Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema

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ABSTRACT

Background: *The plasma-derived, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH) is approved in the United States as an intravenous (IV) on-demand treatment for hereditary angioedema (HAE) attacks, and, in Europe, as on demand and short-term prophylaxis.*

Objective: *This analysis evaluated Berinert Patient Registry data regarding IV pnfC1-INH used as long-term prophylaxis (LTP).*

Methods: *The international registry (2010–2014) collected prospective and retrospective usage, dosing, and safety data on individuals who used pnfC1-INH for any reason.*

Results: *The registry included data on 47 subjects (80.9% female subjects; mean age, 44.8 years), which reflected 4082 infusions categorized as LTP and a total of 430.2 months of LTP administration. The median absolute dose of pnfC1-INH given for LTP was 1000 IU (range, 500–3000 IU), with a median time interval between infusion and a subsequent pnfC1-INH–treated attack of 72.0 hours (range, 0.0–166.4 hours). Fifteen subjects (31.9%) had no pnfC1-INH–treated HAE attacks within 7 days after pnfC1-INH infusion for LTP; 32 subjects (68.1%) experienced 246 attacks, with rates of 0.06 attacks per infusion and 0.57 attacks per month. A total of 81 adverse events were reported in 16 subjects (34.0%) (0.02 events per infusion; 0.19 events per month); only 3 adverse events were considered related to pnfC1-INH (noncardiac chest pain, postinfusion headache, deep vein thrombosis in a subject with an IV port).*

Conclusion: *In this international registry, IV pnf-C1-INH given as LTP for HAE was safe and efficacious, with a low rate of attacks that required pnfC1-INH treatment, particularly within the first several days after LTP administration.*

Hereditary angioedema (HAE) is a rare autosomal dominant disease,[1–3] with several subtypes, depending on the underlying pathology. The most common variants, HAE with deficient C1-inhibitor (C1-INH) (C1-INH-HAE type 1) and HAE with dysfunctional C1-INH (C1-INH-HAE type 2), result from mutations in the gene *SERPING1*, which encodes the C1-INH protein.[4] A third and less common type of HAE, referred to as HAE with

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normal C1-INH, may also be familial, with some cases associated with mutations in the F12 gene.[5,6]

Classic symptoms of HAE include episodic, nonpruritic, localized, nonpitting, spontaneous, and painful subcutaneous edema of the skin and mucosal tissues that primarily affects the face, intestinal tract, extremities, genitals, and upper airway.[2,3] Laryngeal attacks can be life-threatening,[7,8] and mortality rates are estimated at 30% in patients who are not properly diagnosed or treated.[2,3] Individuals with HAE, particularly those who experience frequent and severe attacks, report diminished quality of life,[9] a significant negative impact on daily activities (*e.g.*, diminished school or work productivity, absenteeism, impaired work performance, lost leisure time, and activities)[9,10] as well as higher rates of anxiety and depression compared with the general population.[9–11] HAE attacks can lead to missed school or work attendance and patients also report impaired productivity.[9,10]

Long-term prophylaxis (LTP) can be an option for some patients based on factors such as attack severity and frequency, and quality-of-life issues.[1,12,13] Long-term prophylaxis with intravenous (IV) C1-INH concentrate reduces HAE attack frequency[14–17] and improves quality of life in patients with C1-INH-HAE.[17] The plasma-derived C1-INH concentrate Berinert (pnfC1-INH) (CSL Behring, King of Prussia, PA) has been available in a pasteurized, nanofiltered formulation since 2010, with a pasteurized predecessor version first marketed in 1985 in the European Union, where it is approved for on-demand treatment and short-term prophylaxis in patients of all ages. In the United States, pnfC1-INH has been available since 2009 and is approved for the treatment of abdominal, facial, or laryngeal attacks in patients of all ages. HAE treatment guidelines recommend IV C1-INH as an option for LTP,[4,18,19] although Berinert is not specifically approved for this use. Another IV plasma-derived, pasteurized, nanofiltered C1-INH concentrate (Cinryze; Shire, Boston, MA) is approved for routine prophylaxis in the United States[20] as well as on-demand treatment and prophylaxis in the European Union for adolescents and adults. The Berinert Patient Registry (hereafter, "Registry") collected observational data on pnfC1-INH use in the United States and Europe,[21,22] and included a sizable number of patients who used pnfC1-INH as LTP. This report describes usage patterns, safety findings, and HAE attack data in these patients.

