIV, bovine viral diarrhea virus (a model virus for HCV), West Nile virus and pseudorabies virus (a nonspecific model virus for large enveloped DNA viruses), as well as the nonenveloped viruses hepatitis A virus and B19V. Robustness studies covering the pasteurization as well as the chromatography steps have confirmed, under production conditions, reliable and reproducible virus reduction. Efficient overall prion reduction occurs during the manufacture of Berinert P, based on investigational studies of the manufacturing process for Berinert P and other plasma-derived products from CSL Behring, or based on published data for comparable manufacturing steps [42].

The manufacturing process for Berinert incorporates procedures for eliminating and inactivating possible viral contaminants. C1-INH is separated from cryo-depleted human plasma by adsorption and precipitation, and is subsequently pasteurized by heat treatment in aqueous solution for 10 h at 60°C. Further purification of the product occurs via chromatography, followed by filtration and lyophilization under sterile conditions in the absence of preservatives [41]. As with other human pasteurized C1-INH concentrates, Berinert P is administered by slow intravenous infusion. One unit of C1-INH in Berinert P is equal to the amount of C1-INH in 1 ml of human plasma, and is therefore equivalent to 270 mg/l or 2.5 µM/l of plasma [41].

Chemistry

C1-INH is a protein, with a molecular mass of 104 kDa, that inhibits complement components (specifically C1-esterase), Factors XIIa and XIa, and kallikrein as well as the fibrinolytic proteases plasmin and tissue-type plasminogen activator. In this way, C1-INH regulates bradykinin generation and prevents the development of angioedema (FIGURE 1). Berinert P is a highly purified, virus inactivated, human plasma-derived C1-INH concentrate.

Pharmacokinetics & metabolism

In a prospective study, the pharmacokinetics of Berinert P were investigated during an attack-free interval in six children and 34 adults with mild-to-severe HAE-C1-INH. The patients received either on-demand treatment or a treatment very early in the course of an attack (individual replacement therapy [IRT]). The median half-life of functional C1-INH plasma levels in children with mild HAE-C1-INH receiving on-demand therapy was 32.9 h (mean: 31.5 h). In adults, the median half-lives of functional C1-INH plasma levels were 39.1 h (mean: 47.8 h) in patients with mild HAE-C1-INH receiving on-demand therapy and 30.9 h (mean: 33.3 h) in patients with severe HAE-C1-INH on IRT [43]. These half-lives were shorter than the previously reported median value of 4.48 days, and were at the lower end of the previously reported range of 1.13–12.40 days [41]. In a retrospective population PK model of the IMPACT 1 study the estimated mean half-life was 32.7 h. This was based on 97 patients treated for acute HAE attacks [44].

