

Letter to the Editor

Treatment of attacks with plasma-derived C1-inhibitor concentrate in pediatric hereditary angioedema patients

To the Editor:

Hereditary angioedema due to C1-inhibitor (HAE-C1-INH) deficiency is a disorder with autosomal-dominant inheritance, resulting from the mutation of the C1-INH gene. It is characterized by paroxysms of edema in the subcutis and/or the submucosa of the upper airways, as well as of the gastrointestinal tract.¹ Edema formation is caused by the release of bradykinin, following the activation of the kinin-kallikrein system.¹

The management of HAE comprises 2 essential stages: the treatment of edematous attacks and the prevention of their recurrence.² In clinical practice, the current agents for relieving edematous attacks include plasma-derived (pd) or recombinant human C1-INH concentrates, ecallantide (a kallikrein inhibitor), and icatibant (a bradykinin B₂ receptor antagonist). International and national consensus statements published during recent years recommend administering the pdC1-INH concentrate to relieve attacks of edema in pediatric patients.²⁻⁴

There is no published information available on the use of recombinant C1-INH concentrate, ecallantide, or icatibant in children. Only limited original data exist on the treatment of attacks in the pediatric population with the pdC1-INH concentrate (Berinert; CSL Behring, Marburg, Germany), which is the sole drug licensed for use in patients of all ages.^{3,5,6} Original, retrospective, or prospective studies, conducted on large patient populations, have been published by 2 groups.^{7,8}

The aim of this study was to analyze prospectively the efficacy and safety of the pdC1-INH concentrate (Berinert) used in the treatment of attacks in pediatric patients with HAE.

Our prospective study was conducted in a group of 50 patients with type I or type II HAE, aged younger than 18 years, and diagnosed at the Hungarian HAE Center between 1992 and 2010 (see Table E1, Study Design, Treatment, and Statistical analysis in this article's Online Repository at www.jacionline.org).

Of the enrolled patients, 23 did not require treatment with the pdC1-INH concentrate (including 8 who did not experience an attack during the follow-up period), while 27 patients were treated with the pdC1-INH concentrate; 28% of these were managed at home and 72% at the clinic. Median age at the time of diagnosis was 8 years (interquartile range, 4.5-11.5 years), and median age at initial onset of symptoms was 5 years (interquartile range, 2.8-10 years) (Fig 1). The mean age of the subjects at the time of initial treatment with the pdC1-INH concentrate was 12.4 years (median, 12 years; range, 6-18 years; interquartile range, 9-16 years) (Fig 1). All attacks (46 of 46) of upper airway edema (UAE), 17% (49 of 282) of abdominal edema, and 5% (57 of 1064) of subcutaneous attacks required pdC1-INH therapy. The anatomic distribution of all (n = 1392) attacks (Fig E1, A) and of attacks treated with the pdC1-INH concentrate (n = 152) (Fig E1, B) during the study are shown in Fig E1 (in the Online Repository available at www.jacionline.org).

After treatment with the pdC1-INH concentrate, time to initial symptom relief ranged from 15 to 60 minutes in almost all attacks. Time to complete resolution was different, depending on the location of the attack. It took 48 hours at the longest, but in all

attacks of UAE, it took less than 12 hours. Times to initial symptom relief (Fig 2, A) and to the complete resolution of symptoms (Fig 2, B) at the individual locations are shown in Fig 2. After treatment with the pdC1-INH concentrate, attacks did not progress nor did they recur during the next 48 hours.

No adverse events potentially related to treatment were recorded; neither was there any serologic evidence of the transmission of viral infection (with hepatitis B virus, hepatitis C virus, HIV, parvovirus B19) in any of the subjects. When measured 4 weeks after the last dose of the pdC1-INH concentrate, the titers of antibodies against C1-INH were similar when comparing treated and untreated patients. There was no significant difference in IgG-, IgM- and IgA-anti-C1-INH titers in patients who received more than 3 vials and in those who received fewer doses (see Fig E2 and additional Results in this article's Online Repository at www.jacionline.org).

