

Original Article

Safety and Usage of C1-Inhibitor in Hereditary Angioedema: Berinert Registry Data



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What is already known about this topic? The safety of plasma-derived C1-inhibitor (C1-INH; Berinert) has been well documented in studies in patients with hereditary angioedema (HAE) treated with recommended doses. Rare cases of thromboembolic events have been reported with C1-INH use, generally off-label and at supratherapeutic doses.

What does this article add to our knowledge? This large, international, registry of patients using C1-INH is the most extensive of its kind, providing real-world data regarding general safety and intentional surveillance for issues of particular interest, including thromboembolism and possible viral transmission.

How does this study impact current management guidelines? Recent HAE guidelines consistently recommend self-administration of C1-INH. The Berinert registry data provide real-world evidence for widespread implementation of this practice and support the feasibility and safety of C1-INH administration outside of a health care setting.

BACKGROUND: The plasma-derived, highly purified, nano-filtered C1-inhibitor concentrate (Berinert; “pnfC1-INH”) is approved in the United States for treating hereditary angioedema (HAE) attacks and in many European countries for attack treatment and short-term prophylaxis.

OBJECTIVE: The objective of this study was to describe safety and usage patterns of pnfC1-INH.

METHODS: A multicenter, observational, registry was conducted between 2010 and 2014 at 30 United States and 7 European sites to obtain both prospective (occurring after enrollment) and retrospective (occurring before enrollment) safety and usage data on subjects receiving pnfC1-INH for any reason.

RESULTS: Of 343 enrolled patients, 318 received 1 or more doses of pnfC1-INH for HAE attacks (11,848 infusions) or for

prophylaxis (3142 infusions), comprising the safety population. Median dosages per infusion were 10.8 IU/kg (attack treatment) and 16.6 IU/kg (prophylaxis). Approximately 95% of infusions were administered outside of a health care setting. No adverse events (AEs) were reported in retrospective data. Among prospective data (n = 296 subjects; 9148 infusions), 252 AEs were reported in 85 (28.7%) subjects (rate of 0.03 events/infusion); 9 events were considered related to pnfC1-INH. Two thromboembolic events were reported in subjects with thrombotic risk factors. No patient was noted to have undergone viral testing for suspected blood-borne infection during registry participation. **CONCLUSIONS:** The findings from this large, international patient registry documented widespread implementation of pnfC1-INH self-administration outside of a health care setting

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Abbreviations used

AE- Adverse event
 C1-INH- C1 inhibitor
 DVT- Deep vein thrombosis
 EU- European Union
 HAE- Hereditary angioedema
 HIV- Human immunodeficiency virus
 MedDraRA- Medical Dictionary for Regulatory Activities
 pnfC1-INH- Plasma-derived, highly purified, pasteurized,
 nanofiltered C1-inhibitor concentrate
 SAEs- Serious adverse events
 SMQ- Standardized MedDRA Queries
 TEEs- Thromboembolic events
 TIA- Transient ischemic attack

consistent with current HAE guidelines. These real-world data revealed pnfC1-INH usage for a variety of reasons in patients with HAE and showed a high level of safety regardless of administration setting or reason for use. © 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2016;4:963-71)

Key words: Berinert; Plasma-derived C1-INH; Patient registry; Thromboembolic event; Real-world; Prophylaxis; On demand; Self-administration; Safety; Dosing

Hereditary angioedema (HAE) is a rare genetic disorder with several subtypes. Type 1 and 2 HAE result from mutations in the gene *SERPINC1* encoding the blood protein, C1 inhibitor

(C1-INH).¹ These mutations result in quantitative or qualitative deficiency of C1-INH activity. A third type of HAE, referred to as HAE with normal C1-INH, may also be familial, with some cases associated with factor XII activation mutations.² Clinically, HAE is characterized by episodes of localized subcutaneous or submucosal swelling usually involving the skin (without urticaria), upper airways, and gastrointestinal and urogenital tracts.¹ Laryngeal edema is the least frequent type of attack, but is potentially life threatening if not properly treated.^{3,4}

Recommended strategies for HAE management include access to on-demand treatment of HAE attacks for all patients, short-term prophylaxis for patients anticipating events that might trigger an HAE attack, and long-term prophylaxis in appropriate patients.⁵⁻¹⁰ There is an increasing trend toward patient-administered HAE therapy outside of a health care setting (ie, caregiver- or self-administration),^{1,5,6,8-14} an approach that offers the benefits of rapid treatment and has proven safe for patients with appropriate technical training and education.¹² For intravenously administered products such as C1-INH concentrate, most patients can be adequately trained over several training sessions to reconstitute and self-administer their infusions using a butterfly needle or through an indwelling port, enlisting the help of a family member or other caregiver if necessary.¹⁵ Survey data gathered between 2010 and 2013 in the United States (US) suggested that more than two-thirds of patients using C1-INH were being infused at home.¹⁶

The plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate Berinert (pnfC1-INH; CSL Behring) is approved in the United States for the treatment of HAE attacks in adults and adolescents 12 years and older, and in Europe for the treatment of HAE attacks and short-term prophylaxis in

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adults and children. This product has a well-established safety and efficacy profile, with more than 35 years of availability in Europe.¹⁷

The Berinert Patient Registry (hereafter, “Registry”) was created to evaluate the safety of pnfC1-INH in a “real-world” setting and to gather more information on usage patterns for pnfC1-INH. Information on thromboembolic events (TEEs) was a particular focus of the Registry, given previously reported events in patients treated with plasma-derived C1-INH,¹⁸⁻²⁰ in many cases for unapproved uses and/or at supratherapeutic doses. As with any plasma-derived product, potential transmission of blood-borne viruses was also of interest. The Registry was active from 2010 to 2014; retrospective data from 2009 were also captured through medical chart review. A planned 3-year interim analysis was published previously, including data on 135 subjects and 3196 pnfC1-INH infusions.²¹ The final dataset reported here is substantially larger, reflecting 15,000 pnfC1-INH infusions in 318 subjects. In addition, criteria for defining adverse events (AEs) were refined since the interim analysis such that nonserious HAE attack signs and symptoms were no longer classified as AEs, allowing for a more specific analysis of pnfC1-INH safety and tolerability.

METHODS

Study design

This multicenter, observational, patient Registry (NCT01108848) was conducted at 30 US and 7 European sites (Germany, 5; Denmark, 1; Switzerland, 1). Procedures were conducted in accordance with local regulatory requirements pertaining to noninterventional studies; all subjects provided informed consent for collection of treatment data. The study protocol and master informed consent form were reviewed and approved by relevant institutional review boards and independent ethics committees.

Data collection and analysis

The Registry enrolled individuals of any age using pnfC1-INH (Berinert) for any reason. Both retrospective (infusion occurring before enrollment) and prospective (infusion occurring after enrollment) data on the use of pnfC1-INH were obtained. The following data were collected: patient demographics; reason for pnfC1-INH administration; pnfC1-INH dose; place of administration (health care setting or outside of a health care setting); anatomic location and severity of attacks; and AEs, including potential TEEs, appearance of anti-C1-INH antibodies, and suspected viral transmission. HAE attack data were collected only for attacks treated with pnfC1-INH. Investigators were required to record the reason for C1-INH infusion as acute treatment, prophylaxis, or other. Treatment outside of a health care setting included any pnfC1-INH infusion that was administered by the subject, a family member, friend, or other caregiver in a non-health care setting. Treatment in a health care setting included any pnfC1-INH infusion that was administered by a health care professional (eg, a physician or nurse) in a health care institution (eg, hospital or clinic).

TEEs were identified using the Medical Dictionary for Regulatory Activities (MedDRA), Standardized MedDRA Queries (SMQ) for embolic and thrombotic events. A separate questionnaire was completed for suspected TEEs to obtain additional information. Monitoring of suspected viral transmissions was per usual clinical practice; investigators were to test for viral transmission based on their medical judgment and routine standard of medical care. Prospectively, patients were queried about AEs at

TABLE 1. Registry population demographics (subjects who received at least 1 administration of pnfC1-INH)

Safety population Total N = 318	
Sex, n (%)	
Male	111 (34.9)
Female	207 (65.1)
Race, n (%)	
Asian	2 (0.6)
Black/African American	8 (2.5)
White	298 (93.7)
Other	9 (2.8)
Missing	1 (0.3)
Age (y)	
Mean (SD)	38.8 (17.92)
Range	5-83

pnfC1-INH, Plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate; *SD*, standard deviation.

each clinic visit; medical charts were reviewed for possible AEs related to prospectively recorded infusions (administered before enrollment). All AEs were recorded, regardless of suspected causality to pnfC1-INH administration. The collection period for AEs reflected a 1-month period after each administration of pnfC1-INH. Causality was evaluated by the investigator as either not related, unlikely related, possibly related, probably related, or related. The intensity of each AE was graded by the investigator as mild (easily tolerated, no interference with daily activities), moderate (causing some interference with daily activities), or severe (incapacitating; inability to do work or perform usual activities). Serious AEs (SAEs) were those resulting in death, life-threatening circumstances, requiring hospitalization, or resulting in persistent or significant disability or incapacity. In this report, signs and symptoms of HAE attacks, as reflective of the condition under study, were not reported as AEs. The exception was for HAE attacks that also met SAE criteria; these were dually reported as SAE and HAE attacks. Of note, in the previously published interim report, the overall number of AEs did include nonserious HAE attacks.²¹ AEs were followed by the investigator until such time that the AE was considered resolved or was deemed a permanent condition.