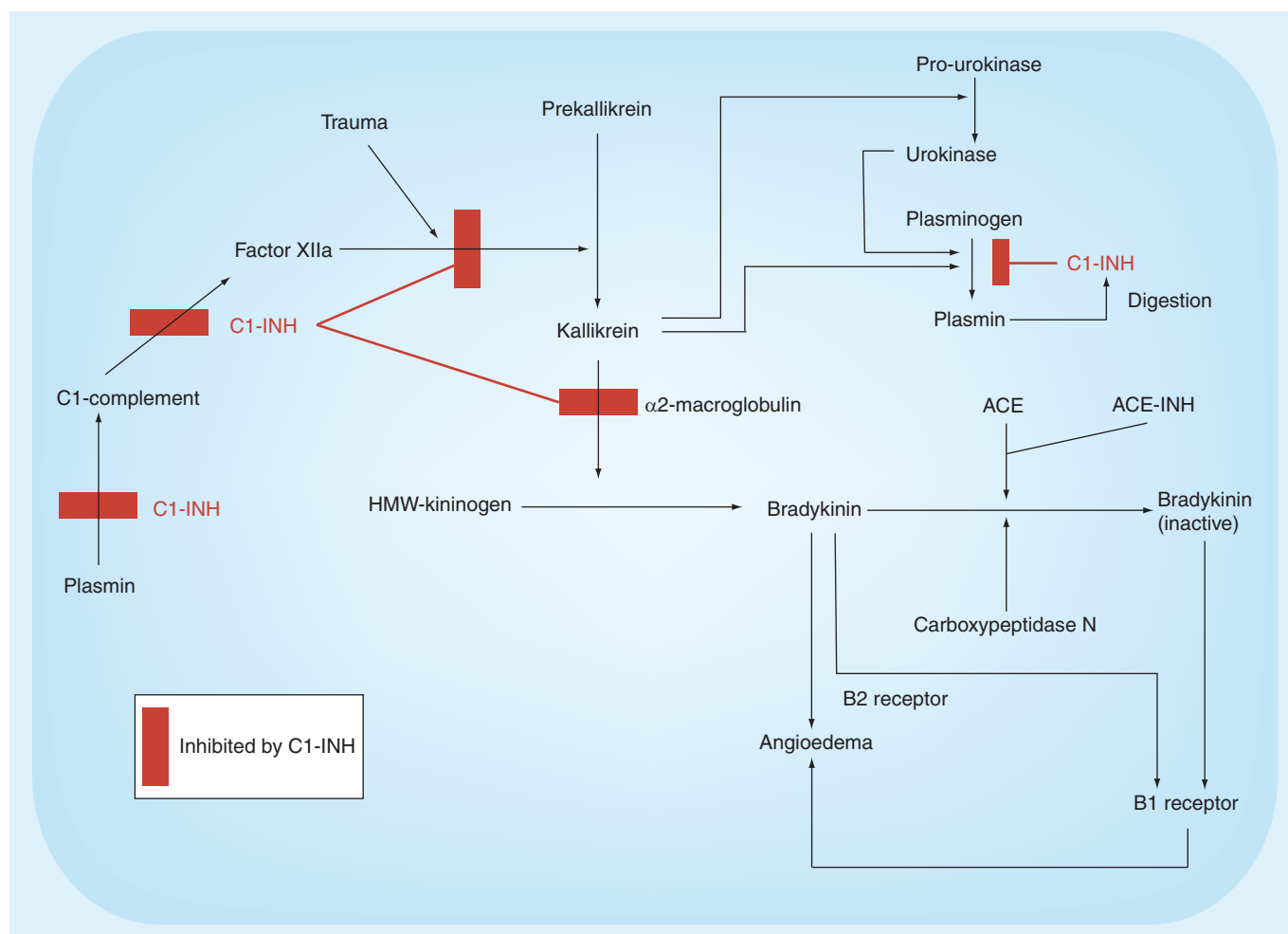


Figure 1. Pathways inhibited by C1 inhibitor.

ACE: Angiotensin-converting enzyme; HMW: High molecular weight; INH: Inhibitor.

Clinical efficacy

Treatment of HAE attacks with human pasteurized C1-INH concentrate

C1-INH concentrate derived from human plasma has been used for the treatment of HAE attacks since 1973 [17]. It was originally regarded as an emergency treatment because of the concern that C1-INH concentrate derived from human plasma could transmit viral infections. After introduction of virus inactivation steps into the manufacturing process, the use of C1-INH was then extended to include treatment of moderate symptoms of the disease. Various studies have shown that purified and virus-inactivated human C1-INH concentrates are effective in treating and preventing laryngeal attacks as well as abdominal pain attacks and skin swellings in patients with HAE-C1-INH (TABLE 1).

A case collection study of patients with HAE-C1-INH by Bork *et al.* compared the treatment of laryngeal attacks with Berinert P with a historical control group of patients who had not received Berinert P for the treatment of laryngeal attacks. Berinert P effectively treated these attacks in all patients, with the time to relief of symptoms ranging from 10 min to 4 h (mean $\pm$ standard

deviation [SD], 42.2 ± 19.9 min). In this study, the mean $\pm$ SD duration of laryngeal attacks was 15.3 ± 9.3 h in patients treated with Berinert P and 100.8 ± 26.2 h in untreated patients [22]. In 2003, Bork *et al.* expanded their published data on the basis of 25 patients with HAE-C1-INH treated with Berinert P for a total of 208 laryngeal attacks. Relief and resolution of symptoms began 30–60 min after injection and the duration of attacks was reduced [45].

Berinert P was also effective in the case of one patient who had 11 episodes of soft palate edema, where all attacks regressed within 5 h of administering Berinert P at a dose of 1000 U [46].

Berinert P was further assessed in a retrospective study of 75 patients with HAE-C1-INH experiencing abdominal attacks [23]. The mean duration of abdominal attacks was reduced in patients treated with Berinert P compared with untreated patients (39.9 vs 92.0 h). Furthermore, this study also addressed the need for rapid treatment of HAE attacks. The mean time to relief of symptoms was 53.5 min in patients treated early (within 2 h after beginning of the abdominal complaints) compared with 114 min when treatment was delayed [23].

Table 1. Clinical studies of human pasteurized and steam-heated C1-inhibitor concentrates in the treatment of hereditary angioedema attacks.