In this study, 54% of the pediatric patients required acute treatment with the pdC1-INH concentrate and 6% (3 of 50) received 42% of all treatments. Our results show that about one half of the pediatric patients with HAE may be expected to experience an attack requiring emergency intervention before reaching adulthood. The cumulative number of attacks is approximately 10 times greater in children who experience a severe attack requiring treatment with the pdC1-INH concentrate than in those who do not experience such episodes. Interestingly, in our group of children in whom hormonal influences might have a lesser role, disease frequency is equal in male and female patients.

We found that the administration of the pdC1-INH concentrate (Berinert) during all types of attacks was followed by regression of symptoms. Times to complete resolution were different depending on the location of attacks, just as in adults.⁷ Subcutaneous edema usually responded more sluggishly to emergency intervention.^{7,9} We observed the quickest response to the pdC1-INH concentrate in cases of UAE, which constituted one third of the treated acute episodes (patients with UAE were hospitalized until their symptoms resolved completely). Repeated dosing was necessary only infrequently, when the symptoms persisted. Recurrence of the attack was not observed within 48 hours; this may be explained by the long half-life of the pdC1-INH concentrate (~33 hours in pediatric patients). Neither repeating nor increasing the dose of the pdC1-INH concentrate changed the therapeutic efficacy.

Usually, we administered 500 IU of the pdC1-INH concentrate (in compliance with the dosage recommended before 2010), and it was effective for most cases. As demonstrated by placebo-controlled clinical trials, the effective dose of the pdC1-INH concentrate is 20 IU/kg body weight. Accordingly, we have been recommending this dose since 2010.⁹ Another important finding from our study is that there were no treatment-related adverse events with the pdC1-INH concentrate either during use at home or in the hospital setting. Dosing with the pdC1-INH concentrate was not associated with the formation of antibodies against this agent.

Our prospective study demonstrated that the pdC1-INH concentrate is effective and safe for the treatment of attacks of edema in pediatric patients with HAE. This holds true regardless of attack location and the number of doses administered previously. The patient's quality of life can be improved substantially through

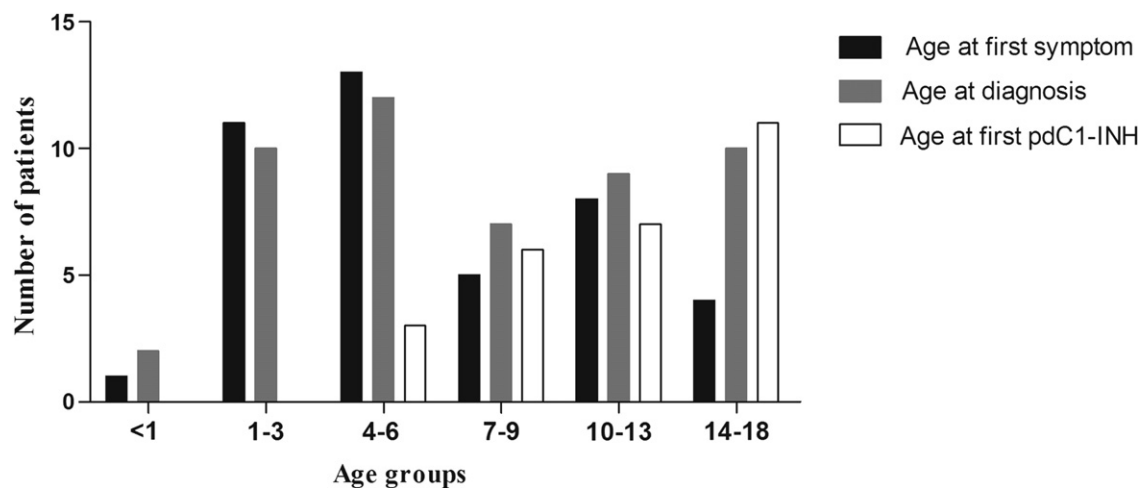


FIG 1. Age at the first onset of HAE symptoms, at the diagnosis of HAE, and at the first administration of the pdC1-INH concentrate (years).