AEs that were missing a reported intensity grading were conservatively assumed to be “severe” and reported in data tables in both the “severe” and “missing” categories. Events with missing causality were categorized by convention as “related.” Data were summarized using descriptive statistics. AE rates were plotted by dose, and the coefficient of correlation (*R*) was calculated.

RESULTS

Subjects

Of 343 patients who enrolled in the Registry, 318 received 1 or more doses of pnfC1-INH and comprised the safety population for this analysis. Subjects were predominantly female (65.1%) and white (93.7%) and ranged in age from 5 to 83 years (Table 1). A majority of subjects (n = 213, 67.0%) used pnfC1-INH for treatment of HAE attacks only, 13 subjects used pnfC1-INH as prophylaxis only, and 92 subjects used pnfC1-INH for both attack treatment and prophylaxis. Among subjects who received pnfC1-INH exclusively in a non-health care setting,

TABLE II. HAE attack characteristics and corresponding mean pnfC1-INH doses

	Attacks, n (%)	Subjects with attacks, n (%)	pnfC1-INH dose per attack (IU/kg) Median (range)
Total	11,844	305 (95.9)	11.6 (3.4-37.8)
Anatomic location of attack*			
Abdominal	4839 (40.9)	239 (78.4)	12.2 (3.6-35.7)
Facial	349 (2.9)	123 (40.3)	14.6 (3.4-35.7)
Laryngeal	242 (2.0)	85 (27.9)	14.7 (4.0-37.8)
Peripheral	2742 (23.2)	166 (54.4)	9.7 (3.5-31.5)
Thoracic	347 (2.9)	56 (18.4)	10.4 (3.6-23.3)
Other (or multiple locations)	1494 (12.6)	144 (47.2)	12.0 (3.5-32.3)
Unknown	1831 (15.5)	68 (22.3)	—
Attack intensity†			
Mild	3748 (31.6)	9 (3.0)	6.7 (3.5-32.6)
Moderate	4734 (40.0)	64 (21.0)	12.2 (3.4-32.3)
Severe	1764 (14.9)	228 (74.8)	14.1 (3.5-37.8)
Unknown	1598 (13.5)	4 (1.3)	—

HAE, Hereditary angioedema; IU, international units; kg, kilograms; pnfC1-INH, plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate.

*For per subject reporting of anatomic location, the n value represents the number of subjects who experienced ≥ 1 attack in the anatomic location.

†For per subject reporting of attack intensity, each subject is included in only 1 category based on the maximum intensity attack.

98.3% were white, 1.1% were of other race(s) (0% black/African American), and 0.6% were Asian.

HAE attack characteristics

The most frequent types of HAE attacks treated with pnfC1-INH were abdominal (40.9%) and peripheral (23.2%), experienced at least once by 78.4% and 54.4% of subjects, respectively (Table II). Facial and laryngeal attacks were experienced by 40.3% and 27.9% of subjects, respectively. Most attacks (40.0%) were moderate in intensity. However, 75% of subjects experienced at least 1 severe attack.

pnfC1-INH infusions

The Registry captured data on a total of 15,000 pnfC1-INH infusions (Figure 1, A), of which 11,848 (79.0%) were administered for on-demand treatment of HAE attacks, and 3142 (20.9%) were given for HAE prophylaxis (reason unknown for 10 infusions). The number of pnfC1-INH infusions per subject varied considerably and ranged from 1 to 612. Of the 15,000 pnfC1-INH infusions, 5852 (39.0%) were administered before (retrospective to) a subject's Registry enrollment; these data were gathered via a chart review after a subject's enrollment into the Registry. Data on 9148 (61.0%) infusions were collected on an ongoing, prospective basis during the Registry period. The majority of pnfC1-INH infusions (70.7%) were documented in European subjects (Figure 1, B). For European and US sites, respectively, 53% and 19% of the reported infusions had been retrospectively administered.

pnfC1-INH dosing patterns

Doses of pnfC1-INH per infusion ranged from 3.4 IU/kg to 37.8 IU/kg for on-demand treatment and from 3.6 IU/kg to 33.9 IU/kg for prophylaxis. As shown in Table III, the highest

median doses were noted in the following patient categories: youngest age groups, those receiving prophylactic treatment, US subjects, and those with prospectively collected data. With respect to attack characteristics, the highest median doses were recorded for facial and laryngeal attacks and for severe attacks (Table II).

Setting of pnfC1-INH administration

Administration of pnfC1-INH outside of a health care setting was documented for 14,072 (95.0%) infusions in 224 (70.4%) subjects. A total of 95.2% of attack treatment infusions and 94.1% of prophylactic infusions were administered outside of a health care setting. Changes in the administration setting (non-health care setting to health care setting) occurred 68 times in 29 (9.1%) subjects (Figure 2). "Failure to self-infuse" (inability to find a vein or IV port) was recorded in <0.1% of infusions (13 events in 6 subjects) administered outside of a health care setting, almost all of which were involving treatment of attacks.