Study (year)	Patients (n); acute attacks	Time to onset of relief/resolution of symptoms	Ref.
<i>Berinert P</i>			
Bork and Barnstedt (2001)	13; 193 laryngeal attacks	Mean time to relief of 42.2 min; resolution in mean of 15.3 h with Berinert P vs 100.3 h without Berinert P	[22]
Bork and Koch (2001)	1; 11 soft palate edema attacks	Complete resolution of symptoms within 5 h	[46]
Bork <i>et al.</i> (2003)	25; 208 laryngeal attacks	Onset of relief of symptoms in 30–60 min	[45]
Bork <i>et al.</i> (2005)	75; 4834 abdominal attacks	Onset of relief in 10–150 min; mean time to relief of 53.5 min when treated early	[23]
Farkas <i>et al.</i> (2002)	9; laryngeal or abdominal attacks [†]	Onset of relief in 30–60 min; complete resolution of symptoms in 24–48 h	[56]
Farkas <i>et al.</i> (2007)	61; 468 laryngeal or abdominal attacks, or cutaneous swellings	Onset of relief within mean of 15 min for laryngeal attacks and 30 min for abdominal attacks	[47]
Bork <i>et al.</i> (2008)	47; 2104 skin swellings	Onset of relief in 1.1 h; complete resolution of symptoms in 1.7 days	[48]
Craig <i>et al.</i> (2009)	125; 98 abdominal attacks, 25 facial attacks	Onset of relief in median of 30 min	[51]
Craig <i>et al.</i> (2010)	16; 39 laryngeal attacks	Onset of relief in median of 15 min	[52]
Zanichelli <i>et al.</i> (2011)	44; 376 attacks, 94 laryngeal attacks	Complete resolution of treated attacks in 1.1 days vs 1.85 days untreated	[50]
Wasserman <i>et al.</i> (2011)	53; 663 abdominal attacks, 43 facial attacks	Onset of relief in median of 19.8 min	[53]
<i>Other virus-inactivated human C1-INH concentrates</i>			
Agostoni and Cicardi (1992)	27; 67 laryngeal attacks, 15 abdominal attacks	Onset of relief in 30–90 min	[7]
Cicardi <i>et al.</i> (1982)	104; 14 severe attacks	Prompt reversal	[74]
Kunschak <i>et al.</i> (1998)	36; 166 attacks	Onset of relief in 7.62 h with C1-INH concentrate vs 15.35 h with placebo; resolution of symptoms in 23.98 h	[20]
Visentin <i>et al.</i> (1998)	7; 87 attacks	Onset of relief in 50 min	[21]
Waytes <i>et al.</i> (1996)	11; 55 attacks	Onset of relief in 55 min with C1-INH concentrate vs 563 min with placebo	[19]
Cicardi and Zingale (2003)	Number of infusions: 381 for laryngeal attacks, 238 for abdominal attacks, 11 for cutaneous swellings	Initial regression rapidly induced	[75]

[†]Pediatric patients.
INH: Inhibitor.

In 2007, the clinical experience of treating 468 HAE attacks in 61 patients with Berinert P was reported [47]. The dose administered for each attack was 500 U. Symptoms improved within 15–60 min after administration of Berinert P.

In 2008, a retrospective study on the efficacy of Berinert P in the treatment of skin swellings in patients with HAE-C1-INH was published [48]. From 1976 through 2007, a total of 2104 such attacks in 47 patients were treated with on-demand therapy with Berinert P or its nonpasteurized predecessor, respectively. The results were compared with 9046 untreated skin swellings in the same patients. The first clinical sign of efficacy was a slowdown of symptom progression, accompanied by a decreased feeling of

tension and pain in the swollen area. The mean time to first relief of symptoms was 1.1 ± 1.4 h in treated attacks and 50.4 ± 33 h in untreated attacks. Improvement took longer for facial skin swellings than for swellings of the extremities, genitals or trunk. The duration of skin swellings was 1.7 days for treated swellings and 3.2 days for untreated swellings. In treated swellings, there was long-lasting control and no rebound within the 48 h after drug administration, and no cases of facial edema were succeeded by laryngeal attacks.

In 2009, Kreuz *et al.* studied the frequency of attacks in 22 patients who adapted the frequency of Berinert P self-administration according to the early signs of an HAE attack (i.e. before edema and/or colic-like abdominal pain emerged) very

early in the course of an attack (i.e. IRT) and compared this with the frequency of HAE attacks in patients undergoing long-term prophylaxis with danazol [49]. They found that the median number of attacks per year significantly decreased in patients treated with Berinert P compared with the patients being treated with danazol.

In a prospective cohort study, 44 HAE patients were treated with Berinert P in 376 attacks of which 94 were laryngeal attacks which are the most severe. Attacks treated with C1-INH resolved faster (1.1 days) than untreated attacks (1.85 days) [50].

In a randomized, double-blind, placebo-controlled study (International, Multicenter, Prospective, Angioedema, C1-INH Trial 1 [IMPACT 1]) in 125 patients with HAE-C1-INH, the efficacy of Berinert given at intravenous doses of 10 or 20 U/kg bodyweight was compared with placebo [51]. The efficacy was studied in abdominal attacks and facial swellings. The median time to onset of relief was significantly shorter with 20 U/kg of Berinert than with placebo (0.5 vs 1.5 h). With a dose of 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 vs 1.5 h), and the difference did not reach statistical significance. The conclusion was that Berinert given intravenously at a dose of 20 U/kg is an effective treatment for abdominal and facial attacks in patients with HAE-C1-INH [51]. In this study, however, the time to first symptom relief of only 1.5 h after treatment with placebo seemed unexpectedly short and is conspicuous.

Recently the efficacy of Berinert was assessed in the treatment of 39 laryngeal attacks in 16 patients with HAE-C1-INH in a prospective, uncontrolled, open-label study (IMPACT 2) [52]. The patients received Berinert at a single dose of 20 U/kg for the treatment of each attack. The median time to onset of symptom relief was 15 min. The median time to complete resolution of all symptoms was 8.25 h. These results confirmed a previous report on the efficacy of Berinert P in the treatment of 193 laryngeal attacks [22].

