

Safety of C1-Esterase Inhibitor in Acute and Prophylactic Therapy of Hereditary Angioedema: Findings from the Ongoing International Berinert Patient Registry

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What is already known about this topic? The safety of Berinert has been well-documented through clinical trials and postmarketing surveillance for more 30 years. Recent reports of thromboembolic events have occurred in patients who use a C1 inhibitor, generally off label and at supratherapeutic doses.

What does this article add to our knowledge? This is the largest registry to track safety outcomes with real-world Berinert use, including a large number of infusions given in a home setting, and provides a large data set for tracking thromboembolic event occurrence.

How does this study impact current management guidelines? These registry data support the safety of C1 inhibitor when used as on-demand and prophylactic management of hereditary angioedema and confirm a growing implementation of self administration, as recommended in all recent hereditary angioedema guidelines.

BACKGROUND: The plasma-derived, pasteurized C1-inhibitor (C1-INH) concentrate, Berinert has a 4-decade history of use in

hereditary angioedema (HAE), with a substantial literature base that demonstrates safety and efficacy. Thromboembolic events have rarely been reported with C1-INH products, typically with off-label use or at supratherapeutic doses.

OBJECTIVES: Active surveillance of safety and clinical usage patterns of pasteurized C1-inhibitor concentrate and the more recent pasteurized, nanofiltered C1-INH, with a particular interest in thromboembolic events.

METHODS: A registry was initiated in April 2010 at 27 US and 4 EU sites to obtain both prospective and retrospective safety and usage data on subjects who were administered C1-INH (Berinert).

RESULTS: As of May 10, 2013, data were available for 135 subjects and 3196 infusions. By subject, 67.4% were using C1-INH as on-demand therapy and 23.0% as both on-demand therapy and prophylactic administration. Approximately half of the infusions (49.5%) were administered for prophylaxis and >90% were given by the patient or a caregiver in the home setting. A total of 299 adverse events were reported, for an overall rate of 0.09 events per infusion with only 6 considered related to C1-INH. Two thromboembolic events were reported, both in patients with prothrombotic risk factors.

CONCLUSION: This large pool of real-world clinical usage data in HAE further supports the extensive safety profile of 2 Berinert formulations when used on demand and/or for prophylaxis in both home and health care settings. No evidence was found to suggest that Berinert is an independent, causative risk factor for thromboembolic events. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:213-9)

Key words: C1-INH; Berinert; Registry; Safety; Thromboembolic events; On demand; Prophylaxis; Self administration

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Abbreviations used

AE- Adverse event

C1-INH- C1 inhibitor

HAE- Hereditary angioedema

TEE- Thromboembolic event

Hereditary angioedema (HAE) is a rare genetic disease that results from mutations in the C1-inhibitor (C1-INH) protein,¹ which can present with acute and unpredictable episodes of angioedema. Angioedema of the airway may lead to asphyxiation if not properly treated. As a chronic disease with the potential for high morbidity and mortality, HAE has a substantial quality-of-life impact on affected patients and their families.²⁻¹⁰ Although management strategies are individualized, all patients with HAE should have easy access to an on-demand therapy for treatment of acute attacks and education regarding short-term prophylaxis before known triggers of HAE, including invasive medical or dental procedures. In addition, some patients may require long-term prophylaxis to prevent HAE attacks.

Recently, several treatment options for HAE have been approved in the United States, including 2 plasma-derived formulations of C1-INH (Berinert [CSL Behring, Marburg, Germany] and Cinryze [ViroPharma, Exton, Pa]) as well as medications that specifically target bradykinin production or action, such as ecallantide and icatibant. These new treatment options offer a high degree of efficacy as well as the option to self-administer treatment at home (ecallantide requires health care professional oversight).¹¹ Home-based treatment has become a universal recommendation of recent HAE expert consensus guidelines.¹²⁻¹⁹

For 30 years, Berinert has been used in Europe for treatment and prevention of HAE attacks. It was approved in the United States in 2009, initially for the treatment of abdominal and facial HAE attacks, with later approval for laryngeal attacks and self-administration. Berinert has always been pasteurized, and, in 2012, nanofiltration was added to the purification process. The efficacy and safety of C1-INH for treating acute HAE attacks have been well documented in adults, children, and pregnant women.²⁰⁻²⁴ A small number of thromboembolic event (TEE) cases have been reported in patients who used C1-INH, generally off label and at supratherapeutic doses, although causality with C1-INH administration is unclear.²⁵⁻²⁷ As a requirement for US marketing authorization, and to evaluate the continued safety of the product, a registry was established to gather data on treatment with Berinert. The specific objectives of the registry were to provide a mechanism for active usage surveillance and to facilitate discovery of adverse events (AE), with a particular interest in TEE events. This analysis presents interim findings of the ongoing registry as of May 2013. Hereafter in this article, the term C1-INH should be understood to refer specifically to Berinert.