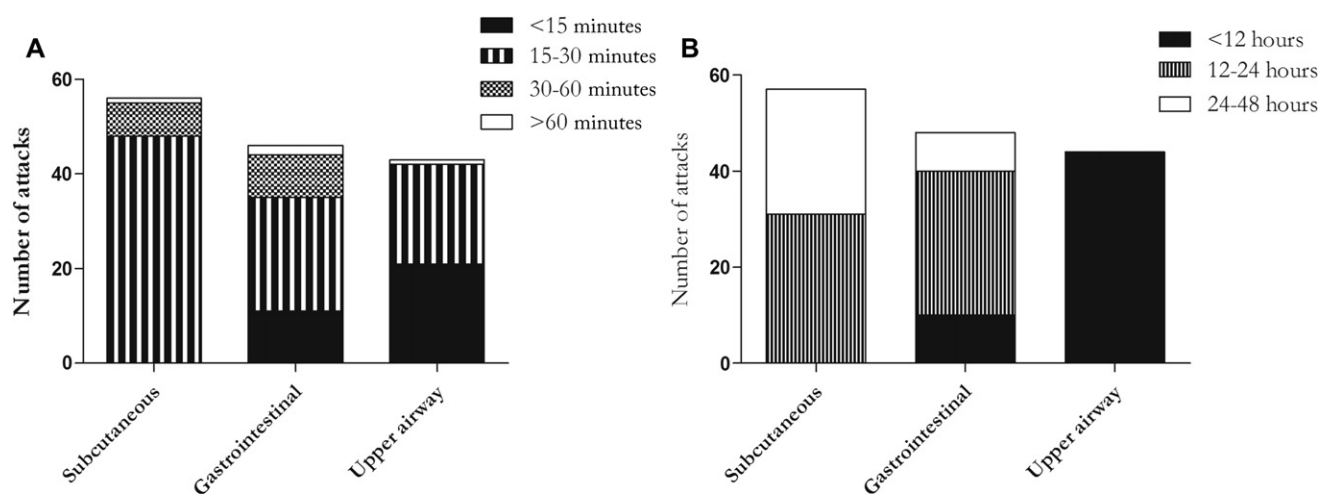


FIG 2. Time to initial relief of symptoms (A) and time to complete resolution (B) of symptoms after the administration of the pdC1-INH concentrate (Berinert, CSL Behring) (minutes).

individual counseling, by administering therapy at home during emergencies, and through regular monitoring and follow-up of the patient.

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METHODS

Study design

In addition to a positive family history and the presence of characteristic clinical manifestations, the inclusion criteria also comprised known HAE confirmed by complement studies. In our study, patients were followed-up from diagnosis until the age of 18 years. The study was approved by the Institutional Review Board of the Semmelweis University, Budapest, Hungary. Written informed consent was obtained from each patient's guardian.

Following diagnosis and counseling, the patients and their relatives were asked to record disease symptoms in the patient diary to accumulate clinical information on HAE attacks. For this purpose, our patients and their relatives received identical questionnaires on triggering factors; the onset, duration, severity, and location of the attacks; and the dosage and efficacy of the treatment administered. The patients recorded the time of onset of relief of symptoms, as well as of their complete resolution. They made an overall assessment—that is, did not evaluate individual symptoms (subcutaneous edema: pain, tightness sensation, swelling, and impaired function of the extremity; intestinal edema: abdominal pain, nausea, and vomiting; and UAE: lump sensation in the throat, feeling of tightness, dysphagia, roughness of voice, difficulty swallowing, and dyspnea).