Safety

There were no AEs reported for infusions administered before enrollment (retrospective infusion data; 39.0% of all infusions). Because of this finding, only prospectively administered infusions (9148 infusions) and individuals who contributed at least 1 prospective data point (n = 296 subjects) were included in the safety analysis. Among these subjects/infusions, 252 AEs were noted in 85 (28.7%) subjects (Table IV), for an overall rate of 0.03 AEs per pnfC1-INH infusion and 0.85 AEs per subject. The most commonly reported AEs (12.8% of subjects) were infections (non-blood-borne viral infections; primarily respiratory tract related) and gastrointestinal disorders (5.7% of subjects). Most AEs were mild (51.2%) or moderate (38.1%) in intensity. The majority (96.4%) of AEs were considered unrelated to pnfC1-INH administration. Nine AEs occurring in 6 subjects were considered to be at least possibly related to pnfC1-INH treatment, including headache (4 events in 3 subjects) and 1 event each of gastroesophageal reflux disease, hematoma, noncardiac chest pain, and fatigue. One serious AE (deep vein thrombosis) was considered at least possibly related to pnfC1-INH; this patient had an indwelling central line (see additional details on this case in a following paragraph). There were no events of anaphylaxis or events suggestive of drug-related hypersensitivity.

The AE rates per subject and per infusion were similar for pnfC1-INH infusions given as prophylaxis (0.63 per subject, 0.03 per infusion) or for attack treatment (0.66 per subject, 0.03 per infusion). The overall AE rate per infusion was higher among infusions given in a health care setting (0.13) compared with those given in a non-health care setting (0.02). The rates of AEs considered related to pnfC1-INH administration were very low in both health care and non-health care settings (<0.005 events per infusion).

One subject treated with pnfC1-INH at doses between 20 and 25 IU/kg had a disproportionate number of AEs (25 of 252 events, or 11% of all AEs reported). Sensitivity analysis comparing dose and adverse events, excluding data from this subject, confirmed that there was no evidence of a dose relationship with AEs in prospective data (Figure 3).

Overall, 34 SAEs were reported in 14 subjects, all of whom were 18 years of age or older. Of the 34 SAEs, 29 occurred after infusions for attack treatment. The most common SAE was HAE

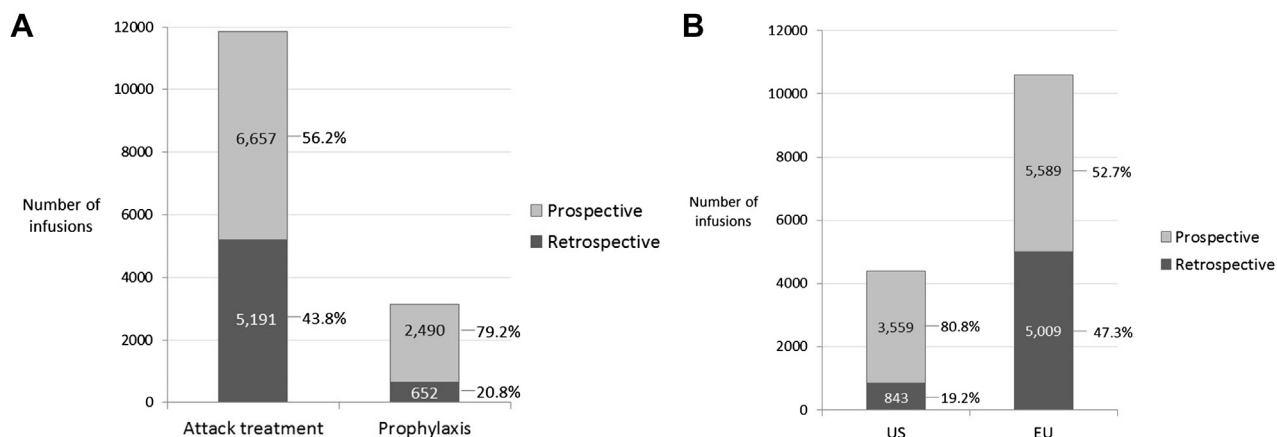
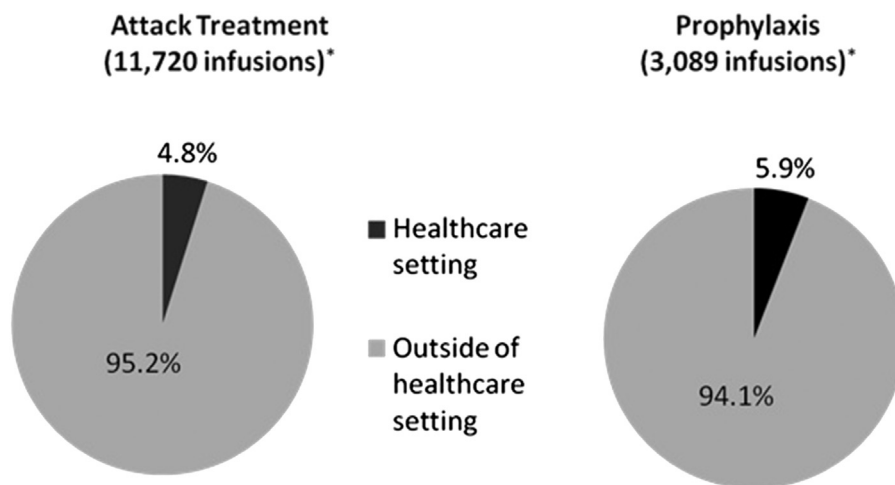


