

Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: A systematic literature review

Konrad Bork, M.D.,¹ Isabella Steffensen, Ph.D.,² and Thomas Machnig, M.D.³

ABSTRACT

Hereditary angioedema (HAE) due to C1 esterase inhibitor (HAE-C1-INH) deficiency is a rare genetic disorder presenting with recurrent episodes of skin swellings, abdominal pain attacks, and potentially fatal laryngeal edema. This study was designed to review the efficacy and safety of pasteurized, human, plasma-derived C1-INH concentrate for the treatment of patients with HAE-C1-INH. A systematic search of electronic databases up to December 2011 was performed without language or date restrictions. Two reviewers completed the study selection using predefined inclusion criteria, tabulated, and analyzed the data. The data were inappropriate for meta-analysis; thus, a qualitative synthesis was performed. We identified 89 studies (≈2000 patients) that investigated C1-INH. Replacement therapy with C1-INH significantly shortened time to onset of symptom relief in HAE attacks compared with placebo in a randomized controlled trial, and similar improvements were consistently reported in observational and descriptive studies, accompanied by improvements in patients' quality of life. C1-INH has been shown to be effective for patients receiving home therapy and short- and long-term prophylaxis. Treatment with C1-INH was generally well tolerated. Administration of C1-INH was not associated with transmission of viruses or development of autoantibodies irrespective of treatment duration. This research provides additional confirmation of the efficacy of C1-INH in the treatment and prevention of HAE attacks. C1-INH is generally safe and well tolerated and has an excellent safety record for over 25 years of clinical use.

(Allergy Asthma Proc 34:312–327, 2013; doi: 10.2500/aap.2013.34.3677)

Hereditary angioedema (HAE) due to C1-esterase inhibitor (C1-INH) deficiency (HAE-C1-INH) is a rare genetic disorder caused by a genetic deficiency of functional C1-INH. There are two types of HAE-C1-INH, involving a quantitative (type I) or a qualitative (type II) deficiency of C1-INH.¹ The disease is characterized by recurrent episodes of self-limiting subcutaneous and submucosal swelling. HAE-C1-INH is a potentially fatal illness because laryngeal involvement may lead to asphyxiation. Mortality in untreated patients with HAE-C1-INH may be as high as 30%. The most common locations for edema during an acute HAE attack are the skin and the abdomen. Laryngeal edema is seen in ~1% of HAE attacks.² More rarely, other organs are affected.

The incidence of HAE-C1-INH is estimated at 1:10,000 to 1:50,000. Although the first HAE attack

usually occurs in the first or second decade of life, the diagnosis of HAE-C1-INH is often made considerably later.

HAE attacks develop over several hours and can last 2–7 days. They are usually not associated with erythema, pruritus, or urticaria. Known triggering factors include trauma (in particular, dental or surgical procedures), emotional distress, infection, and febrile illness. Often, however, there is no apparent trigger. The attack frequency of HAE-C1-INH varies greatly among individuals, ranging from weekly to yearly or less, while some individuals (identified by family screening) remain asymptomatic.

The international consensus algorithm for the diagnosis, therapy, and management of HAE-C1-INH has been updated in 2010.³ Treatment recommendations for acute attacks, short- and long-term prophylaxis of the international consensus algorithm comply with recommendations of the international consensus on hereditary and acquired angioedema, published in 2012⁴ and are in line with recent reviews on the treatment of HAE.^{5,6} The consensus algorithm recommends treating acute attacks as quickly as possible with one of the following first-line therapies: plasma-derived C1-INH concentrate, icatibant (a bradykinin receptor blocker), or ecallantide (a kallikrein inhibitor). A recombinant C1-INH concentrate produced from milk of transgenic rabbits is available in Europe and is approved for the treatment of acute attacks of HAE-C1-INH. For minor interventions, the consensus algorithm recommends

From the ¹Department of Dermatology, Johannes Gutenberg University, Mainz, Germany, ²Thera-Business, Ottawa, Canada, and ³CSL Behring, Marburg, Germany Presented in part at the scientific meeting of the European Society of Immunodeficiencies (ESID), October 6–9, 2010, Istanbul, Turkey

Funded by an educational grant from CSL Behring, Marburg, Germany

K Bork is a consultant to CSL Behring, Shire, and Viro Pharma. T Machnig is an employee of CSL Behring, Germany. I Steffensen is a scientific consultant to CSL Behring Canada and was paid by an educational grant provided by CSL Behring, Marburg, Germany

Address correspondence to Konrad Bork, M.D., Universitaets-Hautklinik, Langenbeckstr. 1, 55131 Mainz, Germany

E-mail address: konrad.bork@unimedizin-mainz.de

Published online May 22, 2013

Copyright © 2013, OceanSide Publications, Inc., U.S.A.

no prophylaxis if C1-INH is immediately available.³ If C1-INH is not available, short-term prophylaxis with attenuated androgens is recommended. For intubation or major procedures, short-term prophylaxis with C1-INH 1–6 hours before the procedure is recommended, with a second dose immediately available. If C1-INH is not available, the consensus algorithm recommends danazol prophylaxis and fresh frozen plasma (preferably solvent/detergent treated) 1–6 hours before procedure. For long-term prophylaxis, the consensus algorithm recommends attenuated androgens (contraindications include pregnancy and lactation, cancer, and childhood), antifibrinolytic agents (less effective than the androgens), or C1-INH.³ Long-term prophylaxis is recommended if a treatment for acute attacks is not sufficiently effective or is not available.

We systematically reviewed the body of literature addressing the efficacy and safety of the C1-INH concentrate Berinert (CSL Behring, Marburg, Germany) in patients with HAE–C1-INH. Berinert is a sterile, pyrogen-free, lyophilized white powder for i.v. administration after reconstitution with supplied diluents. It was first introduced in Europe (Germany) in 1985 and is now approved in >30 countries in Europe, North and South America, Asia, and Australia. Thoroughly tested plasma donations from appropriate donors are processed to the final product using a range of manufacturing steps to purify and concentrate C1-INH and to inactivate and remove viruses and prions that are potentially present in product intermediates. In addition to the dedicated virus reduction steps pasteurization and hydrophobic interaction chromatography, a nanofiltration process has recently been introduced in the manufacturing of Berinert and obtained regulatory approval for the treatment of acute attacks and self-administration in both adult and pediatric patients by European health authorities and in adults and adolescents by the Food and Drug Administration.⁷ Berinert was also recently approved for short-term prophylaxis (pre-procedure prevention) in the European Union. The new proposed abbreviation for the plasma-derived, pasteurized, nanofiltered product is pnfC1-INH. So far, clinical evidence for the efficacy and safety of Berinert documented in the literature has been exclusively generated with the C1-INH product without nanofiltration. However, because the nanofiltration step does not alter the biochemical characteristics, clinical evidence generated for C1-INH is also applicable to pnfC1-INH. In this article, the acronym C1-INH is synonymously used for Berinert, unless noted otherwise.

We addressed three key questions:

- What is the effectiveness of C1-INH therapy in patients with HAE–C1-INH during an acute attack?

- What is the effectiveness of short-term prophylaxis with C1-INH therapy in preventing an acute attack in patients with HAE–C1-INH who are to undergo a dental or surgical procedure or delivery?
- What is the effectiveness of long-term prophylaxis with C1-INH in patients with HAE–C1-INH?

METHODS

An electronic search strategy was used to search Medline (1950 to December 31, 2011; In-Process other Non-Indexed Citations), EMBASE (1980 to December 31, 2011), Biosis Previews (1985 to December 31, 2011), CINAHL (1982 to December 31, 2011), and the Cochrane Library. The search was performed simultaneously as a multilevel search through the Ovid interface. The results of the original Ovid search were downloaded and imported into a secure web-based data management software program for systematic reviews. All authors were involved in the conception and design of this systematic literature research. K. Bork, I. Steffensen, and T. Machnig contributed equally to the writing of the article.

No language or date restrictions were applied. Gray literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. These searches were supplemented by hand searching the bibliographies and abstracts of key papers and conference proceedings.

To be considered for inclusion, studies had to evaluate C1-INH (Berinert) in pediatric or adult patients with HAE–C1-INH.

Screening questions were developed to assess the level of study relevance in terms of availability of primary data on the clinical use of C1-INH. Initially, a broad screen of study titles and abstracts was performed to determine relevance. Studies identified as being potentially relevant were retrieved in full-text format and screened by two independent reviewers. Disagreements were resolved through consensus. A Quality of Reporting of Meta-analysis (QUORUM) flow diagram was used to record the reasons for exclusion of ineligible studies (Fig. 1). Data were extracted systematically by two independent reviewers according to the study design,⁸ participant characteristics, interventions, and outcomes. The data were examined and found to be inappropriate for meta-analysis; thus, a qualitative data synthesis was performed.