METHODS

Study Design

This multicenter, observational, patient registry (NCT01108848) collected data between 2010 and 2014 at 30 U.S. and 7 European sites (Germany, 5; Denmark, 1; Switzerland, 1). Data on usage of C1-INH products other than Berinert were not included. The study was conducted in accordance with local regulatory requirements for noninterventional studies, and patient details and registry data were kept confidential. The study protocol and master informed consent form were reviewed and approved by relevant institutional review boards and independent ethics committees. In compliance with International Conference on Harmonization guidelines, all the subjects provided signed informed consent that was institutional review board approved for collection of treatment data.

Data Collection and Analysis

The Registry collected data regarding patient demographics, reason for pnfC1-INH use, pnfC1-INH dose, anatomic location and severity of HAE attacks, and adverse events (AE), including potential thromboembolic events (TEE) and suspected viral transmission. Data on HAE attacks were recorded only for attacks that were treated with pnfC1-INH and all mentions in this article of attacks after pnfC1-INH LTP infusion should be interpreted as pnfC1-INH–treated attacks, even if not stated explicitly. Both retrospective (infusion occurred before Registry enrollment) and prospective (infusion occurred after enrollment) data on the use of pnfC1-INH were obtained.

For each infusion, investigators were requested to indicate a reason for administration (HAE attack treatment, prophylaxis, or other). The specification of prophylaxis as LTP was based on data analysis rules that defined LTP infusions as those that were investigator designated as prophylaxis and were administered 7 or fewer days apart. In addition, pnfC1-INH infusions that were administered for attack treatment in between LTP infusions were also categorized as LTP infusions for the analyses presented in this article. This convention captured consecutively administered infusions such that they comprised a single LTP dosing interval.

Table 1 Baseline characteristics of subjects who used pnfC1-INH for long-term prophylaxis

Characteristic	Patients (N = 47)
Sex, no. (%)	
Female	38 (80.9)
Male	9 (19.1)
Age, y	
Mean (SD)	44.8 ± 15.9
Range	13–79
Race, no. (%)	
White	46 (97.9)
Other	1 (2.1)
Ethnicity, no. (%)	
Hispanic or Latino	1 (2.1)
Not Hispanic or Latino	46 (97.9)
Body mass index, kg/m^2	
Mean (SD)	29.6 ± 6.5
Range	20–44

pnfC1-INH = Pasteurized, nanofiltered C1-inhibitor concentrate (Berinert); SD = standard deviation.

Data were analyzed on pnfC1-INH–treated attacks that occurred within 7 days after infusions designated as LTP.

Investigators rated the severity of each AE as mild, moderate, or severe. Serious AEs (SAE) were defined as those that resulted in death, a life-threatening reaction that required hospitalization or events that caused persistent or significant physical disability. Signs and symptoms of HAE attacks were not considered AEs for the purpose of this analysis, with the exception of HAE attacks that also met SAE criteria; these were dually reported as both SAEs and HAE attacks. Any suspected TEEs were to be investigated further with a separate questionnaire designed to obtain additional information. Investigators used their clinical judgment and local standards of clinical care to determine if subjects should undergo monitoring for suspected viral transmissions.

RESULTS

Subjects

A total of 343 subjects were enrolled in the Registry, 318 of whom received at least one IV dose of pnfC1-INH. Of these, 47 subjects used pnfC1-INH for LTP. The majority of subjects who used pnfC1-INH for LTP were female and white, with a mean age of 44.8 years (range, 13–79 years) (Table 1).

pnfC1-INH Dosing and Infusions

A total of 4082 pnfC1-INH infusions were categorized as LTP in 47 subjects. The total duration of pnfC1-INH LTP administration for all the subjects was 430.2 months, with a mean duration of LTP dosing interval per subject of 9.2 months. The median dose of pnfC1-INH given for LTP infusion was 13.77 IU/kg (range, 4.0–32.6 IU/kg), and the median absolute dose per infusion was 1000 IU (range, 500-3000 IU). Forty-two subjects administered pnfC1-INH for LTP at least once outside of a health care setting (95.3% [2807/2944] of infusions for which the setting was known).