FIGURE 1. Number of pnfC1-INH infusions captured in the Registry, by nature of data collection (retrospective vs prospective) and **A**, reason for infusion (not recorded for 10 infusions) or **B**, geographical location (US vs EU). *EU*, European Union; *pnfC1-INH*, plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate; *US*, United States.



* Infusions with location information available; missing for 128 attack treatment infusions and 53 prophylaxis infusions

FIGURE 2. Location of pnfC1-INH administration, health care setting vs outside of a health care setting, by indication for use. *pnfC1-INH*, Plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate.

attack requiring hospitalization (15 of 34 events). HAE attacks were generally regarded as a condition under study and not reported as AEs unless they fulfilled criteria defining an SAE, such as hospitalization. The majority of HAE attacks requiring hospitalization (9 of 15 attacks) occurred in a single subject. This subject had a self-directed pattern of treatment typically characterized by delays in treatment initiation of 24 to 48 hours after onset of an HAE attack. In this study, 1 SAE (DVT, described below) was considered to be related to pnfC1-INH treatment. With the exception of 1 case of fatal myocardial infarction, also described below, all SAEs resolved without sequelae.

There were 2 TEEs identified (deep vein thrombosis [DVT] and myocardial infarction) among 296 subjects/9148 infusions with prospective data, for a rate of 0.007 TEEs per subject and

0.0002 TEEs per infusion. A 36-year-old female subject with HAE with normal C1-inhibitor and an indwelling subclavian venous access port experienced an upper extremity DVT, also affecting the chest, which was graded as severe and considered probably related to pnfC1-INH. This subject had been using pnfC1-INH (intravenously) for long-term prophylaxis, and had received pnfC1-INH 11 days before the event (500 IU), 7 days before the event (1000 IU), 3 days before the event (2 doses of 500 IU), and the same day before 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 second TEE was a fatal myocardial infarction that occurred in a 57-year-old male subject 8 months after his last pnfC1-INH infusion. This subject had a

TABLE III. Median pnfC1-INH doses (IU/kg) by age, geographic region, and data collection type (retrospective vs prospective)

	Subjects N	Infusions N	pnfC1-INH	pnfC1-INH
			dose (IU/kg) Median	dose (IU/kg) Range
Age group (y)				
<12	18	275	15.6	6.0-35.7
12 to <17	21	521	14.7	5.6-30.1
17 to <65	252	12,503	12.5	3.4-37.8
65+	27	1701	6.4	5.8-24.4
Reason for use*				
HAE attack treatment	305	11,848	10.8	3.4-37.8
HAE prophylaxis	105	3142	16.6	3.6-33.9
Geographic region				
US	156	4402	18.9	3.4-37.8
EU	162	10,598	9.1	3.5-35.7
Geographic region, prospective data only				
US	131	3559	19.5	3.4-37.8
EU	136	5589	9.7	3.5-34.0
Data collection type†				
Retrospective	251	5852	10.0	3.6-35.7
Prospective	267	9148	13.0	3.4-37.8

HAE, Hereditary angioedema; EU, European Union; IU, international units; kg, kilograms; pnfC1-INH, plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate; US, United States.

*Not known for 10 infusions.

†241 subjects had both retrospective and prospective data; 22 subjects had retrospective data only; 55 subjects had retrospective data only.

TABLE IV. Summary of safety findings (prospective data)

	Subjects, n (%)		Rate/subject†	Rate/infusion n = 9148 infusions‡
	n = 296*	Events		
Any AE	85 (28.7)	252	0.85	0.03
Related AEs	6 (2.0)	9	0.03	0.00
Serious AEs§	14 (4.7)	34	0.11	0.00
Discontinuation secondary to an AE	1 (0.3)	1	0.00	0.00
AE intensity, n (%)¶				
Mild	62 (20.9)	129 (51.2)	0.44	0.01
Moderate	33 (11.1)	96 (38.1)	0.32	0.01
Severe	16 (5.4)	27 (10.7)	0.09	0.00

AE, Adverse event; HAE, hereditary angioedema; SAE, serious adverse events.