A further prospective, uncontrolled study in patients with HAE-C1-INH investigated the efficacy of Berinert given at a dose of 20 U/kg for the treatment of 663 abdominal attacks in 50 patients and for the treatment of 43 facial attacks in 16 patients [53]. The median time to onset of relief was 19.8 min for abdominal attacks and 28.2 min for facial attacks. Only in 0.28% (2 out of 706) of the attacks treated with Berinert was the time to onset of relief of symptoms >4 h. These results confirmed a previous report on the efficacy of Berinert P in the treatment of abdominal attacks and facial swellings [23,48].

Dosage

In the IMPACT 1 study, the treatment of facial swellings and abdominal attacks with Berinert at a dose of 20 U/kg was significantly more effective than treatment with placebo [51]. Treatment with 10 U/kg was also more effective than with placebo; the difference, however, did not reach statistical significance. In this respect, the results of this study contrasted with practical experience published to date on the use of C1-INH concentrates to treat thousands of HAE attacks in hundreds of patients, including patients in a randomized, double-blind study from 1996 conducted in the USA [19]. According to

these studies, in the majority of patients a dose of 500 U (i.e., 7.1 U/kg in a patient weighing 70 kg) was highly effective. In some patients, 1000 U (14.2 U/kg) was necessary to successfully control an HAE attack. In an uncontrolled observational study in 61 patients experiencing 468 HAE attacks, Berinert P given at a dose of 500 U was usually effective, and a dose of 1000 U was needed for the treatment of only nine attacks (2%) [47]. In further studies, a dose of 500 U was effective in treating 68.6% of 4834 abdominal attacks in 75 patients [23], 81% of 2104 skin swellings in 47 patients [48] and 24.9% of 193 laryngeal attacks in 18 patients [22].

The results of the randomized, double-blind IMPACT 1 study [51] led to approval of the 20 U/kg dose of Berinert (i.e., 1400 U in a 70-kg patient [nearly three vials of 500 U]) in Australia, Canada, the USA and numerous European countries for the treatment of HAE attacks.

A dose of 20 U/kg should be obligatory for the treatment of laryngeal attacks due to their potentially life-threatening nature. If an attack is not potentially life-threatening (i.e., skin swellings and abdominal attacks, which together comprise approximately 99% of all HAE attacks), the dose can be adjusted to the patient's individual requirement and administration of 500 or 1000 U per attack may be sufficient.

Berinert P can be stored at room temperature, which is practical and advantageous when patients are traveling with supplies for use in case of a life-threatening attack.

Home therapy

Home therapy programs for the treatment of HAE attacks with C1-INH concentrate are currently being established. Self-administration, or home therapy, could have considerable benefits in terms of improving quality of life, reducing attack frequency and enabling greater patient independence and convenience [54,55]. Training programs being introduced in some countries address practical aspects of administering C1-INH concentrate. However, concerns and practical issues that also have to be addressed include the management of side effects, and medical and legal responsibilities. Further issues to be considered are the potential for problems associated with incorrect administration of intravenous injections and vein obstruction, and how to address these.

Berinert P in children & in pregnancy

In 2002, Farkas *et al.* published their experiences of using Berinert P in the treatment of HAE attacks in nine children with HAE-C1-INH who had experienced laryngeal attacks or severe acute abdominal complaints. Treatment with Berinert P accomplished substantial relief within 30–60 min, accompanied by regression of the edematous swelling. Complete resolution of clinical signs and symptoms occurred within 24–48 h [56]. Further results were published in 2007 [47].

In 2007, the cases were reported of four pregnant women with HAE-C1-INH who were successfully treated with Berinert P for six HAE attacks [47]. A further retrospective study recently reported on the beneficial effect of Berinert P during pregnancy. Nine women were treated for 36 attacks and experienced improvements

in their symptoms within 15–60 min [57]. In a recent study, a dose of 500 or 1000 U of Berinert P effectively controlled HAE attacks before and during 35 pregnancies (37 children) and during breastfeeding, and Berinert P was shown to be safe for the mothers as well as their children [58].

No changes in anti-C1-INH autoantibody status were observed in the patients who had received Berinert P [47].

Rebound attacks

In the treatment of HAE attacks, efficacy can be determined by measuring the time to onset of relief, the maximum intensity of symptoms and the total duration of an attack. However, a further important criterion is the sustainability of efficacy – that is, whether an attack reoccurs at the same or at a different location within hours to several days after treatment. Rebound attacks have not attracted much attention in the past. In several studies, repeated administration of Berinert P was not associated with any decrease in efficacy or in the occurrence of a rebound effect [47,48,51].