RESULTS

Of the 1123 potentially relevant reports identified for retrieval, 612 were excluded at level 1, 397 were excluded at level 2 (393 did not meet inclusion criteria and 4 reports could not be retrieved for detailed re-

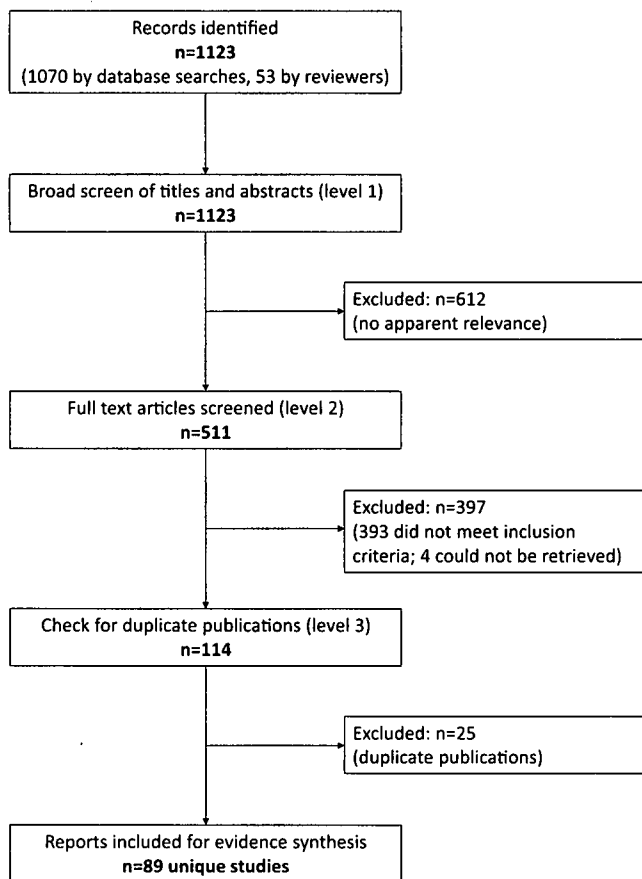


Figure 1. Quality of Reporting of Meta-Analyses (QUOROM) flowchart. QUORUM flowchart shows the number of studies screened and included in the systematic review.

view), and 25 were excluded at level 3 (duplicate publications; Fig. 1). Reports on 89 unique studies were included in this systematic review.

Of the 89 included studies, there was one randomized controlled trial (RCT), 16 observational studies (two case-crossover studies, 13 cohort studies, and one cross-sectional study) and 72 descriptive studies (11 retrospective, 1 prospective/retrospective, and 2 prospective survey studies, 11 case series studies, and 47 case reports). Of the 89 included studies, 78 were reported in peer-reviewed journals and 11 were reported as conference abstracts.

The distribution of included studies according to the indication that they evaluate is shown in Table 1. The RCT, the case-crossover studies, the cross-sectional study, and the cohort and survey studies carry the greatest interpretive value in this article and will be discussed in greater detail in the synthesis of evidence.

Efficacy of C1-INH for Treatment of HAE Attacks

A tabular overview of studies evaluating the efficacy of C1-INH for treatment of acute attacks compared with untreated controls is provided in Table 2. The International Multicenter Prospective Angioedema C1-

INH Trial 1 (I.M.P.A.C.T.1) study was a multinational, double-blind RCT that compared C1-INH (10 U/kg [$n = 40$] and 20 U/kg [$n = 43$]) with placebo ($n = 42$) in patients with HAE-C1-INH experiencing moderate or severe acute abdominal or facial attacks (Table 2).⁹ C1-INH at a single dose of 20 U/kg (but not 10 U/kg) significantly reduced the median time to onset of symptom relief in patients experiencing abdominal ($n = 98$), facial ($n = 25$), or other ($n = 1$) attacks compared with placebo (0.5 hours versus 1.5 hours; $p = 0.003$). The median time to complete resolution of HAE symptoms was also significantly lower with C1-INH at 20 U/kg compared with placebo (4.9 hours versus 7.8 hours; $p = 0.024$). Additionally, the proportion of patients with worsening HAE symptoms after start of treatment was significantly lower with C1-INH at 20 U/kg compared with placebo (4.7% versus 31.0%; $p = 0.001$) with no indication of rebound phenomenon (*i.e.*, no recurrence of a treated attack before its complete resolution).

The efficacy of C1-INH in patients with an acute attack was evaluated in six cohort studies ($n = 363$; $n = 303$ treated with C1-INH): one prospective cohort study,¹⁰ two retrospective cohort studies,^{11,12} and three prospective/retrospective cohort studies.^{13–15} In the open-label extension of I.M.P.A.C.T.1 (I.M.P.A.C.T.2), 57 patients received C1-INH at 20 U/kg for the treatment of 1085 HAE attacks (747 abdominal, 235 peripheral, 51 facial, 48 laryngeal, and 4 other).¹⁰ In I.M.P.A.C.T.2, administration of C1-INH resulted in rapid symptom relief (median time to onset of relief: 15, 19, 30, and 24 minutes for laryngeal, abdominal, peripheral, and facial attacks, respectively) and rapid resolution of symptoms (median time to complete resolution of symptoms: 8, 10, 23, and 28 hours for laryngeal, abdominal, peripheral, and facial attacks, respectively). One case of rebound edema was observed.

Five cohort studies that compared patients treated with C1-INH with untreated patients have been published (Table 2)^{11–15}; C1-INH was found to be effective in treating acute attacks, with significant reductions in relevant outcomes (*e.g.*, duration of attack, pain, vomiting, and diarrhea) in patients treated with C1-INH.

In 10 retrospective survey studies ($n = 612$; $n = 182$ treated with C1-INH),^{1,16–24} in 2 prospective survey studies ($n = 130$; $n = 71$ treated with C1-INH),^{25,26} and in 1 prospective/retrospective survey study ($n = 22$, all patients treated with C1-INH),²⁷ administration of C1-INH to patients with an acute attack was usually associated with first symptom relief within 5–80 minutes and complete resolution of symptoms typically within 48 hours.

In one of the retrospective survey studies, the HAE attacks occurred in 9 pregnant patients,²³ and in the prospective/retrospective survey study, acute HAE attacks were treated with C1-INH in 29 pregnancies.²⁷

Table 1 Distribution of included studies by indication

62 Studies Evaluated Acute Attacks*	34 Studies Evaluated Short-Term Prophylaxis	8 Studies Evaluated Long-Term Prophylaxis
1 Randomized controlled trial	2 Observational Studies	2 Observational Studies
11 Observational studies	2 Cohort studies	2 Cohort studies
2 Case-crossover studies	32 Descriptive studies	6 Descriptive studies
9 Cohort studies	4 Retrospective survey studies and 1 prospective/retrospective survey study	1 Retrospective survey study
50 Descriptive studies	6 Case-series studies	5 Case reports
10 Retrospective survey studies, 2 prospective survey studies, and 1 prospective/ retrospective survey study	21 Case reports	
9 Case-series studies		
28 Case reports		

Note: Some studies evaluated more than one indication and are therefore included in 2 or 3 columns in this table. Some studies are not included in this table because they did not specifically evaluate acute treatment or prophylaxis with plasma-derived C1-esterase inhibitor (e.g., studies evaluating the development of autoantibodies to C1-esterase inhibitor). Overall, 89 unique studies are included in the systematic review.

**Including individual replacement therapy studies.*

In one of the prospective survey studies, health-related quality of life (QoL) improved in the 27 patients who received C1-INH for the treatment of 273 HAE attacks over 16 months.²⁵

In nine case-series studies ($n = 99$; $n = 62$ treated with C1-INH)^{28–36} and 28 case reports ($n = 28$),^{37–64} administration of C1-INH to patients having acute HAE attacks or for short- or long-term prophylaxis was associated with positive clinical outcomes regarding efficacy and safety.

Early treatment of an HAE attack with C1-INH was found to be more effective than treatment late in the attack.¹² Early treatment of an attack, either in the prodromal phase or when the first symptom in the involved organ occurred is also referred to as individual replacement therapy (IRT). For IRT, high-risk patients (*i.e.*, patients with a high frequency of severe attacks [$>1/\text{wk}$]) are advised to administer C1-INH at early signs of an acute attack.⁶⁵ The efficacy of IRT with C1-INH was specifically evaluated in a total of 72 patients in two case-crossover studies by Kreuz *et al.* (Table 2).^{65,66} Patients usually administer a dose of 500–1000 U of C1-INH up to twice a week.

In the first case-crossover study,⁶⁵ 22 adult patients with severe HAE–C1-INH, who were intolerant or not responding to long-term prophylaxis with up to 1000 mg/day of danazol, were “crossed over” to IRT with C1-INH. The study showed a significant decrease in the frequency of annual attacks with C1-INH compared with danazol (median, 0 attacks per year versus 48 attacks per year; overall median decrease of 43

attacks per year; $p < 0.001$), and a reduction in the number of patients suffering severe attacks (10 patients versus 22 patients). Clinical improvements were accompanied by improvements in QoL (increase in the total QoL score from 12.5 during danazol prophylaxis to 48.5 during IRT with C1-INH; $p < 0.001$) and statistically significant reductions in work/school absenteeism and days in the hospital per year.