*22 subjects (6.9%) had retrospective data only and are not included here; 5852 infusions (39%) were retrospectively collected and are not included here.

†Rate/subject calculated as the number of events divided by the number of subjects who contributed \geq prospective data point (n = 296).

‡Rate/infusion calculated as the number of events divided by the number of prospective infusions (9148).

§15 SAEs were HAE attacks requiring hospitalization. See the text for more details.

||Thromboembolic event.

¶If subjects had multiple events of the same intensity, they are counted only once. Subjects could be counted in more than 1 category.

contributory history of severe coronary artery disease, hypertension, and hyperlipidemia. This event was considered unrelated to pnfC1-INH.

A third event of interest, although not matching any of the embolic and thrombotic SMQ event terms, occurred in a 70-year-old female subject who experienced symptoms consistent with a transient ischemic attack (TIA) occurring within approximately 1 day after knee replacement surgery. Prophylactic pnfC1-INH was administered the morning before and the morning after the TIA-like event. The symptoms were considered to the result of a fat embolism secondary to the knee replacement, and were considered unrelated to pnfC1-INH therapy.

As the Registry was designed to document pnfC1-INH use according to local standards of clinical care, routine viral testing was not required, and testing was to be conducted only if a clinician considered it necessary. In the Registry, there were no reports of testing for blood-borne viral infection conducted on any subject beyond baseline, and no subject was reported to have an adverse experience reflective of new infection with a blood-borne virus, including human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, and parvovirus B19 during participation in the Registry.

DISCUSSION

The Berinert Patient Registry dataset represents the largest known registry of Berinert use. The HAE attack characteristics noted in this Registry were generally consistent with patterns previously reported by other authors.²²⁻²⁶ Abdominal and peripheral attacks were most common; laryngeal attacks comprised only 2% of all attacks reported in the Registry, but 28% of subjects experienced at least 1 laryngeal attack.

Analysis of administration patterns revealed wide use of pnfC1-INH for prophylaxis as recommended in recent clinical guidelines,^{1,5-10} despite the absence of regulatory approval of Berinert for this purpose in the United States. As reviewed by Bork et al,²⁷ a number of observational and descriptive (ie, surveys and case reports) studies support the efficacy of C1-INH for short-term prophylaxis before a scheduled procedure. The efficacy of C1-INH for long-term prophylaxis has also been demonstrated in several non-placebo-controlled observational, descriptive, or cohort studies.²⁷⁻²⁹

There was a wide variation of pnfC1-INH dosing in the Registry. Although median pnfC1-INH doses were generally close to the recommended 20 IU/kg, particularly in the United States, there was a great deal of variability noted across the Registry dataset. Recorded doses per single infusion ranged from 3.4 to 37.8 IU/kg, or 500 to 3500 IU. This may indicate a high level of therapy individualization, as is being increasingly recommended among recent HAE consensus guidelines.^{5,6,9,10,14} Not surprisingly, median doses (by weight) were highest for children, severe attacks, and laryngeal and facial attacks. Yet, median doses for the most severe attacks were still lower than the recommended dose of 20 IU/kg, likely influenced by lower median doses represented in the European data. Stratification of subjects by age group revealed a pattern of age-related dosing, with younger subjects receiving higher median doses by weight than older subjects.

The higher median dosages reported for prospective (13.0 IU/kg) versus retrospective (10.0 IU/kg) infusions may reflect a trend toward usage of the recommended weight-based dosages in recent years, particularly in Europe. Dosing of Berinert in Europe before 2009 was according to a fixed-dose