METHODS**Study design**

This multicenter, observational, open patient registry (NCT01108848) was initiated on April 9, 2010, at 27 US and 4 EU sites (Germany, 2; Denmark, 1; Switzerland, 1). The cutoff date for this interim analysis was May 20, 2013. The registry was conducted in compliance with local regulatory requirements applicable to noninterventional studies, and informed consent was obtained for all the subjects. "Informed consent" in this study

referred specifically to the patient's willingness to allow his or her treatment data to be collected and had no bearing on treatment decisions or consent to use C1-INH. All subject details and registry data were kept strictly confidential in accordance with the International Conference on Harmonization guidelines.²⁸

Subjects

Individuals of all ages, who were using C1-INH for any reason, irrespective of product labeling, were considered candidates for the registry. Subjects were recruited from various sources, including but not limited to the following: collaboration with the US subject advocacy group, the Hereditary Angioedema Association, as a means of directly identifying both patients with HAE and HAE-treating physicians; contact with investigators who were actively participating in or had previously participated in other C1-INH studies.

Data collection

Subject data were collected retrospectively through medical chart review on some subjects on entry into the study and then prospectively thereafter for all the participants. Chart review and data entry activities were performed by responsible personnel affiliated with the study site medical facility. Upon enrollment of a patient into the registry, relevant information already contained in the patient's chart was captured as retrospectively collected data. Use of C1-INH after the patient's enrollment in the registry was collected prospectively. Data were recorded by patients who used paper diaries at the time that C1-INH was administered and subsequently entered into electronic case report forms by site personnel. The following information was entered for both prospectively and retrospectively collected data: subject demographics; indication for C1-INH administration; dosing information; setting in which treatment was administered (eg, home, health care facility); HAE history and type (none, type I, type II, or other); details of treated HAE attack(s) (location, intensity, triggers, time to symptom improvement and resolution); concomitant medication use; and AE data, including TEEs, seroconversion, and suspected viral transmission. TEEs were identified by using the Medical Dictionary for Regulatory Activities Standardized Medical Dictionary for Regulatory Activities Queries for embolic and thrombotic events. A separate questionnaire was completed for all TEEs to obtain as much information as possible. With regard to safety, all AEs were recorded, regardless of suspected causality to C1-INH administration. Causality was evaluated by the investigator as either not related, unlikely related, possibly related, probably related, or related. The severity of each AE was graded 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 were those that resulted in death, life-threatening circumstances that required hospitalization or that resulted in persistent or significant disability or incapacity. The collection period for AEs was limited to a 1-month period after each administration of C1-INH. All AEs were followed up by the investigator until such time that the AE was considered resolved or was deemed a permanent condition.

RESULTS

As of May 10, 2013, a total of 135 subjects reported at least 1 administration of C1-INH. There were 3196 total infusions of C1-INH, which form the basis of this report. The demographics of the analysis population are presented in Table 1. The

condition treated by C1-INH administration in all 135 subjects was HAE. The majority of recorded infusions (82.3%) were in the United States.

C1-INH usage patterns

As shown in Table II, a majority of subjects (69.6%) had both retrospectively and prospectively collected data, whereas 4.4% of the subjects had only retrospectively collected data. By subject, the most common administration setting was home only (40.0%), followed by health care facility only (32.6%), with another 20.0% who reported both home and health care facility administration. The majority (67.4%) of the population used C1-INH solely for treatment of acute attacks, 23.0% were using it for both prophylaxis and acute treatment, and 8.9% of subjects reported use solely for prophylaxis. Of 3196 infusions of C1-INH, 2066 (64.6%) were recorded prospectively (Table II). A majority of infusions (2763 [90.1%]) were administered in a home setting. Indication for the infusions was divided almost equally between acute attack treatment (50.5%) and prophylaxis (49.5%).