The second case-crossover study,⁶⁶ which included 50 patients who were switched from long-term prophylaxis with androgens to IRT with C1-INH, showed significant improvements in QoL ($p < 0.001$), a reduction in absence from school or work (from 26 to 0 days; $p < 0.001$), and a reduction in hospitalization (from 32 to 0 per year; $p < 0.001$).

The efficacy of C1-INH was also evaluated in a total of 16 patients in three cohort studies (Table 2).^{67–69} In the prospective cohort study by Bork and Hardt, six patients received IRT with C1-INH, and all patients reported about a 90% decrease in the incidence of severe attacks.⁶⁷ In a retrospective cohort study by Bork and Hardt, all C1-INH injections were effective, with mean times to onset of relief ranging between 20 minutes and 2 hours in three patients who received C1-INH over 18–27 years; almost no severe attacks occurred.⁶⁸

In the prospective cohort study by Bygum *et al.*,⁶⁹ seven adult patients with frequent and severe HAE attacks were initiated on self-administered, on-demand home therapy with C1-INH. There was a significant improvement in QoL (decrease in mean Dermatology

Table 2 Studies evaluating the efficacy of pdC1-INH (Berinert; CSL Behring, Marburg, Germany) for treatment of acute attacks compared with untreated controls

Study	Design	No. of Patients	Result
Craig <i>et al.</i> ⁹	Randomized, double-blind, placebo-controlled phase II/III dose-finding study (I.M.P.A.C.T.1)	125	Single dose of pdC1-INH at 20 U/kg (but not 10 U/kg) provided significant reduction in median time to onset of symptom relief versus placebo (30 min vs 90 min, $p = 0.0025$); effect greatest for severe attacks
Bork <i>et al.</i> ¹⁵	Retrospective and prospective cohort study	47	pdC1-INH treatment effective in all pts (500–1000 U). Time to first relief of symptoms (mean $\pm$ SD) Treated: 1.1 $\pm$ 1.4 hr (2104 attacks) Untreated: 50.4 $\pm$ 33 hr (9046 attacks [historic controls]); $p < 0.001$ Duration of skin edema (mean $\pm$ SD) Treated: 1.7 $\pm$ 1.3 days (2104 attacks) Untreated: 3.2 $\pm$ 1.7 days (9046 attacks [historic controls]); $p < 0.001$
Staubach <i>et al.</i> ¹¹	Retrospective cohort study	81*	Relief of symptoms within 2 hr after pdC1-INH injection (500–1000 U) in 92.5% of attacks Duration of abdominal attacks (mean $\pm$ SD) Treated: 32.8 $\pm$ 21.7 hr (5614 attacks) Untreated: 94.6 $\pm$ 41.3 hr (18271 attacks) Statistically significant reduction in vomiting and in diarrhea in treated vs untreated pts ($p < 0.0001$).
Bork <i>et al.</i> ¹²	Retrospective cohort study	75	PdC1-INH treatment effective in all pts (500–1000 U was typical dose, 2000 U was maximum dose). Duration of abdominal attacks (mean $\pm$ SD) Treated: 39.9 $\pm$ 30.0 hr (4834 attacks) Untreated: 92.0 $\pm$ 40.8 hr (17,444 attacks); $p < 0.0001$ Statistically significant reduction in vomiting and in diarrhea in treated vs untreated pts ($p < 0.0001$)
Bork <i>et al.</i> ¹⁴	Retrospective and prospective cohort study	61	Administration of pdC1-INH (dose not provided) resulted in complete resolution of symptoms in all 25# treated pts (208 attacks); symptom relief and resolution within 30–60 min in 24/25 pts (in 1 pt symptoms resolved within 4 hr) Duration of laryngeal edema (mean): Treated: 15 hr (208 attacks) Untreated: 103 hr (342 attacks)
Bork and Barnstedt ¹³	Retrospective and prospective cohort study	42	All 193 acute episodes in 18 pts effectively treated with pdC1-INH (500–1000 U) Duration of laryngeal edema (mean $\pm$ SD) Treated: 15.3 $\pm$ 9.3 hr (193 attacks) Untreated: 100.8 $\pm$ 26.2 hr (324 attacks); $p < 0.001$
Bork and Hardt ⁶⁸	Retrospective cohort study	27	The number of attacks increased 4- to 12-fold in three women receiving pdC1-INH for 18–27 yr, and control group did not show similar increase in attack rate over comparable time period
Kreuz <i>et al.</i> ⁶⁶	Case-crossover study	50	Pts receiving IRT with pdC1-INH showed significant improvements in QoL ($p < 0.001$), and significant reductions in absence from school or work ($p < 0.001$) and hospitalization ($p < 0.001$)

Table 2 Continued

Study	Design	No. of Patients	Result
Kreuz <i>et al.</i> ⁶⁵	Case-crossover study	22	All pts receiving IRT free of life-threatening attacks (laryngeal edema), which occurred with danazol long-term prophylaxis Median number of attacks per year decreased significantly with pdC1-INH compared with danazol prophylaxis (−43; 95% CI, −52 to −12; $p < 0.001$) QoL parameters improved significantly ($p < 0.001$)
Bygum <i>et al.</i> ⁶⁹	Prospective cohort study	7	Pts receiving IRT with pdC1-INH showed significant improvements in QoL parameters (Dermatology Life Quality Index [$p < 0.001$] and 36-Item Short Form survey scores for the individual and combined components [$p < 0.05$]), along with reduced use of emergency services ($p < 0.05$).

*Seventy-five of 81 pts previously described in a study by Bork *et al.*¹².

#Eighteen of 25 pts previously described in a study by Bork and Barnstedt¹³.

IRT = individual replacement therapy; pdC1-INH = plasma-derived C1-esterase inhibitor; pt(s) = patients; QoL = health-related quality of life; I.M.P.A.C.T.1 = International Multicenter Prospective Angioedema C1-INH Trial 1.

Life Quality Index score from 12.6 to 2.7 compared with baseline [$p < 0.001$] and statistically significant improvements in mean 36-item Short Form survey scores for the individual and combined components) along with reduced use of emergency services ($p < 0.05$).

Preprocedural Short-Term Prophylaxis with C1-INH

A tabular overview of studies evaluating the use of C1-INH in the preprocedural setting is provided in Table 3. Short-term prophylaxis in this setting is used to reduce the risk of a laryngeal attack or other HAE symptoms after surgical procedures, endotracheal intubation, or vaginal delivery.

This review identified the use of short-term prophylaxis with C1-INH in 195 patients (Tables 2 and 3) for 293 instances. Of these, 155 were before dental procedures (extraction and minor dental surgeries),^{13,18,21,24,45,70–75} 26 were before abdominal surgery (cesarean section, hysterectomy, gastroscopy, laparotomy, cholecystectomy, appendectomy, and endotracheal intubation for general anesthesia before other abdominal surgeries),^{13,21,23,36,58,63,71,76–79} 55 were before vaginal delivery,^{23,27,30,36,47,80,81} 15 were before tonsillectomy or adenoidectomy,^{71,82} and 10 were before orthopedic surgeries.²¹ The remaining patients received C1-INH before various other (*i.e.*, cardiopulmonary bypass, septal deviation, eye, and abortion) or unspecified surgical interventions.^{18,23,24,33,44,71,72,83–86}

In a retrospective and prospective cohort study, two patients received C1-INH prophylactically 30 minutes before surgery (one dental and multiple abdominal surgeries, respectively), and in both patients there were no HAE-associated complications during or after the surgery.¹³ In a retrospective cohort study that evaluated 705 tooth extractions in 171 patients with HAE–C1-INH, the rate of facial swelling and/or life-threatening laryngeal edema was 21.5% for 577 extractions without prophylaxis compared with 12.5% for 138 extractions with prophylaxis.⁷⁰ Furthermore, a graded dose-response relationship was observed (none, 500, or 1000 U of C1-INH; $p < 0.05$).

In a prospective and retrospective survey study and 4 retrospective survey studies, no angioedema occurred when C1-INH was used in 64 cases as short-term prophylaxis before delivery or abortion (38),^{21,23,27} before dental procedures (9),^{18,21,24} in patients undergoing endotracheal intubation for general anesthesia (8),²¹ or before other surgical interventions (9).^{18,21,24}

In a case series of 51 pediatric and adult patients undergoing 71 minor or major surgical procedures, C1-INH was administered 1 hour before surgery. No angioedema occurred, irrespective of the duration of the procedure.⁷¹ In five additional case-series studies ($n = 10$),^{30,33,34,36,72} and 21 case reports,^{42,44,45,47,58,63,73–87} there were no cases of angioedema after administration of C1-INH as short-term prophylaxis.