Upon introducing drug therapy, the patients or their parents were requested to record the name and dosage of the medication in the diary. The consumption of the pdC1-INH concentrate, the clinical course of attacks, and any side effects were documented in the patient diary by the subjects, as well as in the medical charts by the physicians. The majority of patients attended follow-up visits at 6-month intervals, although some did so at 1-year intervals. Patients were asked to bring along their diaries and medical reports for review at the follow-up visits. These visits also included measurement of the complete blood cell count, complement parameters (C4, antigenic and functional C1-INH level, as well as C1q [for research purposes only, not indicated for clinical use]), IgA, IgG, and IgM-type anti-C1-INH antibody titers were measured at the follow-up visits scheduled at 6-month or 1-year intervals, according to a standardized methodology, in serum samples stored at -70°C , using Maxisorb ELISA plates (NUNC, Cat. No. 439454).^{E1} Serologic screening for HIV, hepatitis B and C viruses, and parvovirus B19 was performed in addition. Viral serology tests were done at baseline and at the end of study (4 weeks after the last administration of the pdC1-INH concentrate).

The clinical data, as well as the laboratory findings, were recorded continuously in the National HAE Registry.

Treatment

The HAE protocol developed at our clinic was used for the diagnosis, management, and follow-up of patients. The indications for treatment with the pdC1-INH concentrate include UAE of any severity; moderate-to-severe abdominal edema; edema of the face, lips, and neck, as well as of the trunk and/or genitals, and severe edema of the extremities.

The brand of the pdC1-INH concentrate used here (Berinert, CSL Behring) has been available for clinical use since 1986. It was approved in Hungary in 1996, and it is reimbursed at 100% by the Health Insurance Funds Administration. Patients always receive the pdC1-INH concentrate if they meet the criteria outlined above. A 500-IU dose of the pdC1-INH concentrate was administered intravenously whenever this was necessary, and this dose was repeated as recommended in the Summary of Product Characteristics effective at that time. In 2010, however, the recommended dosage changed and accordingly, we have been proposing the use of a 20-IU/kg body weight dose since then. In Hungary, family practitioners are authorized to prescribe the pdC1-INH concentrate when this is recommended by the principal of the HAE center, and all patients are allowed to keep this preparation at home, for administration in an emergency by a medical professional.

Following emergency treatment for UAE at home, patients were always hospitalized for observation until their symptoms resolved. This was similarly recommended in severe abdominal attacks, when treatment did not alleviate symptoms, to rule out any possible surgical emergency.

Statistical analysis of the results

Data on the onset of symptom relief were stratified according to whether the time to relief was less than 15 minutes, 15 to 30 minutes, 30 to 60 minutes, or more than 60 minutes. Similarly, the intervals of time to complete resolution of symptoms were less than 12 hours, 12 to 24 hours, or 24 to 48 hours. Statistical analyses were performed by using GraphPad Prism version 4.0 (GraphPad Software, Inc, San Diego, Calif, www.graphpad.com). Between-group differences in anti-C1-INH titers were evaluated with the Wilcoxon signed rank test for repeated measures. Categorical variables (gender and the type of HAE in patients treated or not treated with the pdC1-INH concentrate) were compared with the χ^2 test. All tests were 2-tailed, and a *P* value of less than .05 was considered statistically significant.

RESULTS

Demographic data of patients with C1-INH deficiency

Among the 50 children (27 females) from 31 families enrolled in the study, HAE was diagnosed in first-degree relatives of 42 (84%); 8 subjects (16%) had no affected family members. The demographic data and clinical characteristics of the 2 groups are shown in Table E1. Gender, HAE type, and age at diagnosis were not different between patients who received pdC1-INH during the study and those who did not require treatment.

More than half (27 of 50) of the children were symptom free at the time of diagnosis but underwent initial screening because of their positive family history for HAE.

Based on patient history and medical charts, the attacks that had occurred before diagnosis involved the subcutis in 459 of 739 (62.2%), the abdomen in 273 of 739 (36.9%), and the upper airway in 7 of 739 (0.9%) instances.