Attacks that Occurred During Long-Term Prophylactic Therapy

Among the 47 subjects who used pnfC1-INH for LTP, 15 subjects (31.9%) had no reported HAE attacks (treated with pnfC1-INH) within 7 days after infusion of pnfC1-INH for LTP. The remaining 32 subjects (68.1%) experienced 246 attacks that occurred within 7 days after infusion of pnfC1-INH for LTP (Table 2), for attack rates of 0.06 per infusion and 0.57 per month. The median time interval between LTP infusion and a subsequent attack was 72.0 hours (range, 0.0–166.4 hours). The most common body locations of HAE attacks that occurred within 7 days of an LTP dose of pnfC1-INH (and treated with pnfC1-INH) were abdominal and peripheral; facial and laryngeal attacks were rare (Table 2). The majority of attacks (170/246 [69.1%]) were considered mild or moderate in severity, with 34 (13.8%) classified as severe (intensity not recorded for 42 attacks). The maximum attack intensity by subject was mild in 3 subjects (9.4%), moderate in 13 subjects (40.6%), and severe in 15 subjects (46.9%).

There were 61 pnfC1-INH–treated attacks reported within 2 days after pnfC1-INH infusions that were categorized as LTP, which represented a cumulative percentage of 1% of LTP infusions, followed by an attack (Fig. 1). The cumulative percentage of pnfC1-INH LTP infusions that were followed by a pnfC1-INH–treated HAE attack were 3% at 3 days (n = 133 attacks); 5% at 4 days (n = 193 attacks); and 6% each for the time windows of 5 days (n = 226 attacks), 6 days (n = 237 attacks), and 7 days (n = 246 attacks) after pnfC1-INH LTP infusion (Fig. 1). Analysis of post-LTP infusion attack rates according to weight-based pnfC1-INH dose showed a trend that indicated an inverse dose-dependent relationship (Fig. 2). The highest rate of attacks that occurred within 7 days of infusion (0.08 attacks per infusion) was documented after the subject's most recent pnfC1-INH LTP dose of <15 IU/kg, whereas the lowest attack rate (0.02 attacks per infusion) was observed after preceding pnfC1-INH doses of ≥25 IU/kg. The subjects who received doses of 15 to <20 IU/kg and 20 to <25 IU/kg demonstrated an

Table 2 HAE attacks in subjects who used pnfC1-INH for long-term prophylaxis

	Subjects (N = 47)
Total no. infusions administered as LTP	4082
Subjects with ≥1 attack, no. (%)*	32 (68.1)
Total no. attacks*	246
HAE attack rates among subjects who used pnfC1-INH for LTP*	
Per subject	5.23
Per infusion	0.06
Per month	0.57
Interval between LTP pnfC1-INH infusion and HAE attack, hr*	
Mean (SD)	73.7 ± 32.5
Median	72.0
Range	0.0, 166.4
Attack location, no. (%)*	
Total attacks	246
Abdomen	85 (34.6)
Peripheral	71 (28.9)
Facial	6 (2.4)
Laryngeal	6 (2.4)
Thoracic	7 (2.8)
Other	41 (16.7)
Missing	30 (12.2)
Attack severity, no. (%)*	
Total attacks	246
Mild	77 (31.3)
Moderate	93 (37.8)
Severe	34 (13.8)
Missing	42 (17.1)

HAE = Hereditary angioedema; pnfC1-INH = pasteurized, nanofiltered C1-inhibitor concentrate (Berinert); LTP = long-term prophylaxis; SD = standard deviation.
*Attacks treated with pnfC1-INH within the 7-day interval after LTP administration of pnfC1-INH.

attack rate of 0.05 attacks per infusion. It should be noted that the highest dose category (≥25 IU/kg) had a small number of subjects (*n* = 4).