Table 3 Studies evaluating short-term prophylaxis with pdC1-INH (Berinert; CSL Behring, Marburg, Germany) in patients with HAE-C1-INH

Study	Design	No. of Patients*	Intervention	Result
Bork <i>et al.</i> ⁷⁰	Retrospective cohort study	48	In 171 pts there were 705 tooth extractions; 577 had no preoperative prophylaxis, 75 were preceded by 500 U of pdC1-INH and 53 were preceded by 1000 U of pdC1-INH	Facial swelling and/or life-threatening laryngeal edema occurred in 124/577 (21.5%) extractions without prophylaxis vs 16/128 (12.5%) with prophylaxis
Czaller <i>et al.</i> ²³	Retrospective survey study	15	One pt received 500 U of pdC1-INH before cesarean section, 1 pt received 500 U of pdC1-INH during delivery of twins, 7 pts received 500 U of pdC1-INH before delivery, and 6 pts received 500 U of pdC1-INH before artificial abortion	No HAE swelling occurred after short-term prophylaxis
Martinez-Saguer <i>et al.</i> ²⁷	Prospective/retrospective survey study	22	All 22 pts received pdC1-INH (500–1000 U) before delivery	None of the pts experienced an attack during delivery
Montinaro and Castellano ³⁶	Case-series study	2	Two identical twin pts received pdC1-INH (1500 U) before delivery (≈4 hr before delivery in 1 pt and 12 hr before delivery in the other pt)	Delivery occurred without complication
Paiva <i>et al.</i> ²⁴	Retrospective survey study	2	One pediatric pt received 500 U of pdC1-INH before dental surgery and before minor surgery of the face, and 1 pediatric pt received 500 U of pdC1-INH before dental surgery	No HAE symptoms occurred
Rusicke <i>et al.</i> ⁷¹	Case-series study	51	Fifty-one pediatric and adult pts received pdC1-INH (500–1000 U) 1 hr before minor or major surgical procedures (71 procedures in total; the most common were dental interventions [13], orthopedic surgeries [10], tonsillectomy [9], adenoidectomy [5], and appendectomy [4])	No HAE attacks occurred during surgery or postoperatively
Farkas <i>et al.</i> ²¹	Retrospective survey study	21	Twenty-one pts received 500 U of pdC1-INH prophylactically: 8 pts undergoing endotracheal intubation for general anesthesia, 6 pts undergoing gastroscopy, 6 pts undergoing dental interventions, and 1 pt undergoing induced abortion	No case of angioedema in any pt during surgery or postoperatively

Table 3 Continued

Study	Design	No. of Patients*	Intervention	Result
Pastó Cardona <i>et al.</i> ¹⁸	Retrospective survey study	3	One pt received pdC1-INH (500 U) prior to dental procedure and 2 pts received prophylaxis with 1000 U prior to other surgical interventions	No HAE attacks occurred
Bork and Barnstedt ¹³	Retrospective and prospective cohort study	2	One pt received 500 U of pdC1-INH 30 min before dental surgery, and 1 pt received 500 U of pdC1-INH 30 minutes before abdominal surgery	No HAE attacks during surgery or postoperatively
Martinez-Saguer <i>et al.</i> ⁷²	Case-series study	3	Three pts with severe HAE received prophylactic administration of pdC1-INH before undergoing surgical procedures (1000 U bolus, followed by 0.5–1 U/kg/hr)	No HAE attacks occurred during surgery or postoperatively
Mohr <i>et al.</i> ³⁴	Case-series study	2	One pt received 500 U of pdC1-INH given 1 hr before general anesthesia and repeated before laparotomy, and 1 pt received 500 U of pdC1-INH administered immediately before four surgical procedures (including one dental)	No HAE-associated symptoms or complications during surgery or postoperatively
Marqués <i>et al.</i> ³³	Case-series study	1	One pt received 1000 U of pdC1-INH 1 hr before eye surgery	No HAE-associated complications during surgery
Böckers and Bork ³⁰	Case-series study	2	Two pts received 500 U of pdC1-INH 1 hr before expulsion phase of delivery	Delivery and postpartal period without complications

Note: Only cohort, survey, and case-series studies reporting on short-term prophylaxis with a sufficient level of detail (e.g., regarding doses used and results) were included in this table. Data for 21 case reports not shown, but in all 21 pts there were no cases of angioedema after prophylactic administration of pdC1-INH.

*Number of pts in the study who received short-term prophylaxis therapy with pdC1-INH.

HAE = hereditary angioedema; pdC1-INH = plasma-derived C1-esterase inhibitor; pt(s) = patient(s).

Long-Term Prophylaxis with C1-INH

A tabular overview of studies evaluating the use of C1-INH for routine prophylaxis is provided in Table 4. Long-term prophylaxis or routine prophylaxis with C1-INH involves ongoing, regular administration to prevent HAE attacks or reduce the frequency and the severity of HAE attacks. Long-term prophylaxis is typically used for years or decades or even life-long.

The efficacy of C1-INH as a long-term prophylactic agent was examined in two prospective cohort studies and a retrospective survey study (Table 4).^{23,67,88} In the prospective cohort study by Bork and Hardt,⁶⁷ 14 pa-

tients received long-term prophylaxis with C1-INH for an average of 9 years. The most important benefit of this treatment was a reduction in symptom intensity; all patients reported that all or most of their attacks were considerably less severe than beforehand (percentage of severe attacks, 93.3% without prophylaxis and 3.8% with prophylaxis).

In the prospective cohort study by Martinez-Saguer *et al.*,⁸⁸ 30 patients were treated with C1-INH two to three times per week, and significant reductions in the number of attacks were observed, compared with pretreatment control data; 15 of the 30 patients who had one or two attacks per week before treatment had no

Table 4 Studies evaluating long-term prophylaxis therapy with pdC1-INH (Berinert; CSL Behring, Marburg, Germany) in patients with HAE-C1-INH

Study	Design	No. of Patients	Intervention	Result
Bork and Hardt ⁶⁷	Prospective cohort study	19*	Fourteen pts received long-term prophylaxis with pdC1-INH (500–2000 U, 1/wk daily), or on-demand with pdC1-INH (6 pts; 1 pt switched from long-term prophylaxis to on-demand after 2 yr); mean treatment time was 9 yr (range, 4–19 yr)	All pts reported fewer severe attacks (≈90% decrease in percent of severe attacks with treatment); for long-term prophylaxis, 8/14 pts had a decrease in frequency of attacks, 5 had an increase, and 1 had no change; in pts receiving on-demand, the mean number of attacks per week increased from 4.3 to 8 (4 attack frequency increased in 4 pts, no change in 2 pts)
Czaller <i>et al.</i> ²³	Retrospective survey study	41	Two pts received long-term prophylaxis with 500 U pdC1-INH as an i.v. bolus injection once per week during the first trimester of pregnancy	No additional attacks occurred during treatment, the subsequent course of pregnancy was uneventful and the 2 pts delivered healthy neonates
Martinez-Saguer <i>et al.</i> ⁸⁸	Prospective cohort study	30	Long-term prophylaxis with 500,000 U pdC1-INH as an i.v. bolus injection two to three times per week	More than 75% of pts (23/30) almost free of symptoms after study start (<1–2 every 6 mo) with 50% of pts (15/30) completely free of symptoms; no life-threatening attacks or attacks requiring hospitalization after study start

Note: Only cohort, survey, and case-series studies reporting on long-term prophylaxis with a sufficient level of detail (e.g., regarding doses used and results) were included in this table. Data for five case reports not shown, but long-term prophylaxis with pdC1-INH was effective in all five patients.

**Three of these pts were previously described in a study by Bork and Hardt⁶⁸.*

pdC1-INH = plasma-derived C1-esterase inhibitor; pt(s) = patients; HAE = hereditary angioedema.

attacks with long-term C1-INH therapy. In the retrospective survey study, two patients with severe HAE-C1-INH received C1-INH once per week during the first trimester of pregnancy and no attacks occurred during treatment.²³

The efficacy of long-term prophylaxis with C1-INH was also evaluated in five case studies.^{63,89–92} One patient was treated with danazol and subsequently with ε-aminocaproic acid over many years. He had to be taken off the medication because of side effects and lack of effect and then received routine prophylactic

therapy with C1-INH for HAE symptom control. His attacks ceased almost completely after 1 year of treatment with 500 U of C1-INH every 4–5 days.⁸⁹ In a second patient, who had danazol-related focal nodular hyperplasia of the liver, disease control was obtained with 1000 U of C1-INH every 4 days.⁹⁰ In a third patient, a significant reduction in attack frequency was only observed when long-term prophylaxis with C1-INH (500 U/wk) was combined with 100 mg/day of danazol (0.7 attacks per month compared with 2.2 attacks per month during the prestudy year).⁹⁰ A fourth

patient became asymptomatic when C1-INH was administered at 1000 U every 2 weeks during pregnancy.⁶³ Finally, a fifth patient became asymptomatic when C1-INH (1000–1500 U) was administered three times a week *via* a portacath and has been asymptomatic for almost 5 years while on this regimen.⁹²

C1-INH as Rescue Therapy in Studies with Other HAE Treatments

A pilot cohort study that evaluated the efficacy of a bradykinin B₂-receptor antagonist (icatibant) for treating acute attacks in 15 patients with HAE–C1-INH (20 acute attacks) used C1-INH as rescue therapy in patients not responding to icatibant.⁹³ In this study, five attacks in four patients (four rebound attacks and one new attack 20 hours after treatment with icatibant) were successfully treated with C1-INH (500 U in two attacks and 1000 U in three attacks).