Short-term prophylactic treatment of HAE-C1-INH with human pasteurized C1-INH concentrate

In patients with HAE-C1-INH, surgery may provoke attacks in the form of swelling of the lips, facial edema, tongue edema and laryngeal attacks with upper airway obstruction. Cases with fatal outcomes have been reported. Pre-operative prophylaxis with C1-INH concentrate has been reported in only a small number of patients [59–63]. However, because HAE symptoms rarely occur after surgical procedures even in the absence of short-term prophylaxis, it cannot be concluded from these reports that the prophylaxis regimens used were effective in preventing postsurgical swelling. To investigate the efficacy of short-term prophylaxis, the frequency of swellings following surgery in the presence and absence of prophylaxis was ascertained in a recent study focusing on tooth extractions, which frequently trigger clinical symptoms of HAE-C1-INH. The study involved 171 patients with 705 tooth extractions, and determined the frequency of extractions that were followed by HAE symptoms in patients with and without pre-operative short-term prophylaxis with 500 or 1000 U of Berinert P [64]. Facial swelling or potentially life-threatening laryngeal attacks, or both, occurred in 124 out of 577 tooth extractions (21.5%) in the absence of prophylaxis. Similar symptoms occurred in a lower proportion of patients undergoing tooth extractions (16 out of 128; 12.5%) following short-term prophylaxis with Berinert P. It was concluded that short-term prophylaxis with Berinert P significantly reduced the risk of HAE symptoms following tooth extraction. A dose dependency was observed: prophylaxis with 1000 U Berinert resulted in fewer attacks than with 500 U Berinert. In some patients, however, facial swellings and laryngeal attacks occurred despite the prophylaxis.

Long-term prophylaxis of HAE-C1-INH with human pasteurized C1-INH concentrate

C1-INH concentrates are also effective for long-term prophylaxis of HAE-C1-INH, and have been recommended for use in this setting, although Berinert P is currently not authorized for use in

this indication. The first prophylactic application of Berinert P was described by Bork *et al.* in one patient with HAE-C1-INH; administration of 500 U of Berinert P every 4–5 days resulted in the patient remaining free of symptoms [65]. Subsequently, the successful use of Berinert P for long-term prophylaxis has been described in a number of patients with HAE-C1-INH [66,67] and in one patient during pregnancy [68]. Another study has also assessed use of Ceter in long-term prophylaxis of HAE-C1-INH. Self-administration of Ceter decreased the number of attacks in ten patients [24]. In 2010, 14 patients were described who received long-term prophylaxis with one or more weekly intravenous injections of Berinert P for an average of 9 years [69]. The most important benefit of this treatment was a reduction in symptom intensity: the vast majority of attacks were only mild or very mild. All patients reported that all or most of their attacks were considerably less severe than beforehand: the percentage of severe attacks was 93.3% without prophylaxis and 3.8% with prophylaxis. The monthly number of attacks was lower at the end of the study in eight patients, higher in five patients (considerably higher in some of these patients), and unchanged in one patient. In the opinion of most patients, the improvement in their quality of life due to weekly long-term treatment with Berinert P, compared with their disease burden before treatment, greatly outweighed the disadvantages. In some patients an increased amount of Berinert P was required to control the disease. Some patients reported rapidly developing attacks and skin swellings at multiple locations, which they had not experienced before commencing prophylaxis. This observation, and the necessity for regular administration of C1-INH concentrate, once a week or more frequently, reflected increased HAE-C1-INH activity in some patients. However, none of the patients reported any loss of effectiveness during the treatment with Berinert P.

Postmarketing surveillance, safety & tolerability

Human plasma-derived products – such as C1-INH concentrate, carry with them the risk of transmitting blood-borne viruses and, theoretically, prion proteins. To minimize this risk, pasteurized C1-INH concentrates undergo various production steps: selection and testing of plasma donations for the absence of pathogenic blood-borne viruses; testing the plasma pool for fractionation for the absence of these viruses; and ensuring that the manufacturing process includes steps for virus inactivation and removal which have to be validated in appropriate studies for their capacity to remove viruses.

Due to the potential risk for viral contamination in human plasma-derived products, virus safety has been a major focus of postmarketing surveillance for Berinert P.

Early clinical reports in a limited number of patients on the use of Berinert P with intensive monitoring for viral safety by Klarmann *et al.* [70] and Bork *et al.* [71] reported no safety concerns with transmission of hepatitis or HIV.

Since the market introduction of Berinert P in 1985, the postmarketing surveillance has revealed a favorable record of clinical safety for Berinert P within the approved indication in over 500,000 treatments administered during the past 25 years.

From 1985 to 30 November 2009, there were 58 cases of suspected adverse drug reactions (ADRs) reported worldwide, of which 42 cases were covered by the product's known safety profile: seven cases of allergic- or anaphylactic-type reactions (in very rare cases involving shock), two cases of chills and fever, 13 cases of lack of effect, five cases of suspected virus transmission and 15 cases of thrombosis. None of the five cases of suspected virus transmission could be attributed to Berinert P. Only one case of thrombosis occurred when Berinert P was used in the labeled indication; causality was excluded after autopsy revealed pre-existing cerebromalacia in this patient. The other 14 cases of thrombosis occurred during off-label use involving substantially higher doses than indicated in the product's label. Sixteen of the 58 ADR cases involved isolated reports of varying symptoms that were not covered by the known safety profile of Berinert P. A causal relationship to the product could not be established for any of these unlisted ADR cases. According to the Council for International Organizations of Medical Sciences (CIOMS) criteria, the overall ADR reporting rate for Berinert P is 'rare' [72]. In some patients receiving weekly treatment with Berinert P for many years, an increase in the disease activity of HAE has been reported (see above) [69,73].