Among 81 subjects who used C1-INH at home, 18 subjects (22.2%) had at least 1 switch in administration setting from home to a health care facility; this occurred in 36 of 2763 home infusions (1.3%). The most common reason for switching to a health care setting was that the subject was already at the clinic for a scheduled visit and received the required infusion while at the facility (6 subjects; 8 infusions); this was the cited reason for the change in administration venue in all 5 situations that involved prophylactic administration. An inability to self-infuse was the cited reason for changing from home to health care setting administration in 8 instances (4 subjects), which represented 0.29% of all home infusions; all occurred in association with treatment of an acute attack. Other cited reasons for switching administration from home to a health care setting included being out of stock or traveling without a supply of C1-INH (4 subjects; 6 infusions), the absence of a caregiver who usually performs infusions (1 subject; 1 infusion), or an otherwise unspecified decision by the patient or caregiver to receive treatment at a health care facility (2 subjects; 4 infusions). In 3 subjects, their treatment protocol stipulated home administration for prophylactic infusions and acute attack treatments given at a health care facility.

C1-INH dosing. Dosing information was available for 3189 C1-INH infusions (Table III). For all the patients, mean dosages reported prospectively were higher than those reported retrospectively. HAE attacks of severe intensity were treated with the highest mean dosage compared with attacks of lesser intensity. By attack location, facial, laryngeal, and “other” received the highest dosage compared with abdominal, peripheral, or thoracic, based on retrospectively reported data; analysis of prospectively collected data suggested comparable dosage regardless of attack location. The administered dose of C1-INH was inversely proportional to patient age, with the highest mean dose (23.4 IU/kg) observed in the youngest category (3 to <12 years). On a per infusion basis, dosing patterns were similar between Europe and the United States.

HAE attack characteristics

Information on HAE attack characteristics was available for 1617 acute HAE attacks treated with C1-INH in 124 subjects. Data were not collected on untreated attacks or attacks treated

TABLE I. Registry population demographics (subjects who reported at least 1 administration of C1-INH)

Study population (n = 135)*	
Sex, no. (%) (n = 134)	
Male subjects	47 (34.8)
Female subjects	87 (64.4)
Race, no. (%) (n = 134)	
Asian	1 (0.7)
Black/African American	8 (5.9)
White	119 (88.1)
Other	6 (4.4)
Age, mean $\pm$ SD (range), y (n = 134)	38.9 $\pm$ 17.7 (7-79)
Body mass index, mean $\pm$ SD (range), kg/m ² (n = 128)	28.0 $\pm$ 7.0 (14-55)

*Data in each category were not available for all 135 subjects.

TABLE II. Disposition of subject and infusion data by collection method, administration setting, and HAE treatment (acute treatment vs prophylaxis)

	Subjects (n = 135)*	Infusions (n = 3196)*
Data collection method, no. (%)		
Retrospective only	6 (4.4)	1130 (35.4)
Prospective only	35 (25.9)	2066 (64.6)
Both retrospective and prospective	94 (69.6)	NA
Administration setting, no. (%)		
Home only	54 (40.0)	2763 (90.1)
Health care facility only	44 (32.6)	305 (9.9)
Both	27 (20.0)	NA
Total†	125	3068
Indication for use, no. (%)		
HAE attack only	91 (67.4)	1613 (50.5)
HAE prophylaxis only	12 (8.9)	1582 (49.5)
Both acute attacks and prophylaxis	31 (23.0)	NA
Total†	134	3068

NA, Not applicable.

*Data in each category were not always available for all subjects or infusions; percentages are calculated based on the full data set n values.

†Category total with data on less than the full subject or infusion data set.