Safety

In the RCT I.M.P.A.C.T.1, neither serious adverse events (SAEs) nor adverse events (AEs) leading to discontinuation occurred within 4 hours after study treatment administration ($n = 85$ treated with C1-INH).⁹ In the subsequent follow-up period, one patient experienced an SAE of worsening HAE symptoms that was considered to be at least possibly related to treatment. Subsequent genetic testing in this patient revealed no gene defect with respect to C1-INH, which made the initial diagnosis of HAE questionable. Within 4 hours after treatment, 19.6% of the 46 patients in the C1-INH 20-U/kg group had an AE compared with 43.9% of the 41 patients in the placebo group. The most common AEs were gastrointestinal events, reported by 10.9% of patients in the C1-INH 20-U/kg group and 31.7% of patients in the placebo group. Most AEs reported in the RCT were reflective of the underlying disease and type of attack.

In the open-label extension of this RCT (I.M.P.A.C.T.2), in which 57 patients received C1-INH at 20 U/kg for the treatment of 1085 HAE attacks, C1-INH was well tolerated during repeat administrations, with no drug-related SAEs and nine attacks associated with AEs possibly related to treatment.¹⁰

In two of the cohort studies, anaphylaxis related to treatment was reported in a patient receiving C1-INH.^{12,67} There was also one report of acute urticaria and hypotension developing in a female patient within 30 minutes after C1-INH administration, which required hospitalization; urticarial reaction reoccurred on three further occasions, including one event that was accompanied by severe hypotension requiring epinephrine.³⁹ With the exception of these three studies^{12,39,67} and the RCT,⁹ none of the remaining included

studies reported SAEs related to treatment in patients receiving C1-INH.

Besides the one RCT⁹ and its open-label extension study,¹⁰ one case-crossover study ($n = 22$ treated with C1-INH),⁶⁵ six cohort studies ($n = 248$ treated with C1-INH),^{11–13,67,69,70} and seven survey studies ($n = 186$ treated with C1-INH)^{16,19–21,23,26,27} reported on treatment-related AEs in patients receiving C1-INH. Eleven of the 14 studies reported no treatment-related AEs.^{11,13,16,19–21,23,26,27,69,70} In the case cross-over study by Kreuz *et al.*,⁶⁵ 3 of the 22 patients receiving C1-INH experienced adverse drug reactions (ADRs, two cases of redness at the injection site and one case of vertigo). In the cohort study by Bork and Hardt,⁶⁷ 3 of the 19 patients experienced ADRs: one case of headache, and light headedness on nine occasions for treatment of nine attacks in 2 patients. In the cohort study by Bork *et al.*,¹² no treatment-related AEs were observed as long as the injections were performed correctly. Treatment-related AEs that appeared to result from improper injection (too fast or too cold) included 1 patient who reported coldness chills, fever, headache, and nausea within 45 minutes of injection; 14 patients who experienced faintness, vertigo, headache, and reddening of the face or feelings of warmth or cold or sweating and paresthesias in the arm at the injection site (which subsided within 10 minutes); and 1 patient who reported abdominal cramping that resolved 5 minutes after injection. No other AEs were observed in patients receiving numerous treatments (352,000 U administered during a 26-year period) in this study.¹²

There were no treatment-related AEs reported in the included case-series studies or case reports.

C1-INH was found to be equally effective and well tolerated in patients receiving repeated doses. Farkas *et al.*²¹ reported that C1-INH continued to be safe and well tolerated in 61 patients who had collectively received >450 ampoules (250,000 U) of C1-INH over their lifetime. Moreover, the effectiveness of C1-INH did not decline after repeated use.²¹ A retrospective cohort study by Bork and Hardt⁶⁸ reported a gradual but continuous increase in the frequency of HAE attacks (between 4- and 12-fold compared with pretreatment) in three patients who received IRT with C1-INH >18–27 years. This pattern was not observed in a control group of patients (patients who had not received an abnormally high number of injections), where the mean number of attacks increased until early adulthood, leveled, and then, in some patients, decreased at an older age. The authors considered this increase potentially related to the large numbers of C1-INH injections received by these patients. In a prospective cohort study by Bork and Hardt,⁶⁷ in which 14 patients received long-term prophylaxis with C1-INH over an average of 9 years, an increased amount of C1-INH was required in some patients to control the

disease. 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. Some patients reported that skin swellings and abdominal attacks developed much more rapidly and that skin swellings developed simultaneously at multiple locations. The patients did not experience this before commencing prophylaxis. These observations and the necessity for regular administration of C1-INH concentrate once a week or more frequently, reflected an increased HAE-C1-INH activity in some patients. However, none of the patients reported any loss of effectiveness during the treatment with C1-INH.

Virus Transmission

One cross-sectional study evaluated the prevalence of antihepatitis C virus in 14 patients with HAE-C1-INH previously treated with C1-INH.⁹⁴ None of the patients had antibodies to hepatitis C virus, human immunodeficiency virus (HIV), hepatitis core antigen, or hepatitis B surface antigen. Immunoglobulin M (IgM) antibodies to hepatitis A virus were also not detected, and no clinical signs of hepatitis were noted.

In addition, virus transmission (seroconversion) with C1-INH therapy was evaluated in one RCT,⁵ one case-crossover study,⁶⁵ two cohort studies,^{10,88} one prospective/retrospective survey study,²⁷ three retrospective survey studies,^{16,21,23} one case-series study,²⁸ and two case reports.^{58,91} In the RCT⁹ and its open-label extension study,¹⁰ there were no proven cases of any infections with HIV, hepatitis virus, or human B19 virus during the studies. In the case-crossover study,⁶⁵ there was no evidence of transmission of HIV, parvovirus B19, or hepatitis virus over the 20-year observation period in 22 patients receiving IRT with C1-INH. In the other studies, there was no evidence of transmission of HIV or hepatitis virus in a total of 192 patients (including adults, children, and pregnant women) who received C1-INH for the treatment of acute attacks or short- or long-term prophylaxis and were followed up for up to 16 years.^{16,21,23,27,28,58,88,91}

C1-Inhibitor Autoantibodies

One prospective cohort study by Varga *et al.*⁹⁵ examined the distribution of C1-INH autoantibodies (IgG, IgA, and IgM) in patients with HAE-C1-INH. The study found that although the frequency of elevated IgM C1-INH autoantibody titers was significantly higher in patients with HAE-C1-INH (32/95) compared with healthy controls (2/54; $p < 0.0001$), the frequency of elevated IgM C1-INH autoantibodies was not significantly different between a group of patients with HAE-C1-INH previously treated with C1-INH and a group of patients naive to treatment with C1-

INH. The study concluded that C1-INH autoantibodies are present with highly elevated frequency in patients with HAE-C1-INH irrespective of prior treatment with C1-INH. A recent prospective cohort study by Varga *et al.*⁹⁶ revisited these findings and examined the distribution of IgM C1-INH autoantibodies in 75 patients with HAE-C1-INH followed up for 9–11 years. IgM C1-INH autoantibodies were found in 51 of 75 patients, with 23 of these patients testing positive in more than three serum samples. There appeared to be some familial clustering of titer-positive patients. Once again, no relationship was observed between prior treatment with C1-INH and presence of autoantibodies. In addition, this study found no relationship between the mean dose (number of ampoules) of C1-INH and positive titers.

In the open-label extension study of the RCT, 19 of 57 patients tested positive for C1-INH autoantibodies at least once (eight patients were already tested positive at screening for the RCT), but none of the C1-INH autoantibodies were inhibitory.¹⁰ In a retrospective survey study by Farkas *et al.*,²¹ 61 patients with HAE-C1-INH treated with C1-INH over a 4-year period showed no significant increase in the titers of C1-INH autoantibodies (IgG, IgA, and IgM). In a case report by Widmer *et al.*,⁹¹ no C1-INH autoantibodies were detected in a patient 2 years after having received 1 year of prophylactic therapy with C1-INH (500–1000 U one to two times per week).

DISCUSSION

This systematic review found C1-INH to be a generally safe, rapid, and effective treatment for both adults and children with HAE-C1-INH. Evidence was synthesized from one multinational RCT, as well as 16 observational and 72 descriptive studies, reporting on ~2000 patients with HAE-C1-INH (~1100 patients treated with C1-INH). The ratio of patients with type I to those with type II HAE was ~9:1, although not all studies reported HAE type.