The median duration of the observational period was 7 years (range, 1-16 years; interquartile range, 4-11 years). During this time, 42 patients experienced 1392 attacks in total. The distribution of these attacks by location is shown in Fig E1. Initial attacks after inclusion involved the subcutis in 39 of 50 (78%) patients, while 3 of 50 (6%) had had an abdominal attack. UAE did not occur as an initial symptom of HAE in our pediatric patient population.

A substantial difference was found in the cumulative number of attacks normalized for the yearlong observational period; this index was much higher in treated patients. The observational period was similarly longer in treated patients (Table E1).

Dose requirement and the efficacy of the pdC1-INH concentrate

Considering all 50 patients, the median dose requirement of the pdC1-INH concentrate throughout the entire follow-up period was 0.1 (25th-75th percentile, 0.0-0.4) vials per annum. The median per capita consumption of pdC1-INH in the whole study population was 3 vials (25th-75th percentile, 2.00-7.25). During the observational period, each treated subject (27 of 50) received at least 1, but not more than 26, vials of the pdC1-INH concentrate; the majority of the patients received 1 vial. Three patients received more than 15 vials during the observational period (16, 22, and 26 vials, respectively); however, the dose necessary to control an individual attack did not exceed 500 IU in any of these 3 subjects.

Only 4 patients experienced an attack that required administering an additional vial. In these cases, the symptoms neither progressed nor improved within an hour of the initial

administration of the pdC1-INH concentrate. Of these, the first patient was a 17-year-old girl (with a body weight of 45 kg) exhibiting the symptoms of UAE, which had become severe by the time the pdC1-INH concentrate was administered. Two children (an 8- and a 14-year-old boy weighing 24 kg and 48 kg, respectively) with abdominal attacks required a repeated dose of the pdC1-INH concentrate owing to unsatisfactory improvement. The fourth patient (a 10-year-old boy with a body weight of 28 kg) had facial edema; it is believed that the effects of a wasp sting may have reduced the rate of response in this case. The first 2 of these patients had received the pdC1-INH concentrate

previously (1 vial on 1 and 1 vial on 3 occasions, respectively), which proved effective. The other 2 patients had been pdC1-INH concentrate naïve until this occasion. After the episodes described above, the subsequent attacks in these 4 patients were successfully controlled by administering a single vial.

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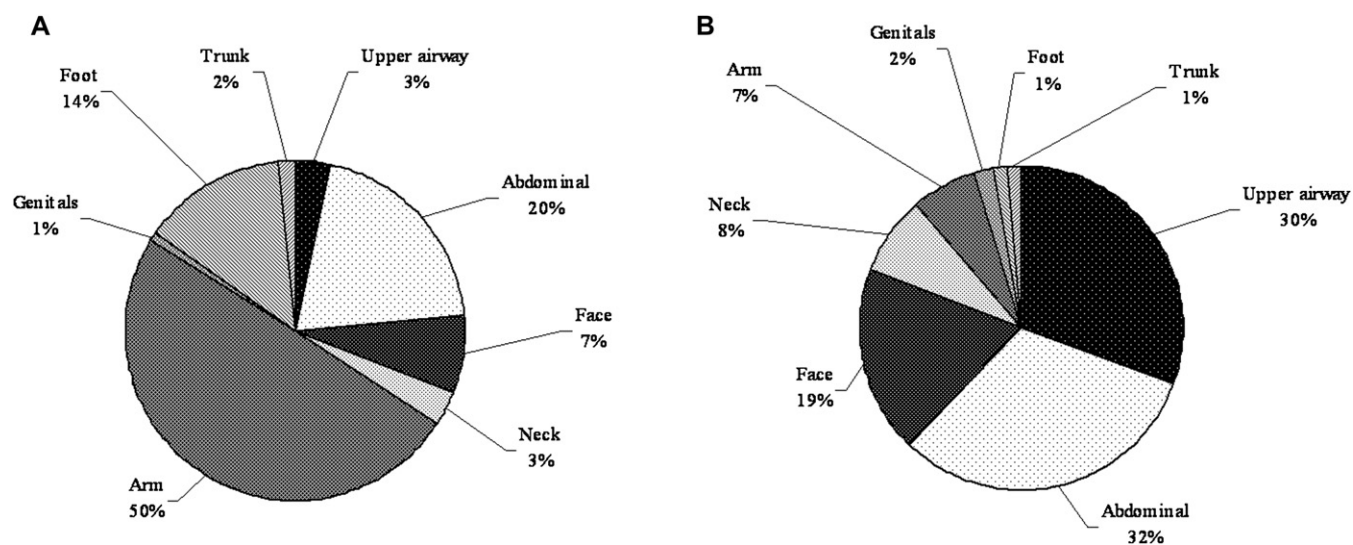