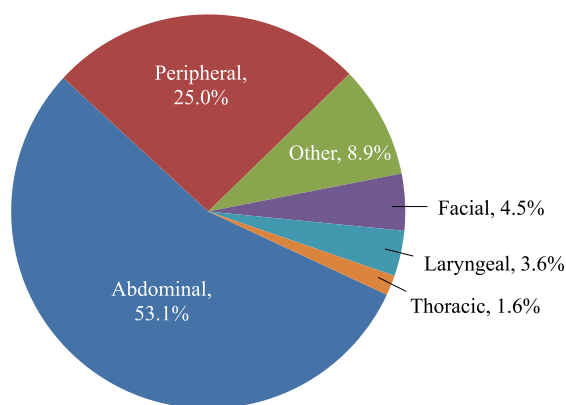
with medications other than C1-INH. The most common attack sites were abdominal (53.1%) and peripheral (25.0%) (Figure 1). Together, laryngeal and facial attacks represented 8.1% of all recorded attacks. However, a notable portion of subjects experienced at least 1 laryngeal (29/135 subjects [21.5%]) or facial (40/135 subjects [29.6%]) attack during their registry participation. HAE attack severity also was rated for 1617 attacks, with symptoms categorized as mild in 23.5% of attacks, moderate in 47.9% of attacks, and severe in 23.5% of attacks.

Safety

Twenty-seven subjects (20.0%) reported a total of 299 AEs over 3196 infusions, which represents an overall rate of 0.09 events per infusion (Table IV). The majority of AEs were rated as moderate in severity. There were 18 serious AEs in 5 subjects, including acute HAE attacks (11 events per 2 subjects); abdominal pain (3 events per 1 subject); and 1 event each of noncardiac chest pain, spontaneous abortion, deep vein

TABLE III. Mean reported administered dosages of C1-INH by attack and patient characteristics

Variable (no. infusions with relevant data)	C1-INH dose, mean $\pm$ SD, IU/kg		
	Prospective	Retrospective	Overall
Treatment type			
Acute (1613)	19.2 $\pm$ 5.1	13.6 $\pm$ 6.8	16.4 $\pm$ 6.6
Prophylaxis (1582)	18.2 $\pm$ 4.5	13.2 $\pm$ 3.6	17.2 $\pm$ 4.8
Attack severity			
Mild (382)	20.9 $\pm$ 3.3	11.0 $\pm$ 5.4	14.5 $\pm$ 6.7
Moderate (775)	17.8 $\pm$ 5.5	12.1 $\pm$ 5.9	15.6 $\pm$ 6.3
Severe (380)	21.0 $\pm$ 4.6	18.9 $\pm$ 7.9	20.0 $\pm$ 6.4
Attack location			
Abdominal (859)	19.4 $\pm$ 4.7	12.4 $\pm$ 6.3	16.8 $\pm$ 6.3
Facial (72)	17.1 $\pm$ 6.0	18.1 $\pm$ 5.7	17.8 $\pm$ 5.6
Laryngeal (58)	20.5 $\pm$ 4.8	15.8 $\pm$ 7.0	18.6 $\pm$ 6.2
Peripheral (405)	18.0 $\pm$ 5.7	12.3 $\pm$ 5.0	14.4 $\pm$ 6.0
Thoracic (26)	18.9 $\pm$ 2.7	12.7 $\pm$ 3.2	14.5 $\pm$ 4.1
Other (144)	20.3 $\pm$ 7.5	21.6 $\pm$ 7.6	21.1 $\pm$ 7.5
Patient age			
3 to <12 y (44)	23.4 $\pm$ 2.9	20.8 $\pm$ 4.6	22.2 $\pm$ 3.9
12 to <17 y (144)	19.6 $\pm$ 5.8	16.8 $\pm$ 4.4	17.9 $\pm$ 5.1
17 to <65 y (2940)	18.5 $\pm$ 4.8	13.1 $\pm$ 6.0	16.7 $\pm$ 5.8
≥ 65 y (67)	17.7 $\pm$ 3.4	14.5 $\pm$ 3.2	17.4 $\pm$ 3.5
Geographic region			
Europe (566)	22.1 $\pm$ 8.6	12.0 $\pm$ 6.9	12.5 $\pm$ 7.2
US (2630)	18.5 $\pm$ 4.7	14.8 $\pm$ 4.8	17.7 $\pm$ 5.0

**FIGURE 1.** Body locations of HAE attacks treated with C1-INH (1585 attacks in 116 patients).

thrombosis, and fat embolism. All serious AEs involved hospitalization, except for the spontaneous abortion; the fat embolism was initially considered life-threatening. The most commonly reported events were gastrointestinal AEs (8.1% of subjects) and infection-related AEs (7.4% of subjects; primarily upper respiratory tract infections). Six AEs (2.0%) were judged at least possibly related to C1-INH: 5 events (nausea, vomiting, noncardiac chest pain, fat embolism, and fatigue) were considered possibly related; 1 event (deep venous thrombosis) was considered probably related (more details are provided below); all related events were reported as resolved. The AE rate was not different for home versus health care facility administration (0.10 AEs per infusion for both settings).