C1-INH is an effective option in the treatment of acute HAE attacks. The multinational RCT (I.M.P.A.C.T.1) indicated that a single dose of 20 U/kg of C1-INH was safe and significantly more effective than placebo for the treatment of facial swellings and abdominal attacks.⁹ This dose-finding study showed for the first time a dose-dependent effect of the C1-INH concentrate for the treatment of acute HAE attacks. At a dose of 20 U/kg of C1-INH concentrate, median times to onset of symptom relief and complete resolution were significantly shorter than with placebo. Although treatment with 10 U/kg was more effective than placebo, it did not reach statistical significance. In this respect, the results of I.M.P.A.C.T.1 are in contrast to practical experience published in nonrandomized studies to date,

in which a dose of 500 U (7.1 U/kg in a patient weighing 70 kg) was effective in the majority of patients.^{11,12,15,21} Although a dose of 500 U was effective in treating 69–81% of almost 7000 abdominal attacks and skin swellings,^{12,15} only 25% of 193 laryngeal attacks were effectively treated with a dose of 500 U.¹⁵ A dose of 20 U/kg should be obligatory for the treatment of laryngeal attacks because of their potentially life-threatening nature. If an attack is not potentially life-threatening (*i.e.*, skin swellings and abdominal attacks), individually adjusted doses lower than the recommended dose of 20 U/kg may be sufficient.

In the open-label extension of I.M.P.A.C.T.1 (I.M.P.A.C.T.2), administration of C1-INH at 20 U/kg resulted in rapid onset of symptom relief and rapid complete resolution of symptoms for 1085 HAE attacks at any body location in 57 patients.¹⁰ In the cohort studies that compared patients treated with C1-INH with untreated patients,^{11–15} C1-INH was effective in treating acute abdominal attacks, skin edemas, and laryngeal attacks. In general, the regression of the symptoms of severe abdominal attacks was slower than that for acute laryngeal attacks. Likely explanations for this difference include differences in the area of tissue available for edematous formation (*i.e.*, smaller in larynx) and amount of vascularization.²¹ Accordingly, rapid regression of the symptoms of acute laryngeal attacks treated with C1-INH concentrate was shown by a prospective/retrospective study.¹³ Relief and resolution of symptoms began 20–60 minutes after injection of a fixed dose of 500 or 1000 U. A placebo-controlled trial in HAE patients with laryngeal attacks is considered unethical, because of the life-threatening nature of the disease.

Early and prompt administration of treatment is the key to the successful management of acute attacks of HAE. In one study, the mean time to relief of symptoms was 54 minutes when patients with abdominal attacks were treated early compared with 114 minutes when treatment was delayed, emphasizing the importance of early treatment.¹² A recent international consensus document recommended that every patient with HAE–C1-INH be considered for home therapy and self-administration training, once the diagnosis of C1-INH deficiency is confirmed.⁹⁷ In Germany, all patients with HAE–C1-INH are requested to store C1-INH concentrate in their home refrigerators.¹⁴ In this systematic review, three studies found that on-demand home therapy was associated with significant improvements in disease control and QoL.^{65,66,69} The opportunity for patients to manage their disease has the potential to improve patient QoL and reduce costs associated with undertreatment (*e.g.*, need for treatment with higher doses, hospital administration, and lost wages/school time).⁹⁷ Home therapy offers the possibility of earlier treatment and better symptom control, allowing

the patient to manage their disease with minimal impact on their ability to live a healthy and productive life.

Short-term prophylaxis is necessary for patients who are not receiving ongoing prophylactic therapy for HAE–C1-INH, but are facing dental procedures or elective surgery. After short-term prophylactic treatment with C1-INH ~30 minutes to 1 hour before surgical intervention or vaginal delivery, generally, no complications occurred before, during, or after surgery or vaginal delivery.^{13,18,21,23,24,27,30,33,36,70,71} However, because HAE symptoms occur only after a minority of procedures without short-term prophylaxis, the effectiveness of short-term prophylaxis in preventing HAE attacks can only be shown in controlled studies. Only for short-term prophylaxis before dental extraction are data from a control group without prophylaxis available. Short-term prophylaxis with C1-INH before dental extraction effectively prevented HAE attacks.⁷⁰

Some patients with HAE–C1-INH who experience frequent and/or debilitating attacks may be considered for long-term prophylaxis with C1-INH or other drugs such as androgens or antifibrinolytic agents. Although the available evidence for long-term prophylaxis with C1-INH is sparse, the severity and the number of attacks decreased considerably in the majority of patients compared with untreated controls or placebo.^{67,88}

In I.M.P.A.C.T.1,⁹ C1-INH concentrate given at a dose of 20 U/kg proved to be safe and well tolerated and AEs were less frequent with C1-INH concentrate than with placebo. This difference was particularly obvious for gastrointestinal disorders, which can be explained by the fact that most of the patients experienced abdominal attacks. Also, most of the other AEs were related to the underlying disease and type of attack. The favorable safety profile of C1-INH concentrate has been confirmed by other observational and descriptive studies. With the exception of nine SAEs of HAE exacerbation occurring in four patients >4 hours after study treatment administration in the RCT,⁹ and three case reports of anaphylactic reaction occurring after administration of C1-INH,^{12,39,67} there were no other reports of treatment-related SAEs in patients treated with C1-INH. ADRs were reported in 22 patients and included chills, nausea, headache, vertigo, and injection site reactions,^{12,65,67} and in at least one-half of the cases were thought to result from too rapid injection or insufficient warming of the solution before injections.²³

C1-INH was generally found to be equally effective and well tolerated in patients receiving repeated doses. In three patients who received frequent on-demand treatment with C1-INH for up to 27 years, a slow but continuous increase in the frequency of HAE attacks has been reported,⁶⁸ and in a few patients receiving

long-term prophylaxis with C1-INH, an increased amount of C1-INH was required to control the disease.⁶⁷ However, such side effects have only been reported in a few individual cases, and the group of patients in whom these side effects may occur is not clearly defined up to now.

C1-INH was also found to be safe and effective in children and in pregnant or lactating women. Pregnant women with HAE-C1-INH were reported to have delivered healthy infants without edematous incidents after prophylactic treatment with C1-INH before delivery or treatment of acute attacks during pregnancy.^{21–23,27,30,36} Similarly, several studies showed that pediatric patients of all age classes were successfully treated with C1-INH for acute episodes of HAE and short-term prophylaxis before surgical procedures, with no AEs.^{16,21,24,28,71}

Treatment with C1-INH was not associated with transmission of viruses, including HIV and hepatitis virus. Furthermore, treatment with C1-INH did not appear to be associated with the development of neutralizing antibodies to C1-INH. The presence of neutralizing antibodies to C1-INH could lead to slow responsiveness and, hence, negatively impact patients being treated for life-threatening laryngeal edemas, as observed in patients with acquired angioedema.^{98,99}

Although C1-INH undoubtedly appears to benefit patients with HAE-C1-INH, based on the various response criteria, there were a number of limitations to this systematic review of the literature. Other randomized, placebo-controlled trials were conducted with two other C1-INH products (vapor-heated C1-INH [Immuno AG, Vienna, Austria] and nanofiltered C1-INH [Cinryze; ViroPharma Biologics, Exton, PA] and were therefore not included in this systematic review.^{100,101} However, these studies also showed a significant benefit of C1-INH in the treatment of acute HAE attacks and as a long-term prophylactic agent. Studies included in this review were predominately retrospective cohort and case-series studies; only one RCT was included. Studies based on clinical records and patient recall are prone to confounders and lack of blinding of assessments, potentially leading to biased results. In addition, simply by the nature of the disease, there is extreme variability in the frequency and severity of HAE-C1-INH not only within affected individuals but between family members sharing the same mutation. Hence, the use of “untreated” controls raises the possibility that the attacks not requiring treatment were less severe than the attacks requiring treatment. Furthermore, for the disease itself, there is a lack of objective, measurable parameters or validated outcome measures to evaluate the onset of an attack, the severity of the episodes, and the resolution of symptoms. Finally, no prospective, parallel, direct comparisons of C1-INH with other HAE-C1-INH treatment options (e.g., other C1-INH products, androgens, antifibrinolyt-

ics, fresh frozen plasma, recombinant C1-INH, icatibant, or ecallantide) are available.

Despite these limitations, the studies of C1-INH have the strength that they included a larger number of patients than would have been feasible with prospective, controlled studies. In addition, the data provided in the included studies are a more accurate reflection of patient response in the “real-life” setting compared with data originating from controlled trials, where treatment and follow-up are strictly controlled.

CONCLUSIONS

C1-INH, which replaces the missing protein, is a safe and effective option for treating and preventing acute edematous attacks in patients with HAE-C1-INH. In adults and children experiencing an acute HAE attack, administration of C1-INH resulted in rapid onset of symptom relief and timely resolution of symptoms. When using appropriate doses, the risk of rebounds was minimal. Short-term prophylaxis with C1-INH was shown to prevent HAE attacks after dental procedures. Likewise, HAE attacks were absent after prophylactic use in various other medical interventions. Long-term prophylaxis with C1-INH significantly decreased the frequency of severe attacks in patients experiencing frequent and/or debilitating attacks. C1-INH was generally safe and well tolerated.