Safety of Long-Term Prophylactic Therapy

A total of 81 AEs were reported in 16 subjects (34.0%) who received at least one prospective infusion of pnfC1-INH for LTP. The majority of AEs were mild (*n* = 21) or moderate (*n* = 57) in severity. The rates of AEs associated with pnfC1-INH use for LTP were 0.02 per LTP infusion, 1.72 per subject, and 0.19 per subject per month. There was no apparent association between pnfC1-INH dose and the frequency or severity of AEs. The majority of AEs (*n* = 78 [96.3%]) were not considered to be related to pnfC1-INH. Three AEs were con-

sidered to be related to pnfC1-INH: two nonserious (noncardiac chest pain, postinfusion headache) and one serious (deep vein thrombosis).

The one SAE considered related to pnfC1-INH used for LTP was a case of upper-extremity deep vein thrombosis, which also affected the chest, in a 36-year-old woman with HAE and with normal C1-INH who had a subclavian venous access port. The subject's most recent pnfC1-INH doses before the deep vein thrombosis event were 11 days before (500 IU), 7 days before (1000 IU), 3 days before (two doses of 500 IU), and the day of the event (500 IU); she also received a 500 IU dose after the event, on the same day, for treatment of an attack. The port was removed, and the event resolved without sequelae. The subject recovered with no further medical complications and discontinued participation in the Registry. There were no other discontinuations secondary to AEs (regardless of seriousness). The other three SAEs (severe HAE attack, urinary tract infection, and gastrointestinal hemorrhage) reported for Registry subjects who used pnfC1-INH for LTP were not considered related to pnfC1-INH. No AEs were reported that were suggestive of new infection with blood-borne viruses, including human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or parvovirus B19.

DISCUSSION

Berinert (pnfC1-INH and its pasteurized predecessor formulation) has been used for HAE treatment since 1985 in the European Union. The first description of the use of this C1-INH concentrate for LTP was a case report published in 1989.[23] Since then, three uncontrolled studies[16,24,25] and numerous case reports and/or case series[3,26–32] described the clinical use of IV Berinert or its predecessor formulation for LTP, including during pregnancy.[3,24,25,27,30] The subgroup of patients in the international patient registry referenced herein has contributed, to date, the largest data set for analysis of pnfC1-INH (Berinert) used for LTP. Although Berinert has not been approved for this indication, all recent treatment guidelines recommend plasma-derived C1-INH as an option for LTP,[4,12,13,18,19,33] and the efficacy of another marketed plasma-derived, nanofiltered C1-INH product (Cinryze) for LTP has been confirmed in two placebo-controlled trials,[15,34] with further support from several uncontrolled trials.[14,15,35]