FIG E1. The distribution of attacks by location. **A**, All attacks (n = 1392) observed during the study. **B**, Attacks (n = 152) treated with the pdC1-INH concentrate (Berinert, CSL Behring) during the study.

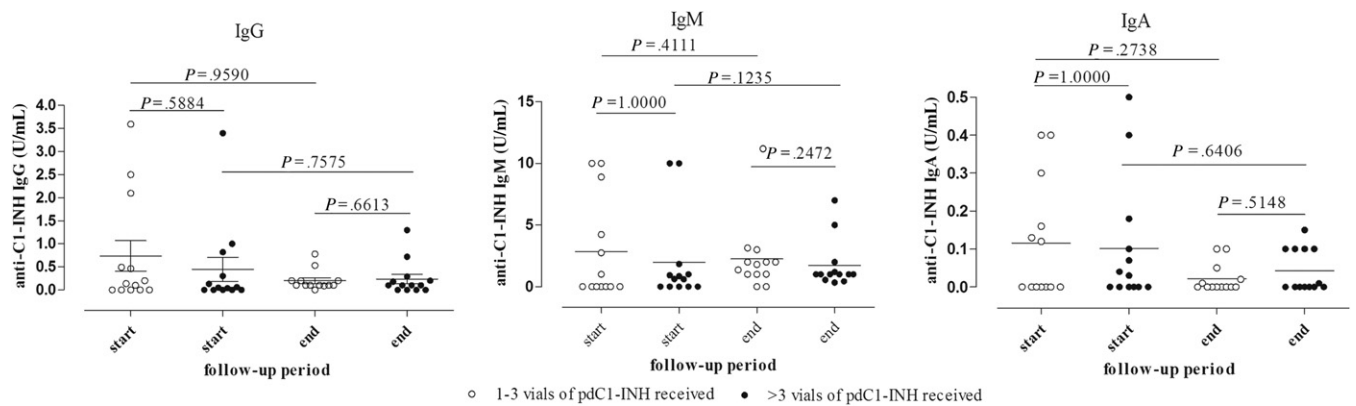


FIG E2. Analysis of the relationship between the number of vials of the pdC1-INH concentrate (Berinert, CSL Behring) received and the titers of antibodies to C1-INH. Two groups ("1-3 vials of pdC1-INH" and ">3 vials of pdC1-INH") were created by dividing the study population into 2 subsets according to median per capita pdC1-INH consumption during the observational period. Start, time of diagnosis (ie, the beginning of the observational period). End, the year when the patient turned 18 years old (ie, the end of the observational period). Horizontal lines represent the upper limit of the normal range for each antibody.

TABLE E1. Demographic and clinical data of patients treated or not treated with the pdC1-INH concentrate

	Not treated with the pdC1-INH concentrate (n = 23)	Treated with the pdC1-INH concentrate (n = 27)	<i>P</i> value
Distribution by gender	10 males, 13 females	13 males, 14 females	.7412
Type of HAE	21 type I, 2 type II	24 type I, 3 type II	.7766
Median age at diagnosis (y) (range)	9 (4-14)	6 (4-11)	.2486
Frequency of attacks (per annum)*	0.25 (0-6)	2.23 (0.8-6.2)	.0066
Duration of follow-up (mo)	5 (2-7)	11 (7-13)	<.0001

*Cumulative number of attacks normalized for the yearlong observational period.