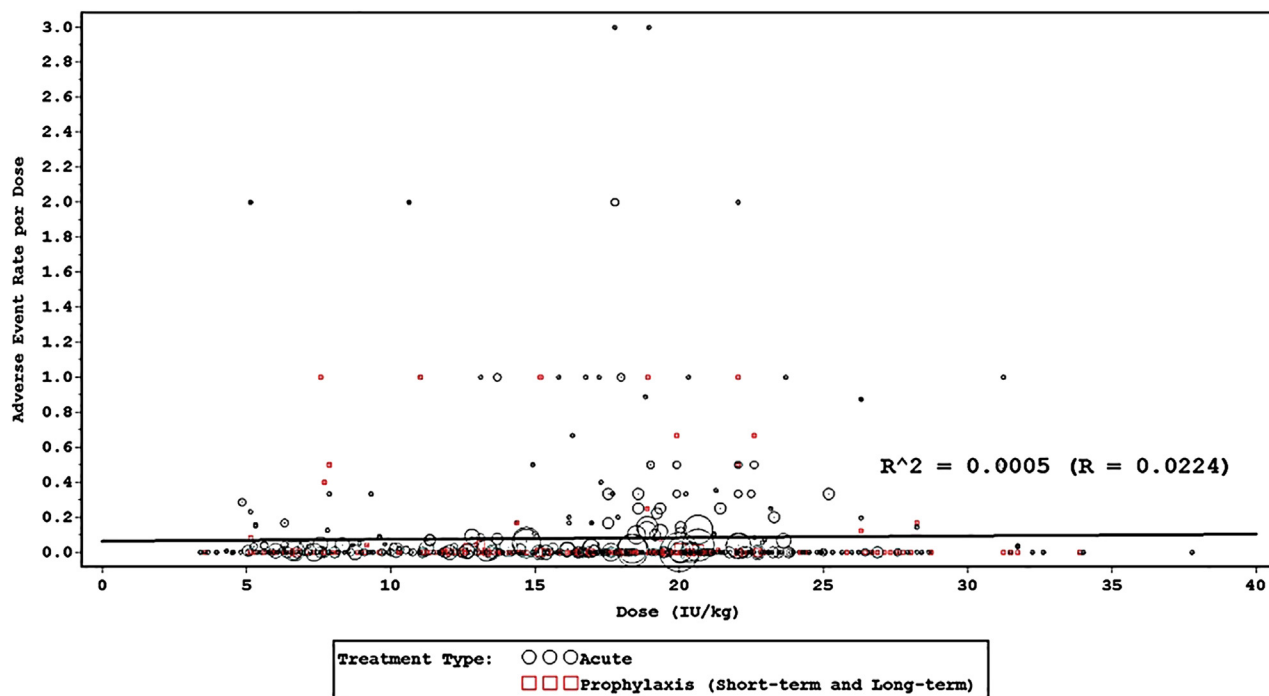


FIGURE 3. Plot of adverse event (AE) rates by pnfC1-INH dose (prospective data only, excluding 1 subject with a disproportionate number of AEs). AE rate calculated as the number of events at the dose divided by the number of infusions of the same dose. The size of each plot symbol (circle) reflects the relative number of subjects with the specified dose. One subject treated with pnfC1-INH doses between 20 and 25 IU/kg had a disproportionate number of AEs (25 of 252 events, or 11% of all AEs reported). *IU*, International unit; *kg*, kilogram; *pnfC1-INH*, plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate.

recommendation (500 to 1000 IU per infusion), which would result in relatively lower doses by body weight in most adults. In 2009, dosing guidelines were changed to reflect weight-based dosing consistent with results of a rigorous phase II/III controlled dose-ranging clinical trial²² and subsequent US labeling. As a result, retrospective data from Europe reflected lower median doses of pnfC1-INH. However, differences in the proportion of data collected retrospectively versus prospectively do not explain the use of higher dosages in the United States, because a clear difference was apparent even when comparing only prospective data (median doses of 19.5 IU/kg in the United States vs 9.7 IU/kg in Europe). It is possible that the lower doses used in Europe reflect a carry-over from years of experience with fixed dosing of pnfC1-INH before the change in dosing recommendations.

Recent HAE expert guidelines consistently recommend training and equipping patients for self- or home-based administration of HAE medications,^{1,5,6,8-10,12,14} and the Registry findings support the safety and feasibility of pnfC1-INH administration outside of the health care setting. Approximately 95% of all infusions captured in the Registry were given outside of a health care setting, whether used for attack treatment or prophylaxis. There were very few instances of subjects having difficulty with administration; failure to self-infuse (successfully administer pnfC1-INH outside of a health care setting) occurred in less than 1 of 1000 self-infusions. Prior reports have also indicated a good safety record with administration of pnfC1-INH outside of a health care setting.^{30,31} The overall rates of AEs per infusion (0.03) and per subject (0.85) were very low,

regardless of administration setting. The relatively higher AE rates noted for infusions given within a health care setting (0.13 per infusion) versus outside of a health care setting (0.02 per infusion) may be a phenomenon caused, in part, by subjects presenting to health care facilities for treatment of more severe attacks and/or subjects presenting to health care facilities for treatment well after attack onset. It has been shown that delayed treatment after onset of HAE attacks is associated with longer time to symptom relief and full attack resolution, and with higher severity of certain symptoms that can be regarded as AEs.^{32,33} The rates of AEs considered related to pnfC1-INH were the same for both types of treatment settings.

Data from the Registry support the overall safety of pnfC1-INH. A very low AE rate (0.03 events per infusion, prospectively collected data) was observed, regardless of reason for use, and there was no apparent dose relationship. The overall number of AEs (252 events) was smaller than the number reported in the interim analysis (299 events),²¹ which is a reflection of the revised reporting of individual symptoms of HAE attacks (eg, pain, swelling) that had been previously reported as AEs, to align with the Registry protocol specifications. Attacks requiring hospitalization were classified as SAEs in the current analysis. The majority of such events (9 of 15) occurred in a single subject whose treatment was often initiated well after the onset of the HAE attack.