Regulatory affairs

Berinert P is currently licensed for the treatment of HAE attacks in 24 European countries, Argentina, Australia, Canada, Israel, Japan and the USA (under the brand name of Berinert in the USA). Berinert P is also available for use on a named patient basis in a number of countries.

Conclusion

Hereditary angioedema is a rare genetic disorder most commonly caused by a deficiency of C1-INH (HAE-C1-INH). Despite an increase in the awareness of HAE-C1-INH, it continues to present an unmet clinical need, with untreated cases of laryngeal attacks often leading to mortality. Human pasteurized C1-INH concentrates provide a treatment for HAE-C1-INH by replacing the deficient C1-INH in these patients. It contains fewer complement proteins and has a reduced risk for transmission of viral contaminants compared with FFP. Therefore, C1-INH concentrates are the preferred treatment option for HAE attacks as well as for short-term prophylaxis of HAE-C1-INH. Berinert P is a well tolerated and effective treatment for HAE attacks, drawing upon more than 25 years of clinical experience. During this time, there have been no proven cases of viral transmission, demonstrating the high level of safety associated with Berinert P. In several guidelines, human pasteurized C1-INH concentrates

are also recommended as the first-line medication for short-term prophylaxis of HAE-C1-INH. Clinical experience may suggest that Berinert P is also effective in long-term prophylaxis of HAE-C1-INH. Recent publications suggest its further benefits in home therapy of HAE attacks.

Expert commentary

The treatment of HAE attacks remains a major focus in reducing the morbidity and mortality associated with HAE-C1-INH. Overall, clinical studies and daily experience in patients treated with human pasteurized C1-INH concentrates document a high degree of effectiveness in treating all types of HAE attacks, together with an excellent safety profile. Key advantages of Berinert P also concern its reliability and sustainability – that is, the lack of a rebound effect at the same or a different location within 48 h after treatment, which has been observed with other treatments for HAE attacks. Another advantage is that Berinert P, if given early in the course of an attack, may completely stop the development of an attack so that the major symptoms can be avoided.

Five-year view

Home therapy programs are currently being established for patients with HAE-C1-INH [54,55]. The benefits of home therapy include improvements in quality of life, reductions in attack frequency and increases in patient independence and convenience. Some countries are introducing training programs to include practical aspects of administering C1-INH concentrates intravenously [54]. There are, however, some other concerns and practical problems that also have to be addressed. Such issues include the management of side effects (even if their occurrence is rare), medical and legal responsibilities, drug storage and availability, the potential for incorrect administration of intravenous injections and vein obstruction.

A number of effective therapies for the treatment of HAE attacks are currently available. These include replacement of the deficient C1-INH by virus-inactivated C1-INH concentrates, together with new options that include inhibitors of the contact system, such as the kallikrein inhibitor ecallantide, a human recombinant C1-INH concentrate, and the bradykinin B2-receptor antagonist icatibant for blocking the bradykinin effect at the endothelium. With increasing practical experience over the next 5 years in the use of these therapies and an expansion in the access to Berinert P for the treatment of HAE attacks, there may be further advances in therapies that impact both the treatment of HAE attacks and the prophylaxis of HAE-C1-INH, with the goal of diminishing the burden of HAE-C1-INH for the patient.

Key issues

- Classical hereditary angioedema (HAE-C1-INH) is caused by C1-inhibitor (C1-INH) deficiency.
- HAE-C1-INH is associated with potentially life-threatening laryngeal attacks and severe colic-like abdominal pain.
- Intravenous infusion of human pasteurized C1-INH concentrate can be used in the treatment of HAE attacks as well as for short-term prophylaxis of HAE-C1-INH.
- Human pasteurized C1-INH concentrate has demonstrated excellent tolerability during more than 25 years of clinical use.
- Home therapy with human pasteurized C1-INH concentrate has demonstrated good safety and efficacy.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This

includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- Quincke H. Über akutes umschriebenes Hautödem. *Monatsh. Prakt. Dermatol.* 1, 129–131 (1882).
- Osler W. Hereditary angioneurotic edema. *Am. J. Med. Sci.* 95, 362–367 (1888).
- Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase. *Am. J. Med.* 35, 37–44 (1963).
- Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. *Science* 148, 957–958 (1965).
- Bowen B, Hawk JJ, Sibunka S, Hovick S, Weiler JM. A review of the reported defects in the human C1 esterase inhibitor gene producing hereditary angioedema including four new mutations. *Clin. Immunol.* 98, 157–163 (2001).
- Kalmar L, Bors A, Farkas H *et al.* Mutation screening of the C1 inhibitor gene among Hungarian patients with hereditary angioedema. *Hum. Mutat.* 22, 498 (2003).
- Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 71, 206–215 (1992).
- Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 356, 213–217 (2000).
- 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.* 343, 1286–1289 (2006).
- Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. *Immunol. Allergy Clin. North Am.* 26, 709–724 (2006).
- Longhurst HJ, Bork K. Hereditary angioedema: causes, manifestations and treatment. *Br. J. Hosp. Med. (Lond.)* 67, 654–657 (2006).
- Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am. J. Gastroenterol.* 101, 619–627 (2006).
- Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am. J. Med.* 119, 267–274 (2006).
- Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin. Proc.* 75, 349–354 (2000).
- Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *J. Am. Dent. Assoc.* 134, 1088–1094 (2003).
- Bowen T, Cicardi M, Farkas H *et al.* 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin. Immunol.* 6, 24 (2010).
- Brackertz D, Kueppers F. Hereditary angioneurotic oedema. *Lancet* 2, 680 (1973).
- First medication of C1-inhibitor (C1-INH) concentrate in hereditary angioedema.**
- Gadek JE, Hosea SW, Gelfand JA *et al.* Replacement therapy in hereditary angioedema: successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. *N. Engl. J. Med.* 302, 542–546 (1980).
- Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N. Engl. J. Med.* 334, 1630–1634 (1996).
- Key randomized, placebo-controlled clinical trial with C1-INH concentrate in hereditary angioedema.**
- Kunschak M, Engl W, Maritsch F *et al.* A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion* 38, 540–549 (1998).
- Visentin DE, Yang WH, Karsh J. C1-esterase inhibitor transfusions in patients with hereditary angioedema. *Ann. Allergy Asthma Immunol.* 80, 457–461 (1998).
- Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch. Intern. Med.* 161, 714–718 (2001).
- Bork K, Meng G, Staubach P, Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 45, 1774–1784 (2005).
- Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J. Allergy Clin. Immunol.* 117, 904–908 (2006).
- Gompels MM, Lock RJ, Abinun M *et al.* C1 inhibitor deficiency: consensus document. *Clin. Exp. Immunol.* 139, 379–394 (2005).
- 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.* 119, 1497–1503 (2007).
- Cicardi M, Banerji A, Bracho F *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N. Engl. J. Med.* 363, 532–541 (2010).
- Zuraw B, Cicardi M, Levy RJ *et al.* Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J. Allergy Clin. Immunol.* 126, 821–827 (2010).
- Cicardi M, Levy RJ, McNeil DL *et al.* Ecallantide for the treatment of acute attacks in hereditary angioedema. *N. Engl. J. Med.* 363, 523–531 (2010).
- Farkas H, Gyenyey L, Gidofalvy E, Fust G, Varga L. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. *J. Oral Maxillofac. Surg.* 57, 404–408 (1999).
- Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N. Engl. J. Med.* 295, 1444–1448 (1976).
- Cicardi M, Bergamaschini L, Cugno M, Hack E, Agostoni G, Agostoni A. Long-term treatment of hereditary angioedema with attenuated androgens: a survey of a 13-year experience. *J. Allergy Clin. Immunol.* 87, 768–773 (1991).