Clinical experience with C1-INH has been available for over 30 years and, so far, undetected side effects are therefore highly unlikely to occur. Accumulated clinical evidence over many decades showed that the efficacy of C1-INH is reliable and sustainable. This long and good clinical experience with C1-INH is also reflected in several first-line treatment recommendations for C1-INH in international consensus guidelines.

ACKNOWLEDGMENTS

The authors thank Andra Morrison for conducting the systematic literature research, Agnes Nemet and David G. Barnes for their help with the systematic evaluation of the literature for medical findings, and Christina Eichhorn from Trilogy Writing & Consulting GmbH for editorial assistance with the article.

REFERENCES

1. Khan DA. Hereditary angioedema: Historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis. *Allergy Asthma Proc* 32:1–10, 2011.
2. Bork K, Meng G, Staubach P, and Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med* 119:267–274, 2006.
3. 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.
4. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 109:395–402, 2012.

5. Christiansen SC, and Zuraw BL. Hereditary angioedema: Management of laryngeal attacks. *Am J Rhinol Allergy* 25:379–382, 2011.
6. Riedl MA. Update on the acute treatment of hereditary angioedema. *Allergy Asthma Proc* 32:11–16, 2011.
7. Gröner A, Nowak T, and Schäfer W. Pathogen safety of human C1 esterase inhibitor concentrate. *Transfusion* 52:2104–2112, 2012.
8. Jepsen P, Johnsen SP, Gillman MW, and Sørensen HT. Interpretation of observational studies. *Heart* 90:956–960, 2004.
9. 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.
10. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks—Final results of the IMPACT2 study. *Allergy* 66:1604–1611, 2011.
11. Staubach P, Meng G, and Bork K. Treatment with pasteurized C1 Inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *J Allergy Clin Immunol* 117(suppl):S179, 2006.
12. Bork K, Meng G, Staubach P, and Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 45:1774–1784, 2005.
13. Bork K, and 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.
14. Bork K, Hardt J, Schicketanz KH, and 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.
15. Bork K, Staubach P, and Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 63:751–757, 2008.
16. Farkas H, Harmat G, Füst G, et al. Clinical management of hereditary angio-oedema in children. *Pediatr Allergy Immunol* 13:153–161, 2002.
17. Göring HD, Bork K, Späth PJ, et al. Hereditary angioedema in the German-speaking region. *Hautarzt* 49:114–122, 1998.
18. Pastó Cardona L, Bordas Orpinell J, Mercadal Orfila G, et al. Prophylaxis and treatment of hereditary and acquired angioedema at HUB; use of the C1-esterase inhibitor. *Farm Hosp* 27:346–352, 2003.
19. Obtulowicz K, Obtulowicz P, and Kapusta M. Hereditary angioedema (HAE) in patients with C1 inhibitor deficiency—Cracow register. *Post Dermatol Alergol XXII*:23–28, 2005.
20. Nowicka E, Najberg E, and Gregorek H. Management of hereditary angioedema (HAE)—Analysis of 39 patients. *Allergia Astma Immunol* 12:200–209, 2007.
21. Farkas H, Jakab L, Temesszentandrás G, et al. Hereditary angioedema: A decade of human C1-inhibitor concentrate therapy. *J Allergy Clin Immunol* 120:941–947, 2007.
22. Chinniah N, and Katelaris CH. Hereditary angioedema and pregnancy. *Aust N Z J Obstet Gynaecol* 49:2–5, 2009.
23. Czaller I, Visy B, Csuka D, et al. 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.
24. Paiva M, Gaspar A, Loureiro V, et al. Hereditary angioedema—Characterization of a paediatric population. *Rev Port Imunoalergol* 18:157–174, 2010.
25. Bewtra A, Jacobson KW, Craig T, et al. C1-INH therapy improves health-related quality of life measures in patients with hereditary angioedema. *J Allergy Clin Immunol* 123(suppl):S103, 2009.
26. Zanichelli A, Vacchini R, Badini M, et al. 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.
27. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, et al. Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. *Am J Obstet Gynecol* 203:131.e1–131.e7, 2010.
28. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, et al. Clinical management of hereditary angioedema in children and adolescents. *Allergy* 63(suppl 88):158–611, 2008.
29. Baraza W, Garner JP, and Amin SN. Hereditary angioedema—A forgotten cause of the “medical” acute abdomen. *Int J Colorectal Dis* 22:1415–1416, 2007.
30. Böckers M, and Bork K. Contraception and pregnancy in hereditary angioedema. *Dtsch Med Wochenschr* 112:507–509, 1987.
31. Dirks K, Deuerling J, and Lutz H. Sonography in hereditary angioedema: Typical findings demonstrated by the example of 3 cases. *Ultraschall Med* 22:186–190, 2001.
32. Kodama J, Uchida K, Sakata T, and Funakoshi F. In vivo function of C1-inhibitor and pathophysiology of edema attack in patients with hereditary angioneurotic edema. *Adv Exp Med Biol* 247B:79–86, 1989.
33. Marqués L, Dordal T, Baltasar M, et al. Hereditary angioedema. Control and treatment in 7 cases. *Med Clin (Barc)* 98:378–380, 1992.
34. Mohr M, Pollok-Kopp B, Götze O, and 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.
35. Papadopoulou-Alataki E, Foerster T, Antari V, et al. Molecular diagnosis and management of hereditary angioedema in a Greek family. *Int Arch Allergy Immunol* 147:166–170, 2008.
36. Montinaro V, and Castellano G. Management of pregnancy and vaginal delivery by C1 inhibitor concentrate in two hereditary angioedema twins. *Clin Immunol* 136:456–457, 2010.
37. Farkas H, Gyeney L, Nemesanszky E, et al. Rare case of hereditary angioedema and concomitant Crohn’s disease. *Med Sci Monit* 4:349–354, 1998.
38. Yang WH. Successful use of daily intravenous infusion of C1 INH concentrate (Berinert P) in the treatment of a hereditary angioedema (HAE) subject with renal and respiratory failure. *J Allergy Clin Immunol* 117(suppl):S171, 2006.
39. Aygören-Pürsün E, Schubert R, Königs C, et al. Anaphylactic reaction against pdC1-Inhibitor concentrate in a patient with hereditary angioedema. Poster presented at 6th C1 Inhibitor Deficiency Workshop, Budapest, Hungary, May 22–24, 2009. Available online at www.haenet.hu/doc/C1INH-abstractbook2009.pdf; last accessed April 28, 2013.
40. Cancian M, Andres AL, Bendo R, et al. Recurrent pancreatitis in HAE. Poster presented at 6th C1 Inhibitor Deficiency Workshop, Budapest, Hungary, May 22–24, 2009. Available online at www.haenet.hu/doc/C1INH-abstractbook2009.pdf; last accessed April 28, 2013.
41. Bork K, and 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.
42. Eckert S, Eifrig B, and Standl T. Perioperative treatment of a patient with hereditary angioedema (HAE) in case of a young patient with osteosynthesis from a femoral fracture. *Anesthesiol Intensivmed Notfallmed Schmerzther* 35:776–781, 2000.
43. Farkas H, Harmat G, Fekete B, et al. Acute abdominal attack of hereditary angioneurotic oedema associated with ultrasound abnormalities suggestive of acute hepatitis. *Acta Paediatr* 91:971–974, 2002.
44. Farkas H, Mészáros Z, Ivaskevics K, et al. Esophageal leiomyoma incidentally recognized during an acute attack of hered-