Although there have been rare postmarketing reports of anaphylactic reactions in patients using pnfC1-INH in Europe,³⁴ there have been no such reports in clinical trials or in this large patient Registry population, suggesting that the risk of systemic hypersensitivity reactions appears to be extremely small.

Given the observational nature of the Registry, viral testing was not mandated. Per routine medical practice, physicians would have tested patients only if viral infection was suspected, and there were no recorded findings of post-Registry enrollment viral testing. The apparent lack of testing during subjects' Registry participation suggests that there was little clinical reason to conduct such testing. The absence of viral transmission during pnfC1-INH therapy has been reported in other prospective studies.^{22,35} Routine testing for viral transmission is not specified in the Berinert or Cinryze prescribing information, nor in most HAE consensus guidelines. However, the World Allergy Organization guidelines do suggest "annual assessment for infections with hepatitis B, C, and HIV," as well as vaccination for hepatitis A and B.⁶

Rare reports of TEEs in patients treated with C1-INH products have led to heightened surveillance regarding this phenomenon and its possible relationship to C1-INH administration. Five such cases, all with risk factors for TEE, were reported during an open label HAE prophylaxis trial with the plasma-derived C1-INH concentrate Cinryze (Shire ViroPharma, Lexington, Mass). A report published in 2000¹⁸ described thrombus formation in 13 neonates and babies who received very high doses of pnfC1-INH/Berinert (up to 500 IU/kg) for the off-label purpose of preventing capillary leak syndrome after cardiopulmonary bypass surgery; 9 of the events were fatal. These children were seriously ill and had multiple other risk factors for TEE, yet the role of pnfC1-INH was considered at least "possible" and ongoing surveillance of this issue has been prudent.

The Registry sought specifically to identify and evaluate reports of TEE among individuals using pnfC1-INH. The observed risk of TEE was extremely low. Two events occurred among 9148 prospectively collected pnfC1-INH infusions; one of these, in a subject with an indwelling port, was considered related. Both subjects had pre-existing risk factors for TEE. A review of the Food and Drug Administration's Adverse Event Reporting System database in 2011 noted rare reports of TEE in patients using Cinryze at recommended doses; no assessments of causality were available in those cases.²⁰ In addition, an international survey of 37 physicians caring for 856 patients with HAE reported 5 "abnormal clotting" events, 3 of which were noted in patients with indwelling catheters.³⁶ 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 thromboembolic events.

This Registry has several limitations. There were no AEs reported to the Registry for infusions given before enrollment (retrospective), the identification of which, during a chart review, may have been hindered, at least in part, by the 30-day post-infusion time window for identifying AEs as specified by the Registry protocol. As a result, only prospective data were used for AE rate calculations. Another limitation inherent to registry studies is that data were limited by what was gathered by the treating physician in the course of routine patient management. Further, as is typical for an observational study, this registry did not have a control group. Because the key requirement for participation was exposure to at least 1 dose of Berinert and because there was no mandatory duration of Registry participation for any subject, a wide range in the number of infusions per subject was recorded, from 1 to several hundred. Such a range could bias results with weighting toward those who contributed greater amounts of information. However, the sheer volume of

15,000 infusions captured for 318 patients with HAE in the Registry over the 5-year period of time supports the clinical value of these observations.

Subjects represented in the Registry comprised a diverse population in terms of geography and age. Approximately two-thirds of subjects were female, despite no known sex-related differences in the prevalence of HAE types 1 and 2³⁷; this may reflect a greater willingness among women to participate in this voluntary registry. With regard to race, the Registry population was quite homogenous, with approximately 94% of subjects being white. Of particular interest are the findings that there were very few black/African American subjects who used pnfC1-INH for prophylaxis, or administered pnfC1-INH in a non-health care setting. It is possible that the underrepresentation of ethnic minorities in the Registry, overall and in specific categories, is related to disparities in access to care, and further studies are needed to explore this possibility.

CONCLUSIONS

This large patient Registry documents the international implementation of pnfC1-INH self-administration outside of the health care setting, as currently recommended by HAE consensus guidelines. The data also indicate substantial use of pnfC1-INH (Berinert) for HAE prophylaxis. There was no evidence of a dose relationship for AEs, and few reported events were considered related to treatment. There were no reported events of suspected blood-borne viral infections; viral testing was not performed as a routine measure in this real-world study. Thromboembolic events were rare, and occurred in patients with pre-existing risk factors, supporting current recommendations to closely monitor patients with known risk factors. There were no reports of anaphylaxis or events suggestive of systemic hypersensitivity to Berinert. Overall, these real-world findings support the safety of pnfC1-INH whether given within or outside of a health care setting and as given for a variety of reasons in patients with HAE.

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