- 33 Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States. *Immunol. Allergy Clin. North Am.* 26, 653–668 (2006).
- 34 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.* 100, 153–161 (2008).
- 35 Cicardi M, Castelli R, Zingale LC, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. *J. Allergy Clin. Immunol.* 99, 194–196 (1997).
- 36 Zurlo JJ, Frank MM. The long-term safety of danazol in women with hereditary angioedema. *Fertil. Steril.* 54, 64–72 (1990).
- 37 Bork K, Schneiders V. Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. *J. Hepatol.* 36, 707–709 (2002).
- 38 Szeplaki G, Varga L, Valentin S *et al.* Adverse effects of danazol prophylaxis on the lipid profiles of patients with hereditary angioedema. *J. Allergy Clin. Immunol.* 115, 864–869 (2005).
- 39 Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. *N. Engl. J. Med.* 287, 452–454 (1972).
- 40 Zuraw BL, Busse PJ, White M *et al.* Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N. Engl. J. Med.* 363, 513–522 (2010).
- **Key randomized, placebo-controlled clinical trial with C1-INH concentrate for prophylaxis in hereditary angioedema.**
- 41 De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. *Transfus. Apher. Sci.* 29, 247–254 (2003).
- 42 Groener A, Nowak T, Schäfer W. An integrate approach to effective pathogen reduction for a plasma-derived C1-inhibitor concentrate. *Haemostaseologie* 28, A96 (2008).
- 43 Martinez-Saguer I, Rusicke E, Aygoren-Pursun E, von Hentig N, Klingebiel T, Kreuz W. Pharmacokinetic analysis of human plasma-derived pasteurized C1-inhibitor concentrate in adults and children with hereditary angioedema: a prospective study. *Transfusion* 50, 354–360 (2010).
- 44 Bernstein JA, Ritchie B, Levy RJ *et al.* Population pharmacokinetics of plasma-derived C1 esterase inhibitor concentrate used to treat acute hereditary angioedema attacks. *Ann. Allergy Asthma Immunol.* 105, 149–154 (2010).
- 45 Bork K, Hardt J, Schicketanz KH, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch. Intern. Med.* 163, 1229–1235 (2003).
- 46 Bork K, Koch P. Episodes of severe dyspnea caused by snoring-induced recurrent edema of the soft palate in hereditary angioedema. *J. Am. Acad. Dermatol.* 45, 968–969 (2001).
- 47 Farkas H, Jakab L, Temesszentandrási G *et al.* Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy. *J. Allergy Clin. Immunol.* 20, 941–947 (2007).
- 48 Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 63, 751–757 (2008).
- 49 Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Heller C, Klingebiel T. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 49, 1987–1995 (2009).
- 50 Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 66, 192–196 (2011).
- 51 Craig TJ, Levy RJ, Wasserman RL *et al.* Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J. Allergy Clin. Immunol.* 124, 801–808 (2009).
- **Key randomized, placebo-controlled clinical trial with C1-INH concentrate in hereditary angioedema.**
- 52 Craig TJ, Wasserman RL, Levy RJ *et al.* Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J. Clin. Immunol.* 30, 823–829 (2010).
- 53 Wasserman RL, Levy RJ, Bewtra AK *et al.* Prospective study of C1 esterase inhibitor in the treatment of successive acute abdominal and facial hereditary angioedema attacks. *Ann. Allergy Asthma Immunol.* 106, 62–68 (2011).
- 54 Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur. J. Dermatol.* 19, 147–151 (2009).
- 55 Longhurst HJ, Farkas H, Craig T *et al.* HAE international home therapy consensus document. *Allergy Asthma Clin. Immunol.* 6, 22 (2010).
- **Recommendations for self-administration and home therapy in hereditary angioedema.**
- 56 Farkas H, Harmat G, Fust G, Varga L, Visy B. Clinical management of hereditary angio-oedema in children. *Pediatr. Allergy Immunol.* 13, 153–161 (2002).
- **Treatment with C1-INH concentrate in children with hereditary angioedema.**
- 57 Czaller I, Visy B, Csuka D, Fust G, Toth F, Farkas H. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 152, 44–49 (2010).
- 58 Martinez-Saguer I, Rusicke E, Aygoren-Pursun E, Heller C, Klingebiel T, Kreuz W. Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. *Am. J. Obstet. Gynecol.* 203, 131–137 (2010).
- 59 Leimgruber A, Jaques WA, Spaeth PJ. Hereditary angioedema: uncomplicated maxillofacial surgery using short-term C1 inhibitor replacement therapy. *Int. Arch. Allergy Immunol.* 101, 107–112 (1993).
- 60 Langton D, Weiner J, Fary W. C1-esterase inhibitor concentrate prevents upper airway obstruction in hereditary angio-oedema. *Med. J. Aust.* 160, 383–384 (1994).
- 61 Maves KK, Weiler JM. Tonsillectomy in a patient with hereditary angioedema after prophylaxis with C1 inhibitor concentrate. *Ann. Allergy* 73, 435–438 (1994).
- 62 Mohr M, Pollok-Kopp B, Gotze O, Burchardi H. The use of a C1-inhibitor concentrate for short-term preoperative prophylaxis in two patients with hereditary angioedema. *Anaesthesist* 45, 626–630 (1996).
- 63 Lehmann A, Lang J, Boldt J, Saggau W. Successful off-pump coronary artery bypass graft surgery in a patient with hereditary angioedema. *J. Cardiothorac. Vasc. Anesth.* 16, 473–476 (2002).
- 64 Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings following tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1-INH

- concentrate; a retrospective study. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 112, 58–64 (2011).
- 65 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.* 83, 677–682 (1989).
 - **First report about long-term prophylactic treatment with C1-INH concentrate.**
 - 66 Martinez-Saguer I, Heller C, Fischer D, Ettingshausen CE, Kreuz W. Prophylactic treatment with pasteurised C1 inhibitor in hereditary angioedema (HAE) – a prospective 32 months follow up. *Blood* 94(Suppl. 1), 2339 (1999) (Abstract 1032).
 - 67 Tallroth GA. Long-term prophylaxis of hereditary angioedema with a pasteurized C1 inhibitor concentrate. *Int. Arch. Allergy Immunol.* 154, 356–359 (2011).
 - 68 Hermans C. Successful management with C1-inhibitor concentrate of hereditary angioedema attacks during two successive pregnancies: a case report. *Arch. Gynecol. Obstet.* 276, 271–276 (2007).
 - 69 Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int. Arch. Allergy Immunol.* 154, 81–88 (2011).
 - 70 Klarmann D, Kreuz W, Joseph-Steiner J, Ehrenforth S. Hepatitis C and pasteurized C1-inhibitor concentrate. *Transfusion* 36, 84–85 (1996).
 - 71 Bork K. Prospective virus safety follow-up after therapy with a pasteurised C1 inhibitor concentrate. *Biomed. Progr.* 2, 59–61 (1992).
 - 72 Bork K, Fremann S, Kreuz W. Long-term safety of C1 inhibitor concentrate in the treatment of acute hereditary angioedema attacks. *Allergy* 65, 204 (2010) (Abstract 506).
 - 73 Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. *Am. J. Med.* 122, 780–783 (2009).
 - 74 Cicardi M, Bergamaschini L, Marasini B, Boccassini G, Tucci A, Agostoni A. Hereditary angioedema: an appraisal of 104 cases. *Am. J. Med. Sci.* 284, 2–9 (1982).
 - 75 Cicardi M, Zingale L. How do we treat patients with hereditary angioedema. *Transfus. Apher. Sci.* 29, 221–227 (2003).