- itary angioneurotic edema. *J Allergy Clin Immunol* 107:926–927, 2001.
45. Goti F, Melcher GA, Späth P, et al. Hereditary angioedema. A rare cause of acute abdominal pain with ascites. *Dtsch Med Wochenschr* 123:1166–1171, 1998.
46. Harten P, Körbächer D, Renk C, et al. Hereditary angioedema. Diagnostic and treatment errors as systemic lupus erythematosus. *Med Klin (Munich)* 94:339–344, 1999.
47. 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.
48. Herrero Gil D, Blanco Carmona JG, Arauzo González A, et al. Familial hereditary angioedema. Digestive manifestations. *Allergol Immunol Clin* 15:209–211, 2000.
49. Klockgether-Radke A, and Radke I. Hereditary angioneurotic edema. A rare cause of airway obstruction in emergency medicine. *Intensivmed Notfallmed* 27:34–37, 1990.
50. Liekenbröcker T, Körner M, Kapp A, and Elsner J. Hereditary C1 esterase inhibitor deficiency type I. Divergence of clinical symptoms and laboratory findings. *Hautarzt* 52:434–438, 2001.
51. Katahashi T. A case of hereditary angioneurotic edema. *Otolaryngol Head Neck Surg (Tokyo)* 71:103–106, 1999.
52. Nomura S, Hashimoto J, and Osawa G. Can C1 esterase inhibitor concentrate be a cause of the exacerbation of hereditary angioneurotic oedema? *Vox Sang* 69:85, 1995.
53. Novoa González J, Pérez Losada AJ, Garcia Burriel JI, et al. Hereditary angioedema. Diagnosis and treatment during childhood. *An Esp Pediatr* 38:452–454, 1993.
54. Ohsawa I, Satomura A, Fuke Y, et al. Worsening fluid retention in a patient with hereditary angioedema and end-stage renal disease. *Intern Med* 43:708–712, 2004.
55. Rice S, Cochrane TJ, Millwaters M, and Ali NT. Emergency management of upper airway angio-oedema after routine dental extraction in a patient with C1 esterase deficiency. *Br J Oral Maxillofac Surg* 46:394–396, 2008.
56. Trachsel D, and Hammer J. A vote for inhaled adrenaline in the treatment of severe upper airway obstruction caused by piercing of the tongue in hereditary angioedema. *Intensive Care Med* 25:1335–1336, 1999.
57. Weidenbach H, Beckh KH, Lerch MM, et al. Precipitation of hereditary angioedema by infectious mononucleosis. *Lancet* 342:934, 1993.
58. Witschi A, Krähenbühl L, Frei E, et al. Colorectal intussusception: An unusual gastrointestinal complication of hereditary angioedema. *Int Arch Allergy Immunol* 111:96–98, 1996.
59. Guilarte M, Luengo O, Nogueiras C, et al. Acquired angioedema associated with hereditary angioedema due to C1 inhibitor deficiency. *J Investig Allergol Clin Immunol* 18:126–130, 2008.
60. Ventura G, Meneghetti R, Pilia MP, et al. A recurrent angioedema. *Med Bambino* 27:257–259, 2008.
61. Wakisaka M, Shuto M, Abe H, et al. Computed tomography of the gastrointestinal manifestation of hereditary angioedema. *Radiat Med* 26:618–621, 2008.
62. Sanchez A, Ecochard A, Maestracchi M, and Rodiere M. Hereditary angioedema causing colocolic intussusception. *Arch Pediatr* 15:271–274, 2008.
63. Gorman PJ. Hereditary angioedema and pregnancy: A successful outcome using C1 esterase inhibitor concentrate. *Can Fam Physician* 54:365–366, 2008.
64. Czaller I, Molnár K, Csuka D, et al. Successful outcome using C1-inhibitor concentrate in acute pancreatitis caused by hereditary angioedema. *Gastroenterol Nurs* 34:60–63, 2011.
65. Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, et al. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 49:1987–1995, 2009.
66. Kreuz W, Martinez-Saguer I, Rusicke E, et al. Impact of the Frankfurt HAE therapy protocol on health-related quality of life (HRQoL) in 50 patients with hereditary angioedema. Poster presented at the 6th C1 Inhibitor Deficiency Workshop, Budapest, Hungary, May 22–24, 2009. Available online at www.haenet.hu/doc/C1INH-abstractbook2009.pdf; last accessed April 28, 2013.
67. Bork K, and 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.
68. Bork K, and Hardt J. Hereditary Angioedema: Increased number of attacks after frequent treatments with C1 inhibitor concentrate. *Am J Med* 122:780–783, 2009.
69. Bygum A, Andersen KE, and 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.
70. Bork K, Hardt J, Staubach-Renz P, and Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: A retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 112:58–64, 2011.
71. Rusicke E, Martinez-Saguer I, Aygören-Pürsün E, et al. Short-term prophylaxis with C1-inhibitor concentrate in patients with hereditary angioedema prior to surgical procedures. *J Allergy Clin Immunol* 125(suppl AB):164, 2010.
72. Martinez-Saguer I, Heller C, and Kreuz W. Continuous infusion of a pasteurized C1 inhibitor concentrate in patients with severe hereditary angioedema (HAE). *Eur J Pediatr* 158(suppl 3):S211–S220, 1999.
73. Leimgruber A, Jaques WA, and Spaeth PJ. Hereditary angioedema: Uncomplicated maxillofacial surgery using short-term C1 inhibitor replacement therapy. *Int Arch Allergy Appl Immunol* 101:107–112, 1993.
74. Maeda S, Miyawaki T, Nomura S, et al. Management of oral surgery in patients with hereditary or acquired angioedemas: Review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 96:540–543, 2003.
75. Socker M, Boyle C, and Burke M. Angio-oedema in dentistry: Management of two cases using C1 esterase inhibitor. *Dent Update* 32:350–352, 354, 2005.
76. Ebert A, Pritze W, and Weitzel HK. C-1 esterase inhibitor deficiency as an obstetric problem: A case report. *Zentralbl Gynakol* 114:519–522, 1992.
77. Minville V, Saada J, Cartron G, et al. Caesarean section in a parturient with C1 esterase inhibitor deficiency (angioneurotic oedema). *Ann Fr Anesth Reanim* 25:315–316, 2006.
78. Ros J, Metje T, Estanyol N, and Parramón J. Hereditary angioneurotic edema: Anesthetic considerations. *Rev Esp Anestesiol Reanim* 40:42–43, 1993.
79. Spyridonidou A, Iatrou C, Alexoudis A, et al. Peri-operative management of a patient with hereditary angioedema undergoing laparoscopic cholecystectomy. *Anaesthesia* 65:74–77, 2010.
80. Caliskaner Z, Ozturk S, Gulec M, et al. A successful pregnancy and uncomplicated labor with C1INH concentrate prophylaxis in a patient with hereditary angioedema. *Allergol Immunopathol (Madr)* 35:117–119, 2007.
81. Lovsin B, Guzej Z, Vok M, et al. C-1 esterase inhibitor prophylaxis for delivery in hereditary angioedema. *J Obstet Gynaecol* 19:537–538, 1999.
82. Moncrief T, Uygungil B, and Zuo L. Purified C1 inhibitor as pre-operative prophylaxis in a pediatric patient with heredi-

- tary angioedema. *Ann Allergy Asthma Immunol* 105(suppl): A88, 2010.
83. Cace N, Brusich S, Dessardo S, and Ahel J. Cardiopulmonary bypass in a child with hereditary angioedema. *Pediatr Int* 47:214–216, 2005.
 84. Martín MJ, Carballo JC, and Baños G. Anesthesia in a case of hereditary angioneurotic edema. *Rev Esp Anesthesiol Reanim* 40:29–31, 1993.
 85. Saito T, Namura O, Honma T, and Hayashi J. Supplementation of C1-esterase inhibitor concentrates for a patient suffering from hereditary angioedema undergoing complex open-heart surgery. *Eur J Cardiothorac Surg* 37:975–977, 2010.
 86. Bernstein JA, Coleman S, and Bonnín AJ. Successful C1 inhibitor short-term prophylaxis during redo mitral valve replacement in a patient with hereditary angioedema. *J Cardiothorac Surg* 5:86, 2010.
 87. Libert N, Schérier S, Dubost C, et al. Anaesthetic management of vaginal delivery in a patient with C1 esterase deficiency. *Ann Fr Anesth Reanim* 28:375–380, 2009.
 88. Martinez-Saguer I, Heller C, Fischer D, et al. Prophylactic treatment with pasteurised C1 inhibitor in hereditary angioedema (HAE)—A prospective 32 months follow up. *Blood* 94(suppl 1):2339, 1999.
 89. Bork K, and 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.
 90. Helsing P, and Nielsen EW. Hepatocellular focal nodular hyperplasia after danazol treatment for hereditary angio-oedema. *Acta Derm Venereol* 86:272–273, 2006.
 91. Widmer M, Späth P, and Wüthrich B. C1-INH replacement therapy in the common form of hereditary angioedema. *Allergologie* 12:432–439, 1989.
 92. Tallroth GA. Long-term prophylaxis of hereditary angioedema with a pasteurized C1 inhibitor concentrate. *Int Arch Allergy Immunol* 154:356–359, 2011.
 93. Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 119:1497–1503, 2007.
 94. Klarmann D, Kreuz W, Joseph-Steiner J, and Ehrenforth S. Hepatitis C and pasteurized C1-inhibitor concentrate. *Transfusion* 36:84–85, 1996.
 95. Varga L, Széplaki G, Visy B, et al. C1-inhibitor (C1-INH) autoantibodies in hereditary angioedema. Strong correlation with the severity of disease in C1-INH concentrate naïve patients. *Mol Immunol* 44:1454–1460, 2007.
 96. Varga L, Füst G, Csuka D, and Farkas H. Treatment with C1-inhibitor concentrate does not induce IgM type anti-C1 inhibitor antibodies in patients with hereditary angioedema. *Mol Immunol* 48:572–576, 2011.
 97. Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 6:22, 2010.
 98. Alsenz J, Bork K, and Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 316:1360–1366, 1987.
 99. Jackson J, Sim RB, Whelan A, and Feighery C. An IgG autoantibody which inactivates C1-inhibitor. *Nature* 323:722–724, 1986.
 100. 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.
 101. Waytes AT, Rosen FS, and Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 334:1630–1634, 1996. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.