The Registry provided data on 4082 pnfC1-INH infusions characterized as LTP. Approximately one-third of LTP users in the Registry had no HAE attacks reported that required on-demand treatment with pnfC1-INH. It is possible that there were mild attacks that did not require treatment or attacks treated with other interventions that were not captured by the Registry. Within 7 days after LTP administration of pnfC1-
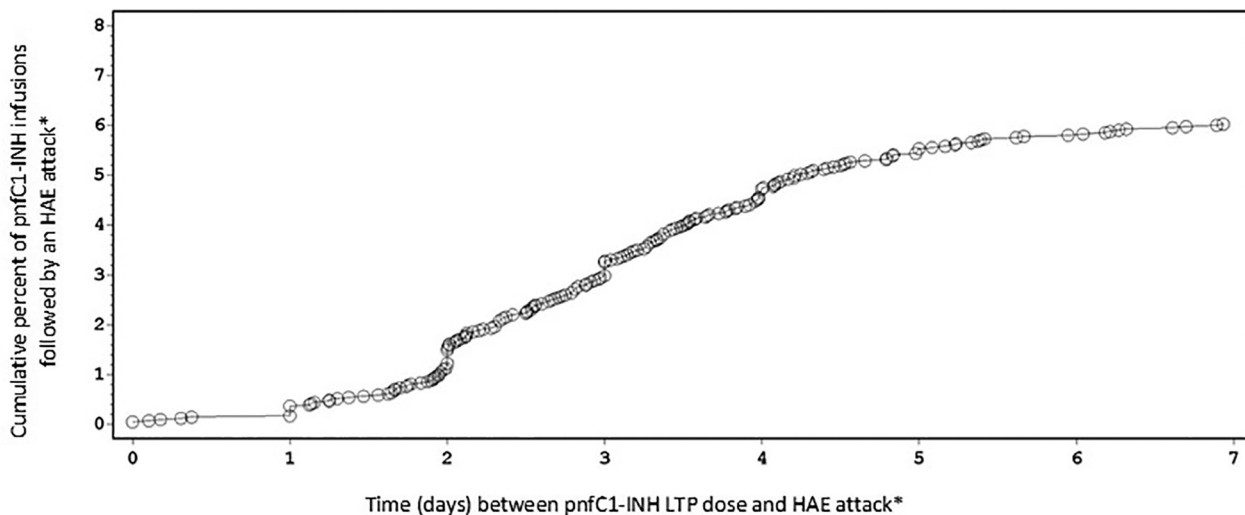
Figure 1. *Cumulative percentage of pnfC1-INH infusions, followed by a hereditary angioedema attack treated with pnfC1-INH that occurred within 7 days of pnfC1-INH infusions designated as long-term prophylaxis. pnfC1-INH = pasteurized, nanofiltered C1-inhibitor concentrate (Berinert). Each circle represents one HAE attack. *HAE attacks treated with pnfC1-INH.*
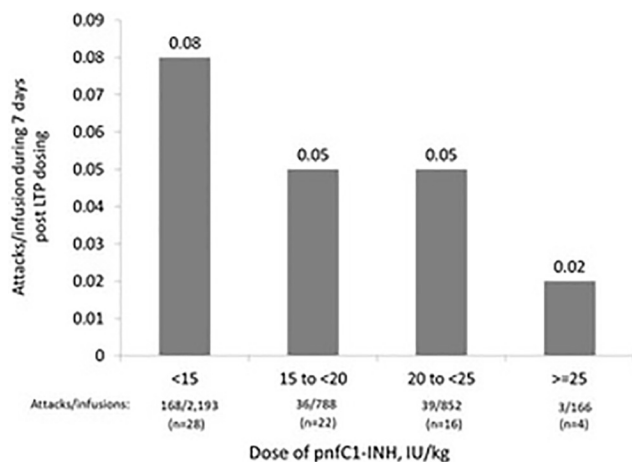

Figure 2. *Rate of hereditary angioedema (HAE) attacks treated with pnfC1-INH within 7 days after pnfC1-INH infusions designated as long-term prophylaxis (LTP), categorized by weight-based dose. pnfC1-INH = pasteurized, nanofiltered C1-inhibitor concentrate (Berinert).*

INH, HAE attacks that required treatment with pnfC1-INH were reported at rates of 0.57 attacks per month and 0.06 attacks per LTP infusion. Within the first 72 hours after LTP administration of pnfC1-INH, the attack rate was 0.03 per infusion. These results were consistent with those reported with nanofiltered C1-INH (Cinryze). An open-label study that involved 146 patients with HAE who used Cinryze for LTP (fixed dose of 1000 units every 3–7 days) reported a mean breakthrough attack rate of 0.47 attacks per month.[34] The percentage of patients with no attacks in the Cinryze study was 34.9%, similar to that seen in the current study (31.9%).

Analysis of the Registry data implied that prophylaxis efficacy was greatest within the first 72 hours after

pnfC1-INH administration and an LTP dosing strategy of every 3 to 4 days was appropriate and logical. Analysis of the data also indicated a trend toward greater efficacy of LTP with higher weight-based doses of pnfC1-INH. In a recent study that involved 20 patients with HAE inadequately controlled on a fixed, regular dose of Cinryze 1000 units for LTP, dose escalation up to 2500 units was necessary in 12 of them.[14] These findings reinforce the need for individualization of LTP regimens. The Registry data reflected a wide range of pnfC1-INH dosing for LTP, with absolute doses that ranged from 500 to 3500 IU per infusion.

The safety of pnfC1-INH used as LTP in patients with HAE is of particular interest, given the regular, ongoing frequency of infusions, typically one to two times per week, over long periods of time. Thus, the cumulative exposure to pnfC1-INH is typically greater compared with less frequently administered acute HAE therapy. Analysis of the Registry data supported the overall safety of pnfC1-INH when used for LTP, with a very low rate of AEs per LTP infusion (0.2), and no evidence of a dose-response relationship for AEs. Although there have been rare postmarketing reports of systemic allergic reactions and/or anaphylaxis with the use of pnfC1-INH in Europe,[36] there were no such reports in this large international registry nor in other clinical trials with pnfC1-INH that indicated that the risk of hypersensitivity seemed to be extremely small.

The observed risk of TEE was low, with one TEE reported among subjects who used pnfC1-INH for LTP over a duration of 430 months for all the subjects and which occurred in a patient with preexisting risk factors for TEE. Similarly, a worldwide survey of HAE-treating physicians, which reflects experience with 856 patients with HAE, revealed a minimal risk of TEE;

three of five reported TEEs were associated with the use of indwelling catheters.[37] It should be noted that the official product labeling for both Berinert and Cinryze includes a precaution to closely monitor patients with known risk factors for TEEs.

One clear limitation of the Registry data with regard to assessing LTP efficacy is the lack of a control group or comparative historic attack frequency. In addition, because the Registry was designed to gather data on pnfC1-INH use, breakthrough attacks were only captured if they were treated with pnfC1-INH; attacks that went untreated or may have been managed with other on-demand HAE medication were not recorded. However, it is likely that most patients who used pnfC1-INH for prophylaxis would also use it to treat breakthrough attacks. At minimum, analysis of the data provides strong evidence that the incidence of HAE attacks of a severity that warranted pnfC1-INH treatment was very low for several days after LTP infusion and increased gradually over the 7-day postinfusion period. Further, the attack patterns found in the Registry data mimic those reported in other reports.

Investigators and subjects who participated in the Registry adhered to routine practices regarding pnfC1-INH use and dosing. Therefore, the use of IV pnfC1-INH varied according to local standards of care in different countries and between individual prescribers. Although this can be considered a limitation in some regards, it also adds value to the data with regard to understanding usage patterns and outcomes in a real-world setting. Further, although Berinert is not indicated for prophylaxis, "prophylaxis" was offered as one reason for pnfC1-INH use that the investigator could choose to report because such use is consistent with HAE treatment guidelines. However, specification of short-term prophylaxis or LTP was not offered. Therefore, a designation of prophylaxis as LTP was determined according to data analysis rules as described in the Methods section. Also, given the nature of the Registry and its focus on collecting Berinert usage and safety data, concomitant medication data were often incomplete; thus it was possible that some subjects were using other prophylactic medications. Another potential limitation of a registry-based data set was the possibility of self-selection bias, given that participation was voluntary. Therefore, the findings may not be entirely reflective of the HAE population in general. Yet, this study, of 318 subjects with HAE and >4000 pnfC1-INH infusions given for LTP, represents one of the largest data sets for this indication to date. Also, although the Registry population was diverse with respect to geography, age, and sex, it was a racially homogenous group, with only one nonwhite subject.

CONCLUSION

The results of this large international patient registry indicated that IV pnfC1-INH was being used for LTP of HAE attacks in both the United States and Europe with good safety and no observable dose-response for AE occurrence. Such use was associated with a low 7-day post-LTP infusion attack rate. A possible dose-response phenomenon was evident for weight-based dosing regimens, which indicated that higher doses provide better protection. Analysis of these data support a role for the use of IV pnfC1-INH in patients with HAE who are considered candidates for LTP.

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