TABLE IV. Summary of safety findings

	Subjects, no. (% of subjects) (n = 135)	Events, no. (% of infusions) (n = 3196)
AE		
Any AE	27 (20.0)	299
Excluding subject no. 7502*	26 (19.3)	92
AE event types that occurred $\geq 5\%$		
Gastrointestinal	11 (8.1)	68 (2.3)
Infections and/or infestations	10 (7.4)	36 (1.1)
AE severity ratings		
Mild		24 (8.0)
Moderate		262 (87.6)
Severe		13 (4.3)
Serious AEs	5 (3.7)	18 (0.6)†
Thromboembolic events	2 (1.5)	2 (0.06)
Discontinuation secondary to an AE	2 (1.5)	2 (0.1)
AE rate per infusion		
Overall		0.09
Acute treatment		0.05
Prophylaxis		0.14
AE rate by administration setting		
Home		0.10
Health care facility		0.10

*A disproportionately high number of AEs reported in this subject accounted for 69.2% of all reported AEs (207/299); none of the AEs in this patient were considered related to C1-INH; all other data in this table are inclusive of AEs reported by subject no. 7502.

†Serious AEs included hospitalization for acute HAE attacks (11 events per 2 subjects); abdominal pain (3 events per 1 subject); and 1 event each of noncardiac chest pain, spontaneous abortion, deep vein thrombosis, and transient ischemic attack.

A disproportionately high number of AEs were observed in 2 subjects. One subject (no. 7506) reported 207 AEs, which accounted for 69.2% (207/299) of all reported AEs in the registry. The second subject (no. 7502) reported 32 AEs, which represented 10.7% of all reported AEs. None of the events reported by these 2 subjects was considered related to C1-INH treatment. Both subjects were administering C1-INH every 3 to 4 days for HAE prophylaxis, with each dose ranging from 20 to ≥ 25 IU/kg. Data from the entire safety population showed an increasing AE rate with increasing C1-INH doses up to 25 IU/kg (AE rates per infusion: 0.01, 0.05, 0.23, and 0.14 for <15 IU/kg, 15 to <20 IU/kg, 20 to <25 IU/kg, and ≥ 25 IU/kg dose groups, respectively). A sensitivity analysis was performed, which conservatively excluded the data from subject no. 7506 only (the greatest single contributor to AE totals). When the AEs reported by this subject were removed, there was no consistent trend noted between dose group and AE rate, either by subject or infusion (coefficient of determination = 0.0005).

There were 2 reported TEEs in 2 separate subjects (2/135 subjects [1.5%]). Both occurred in subjects who used C1-INH at doses lower than the recommended dose of 20 IU/kg and both in patients with prothrombotic risk factors. The rate of reported TEEs per infusion was 0.06%. One event occurred in a 36-year-old female subject with a permanent indwelling left subclavian venous catheter, which was used to administer C1-INH for prophylaxis and on-demand treatment for acute HAE attacks. The subject presented to the emergency department with a

swollen and blue left arm, and received C1-INH (5.1 IU/kg) as treatment for an HAE attack. A second infusion of C1-INH (5.1 IU/kg) was administered 6 hours later. Ultrasound duplex of the left upper extremity identified an extensive thrombus. Her subclavian catheter was removed due to thrombosis, and she was treated with anticoagulants. The subject was discharged to home in a week, and the event was considered resolved 3 months later.

The second TEE was a transient ischemic attack reported in a 70-year-old female subject who used C1-INH on demand for infrequent HAE attacks. She received a prophylactic dose of C1-INH (18.9 IU/kg) on the day of knee replacement surgery. Her last on-demand dose of C1-INH was approximately 3 months earlier. On the day after surgery, staff members noticed sudden onset of right side hemiplegia, facial droop, and aphasia, all of which lasted for approximately 15 minutes. Medical evaluation concluded mild stroke-like symptoms of unknown etiology, possibly transient ischemic attack or fat embolism secondary to the knee replacement surgery. Further workup using computed tomography and magnetic resonance imaging found no evidence of acute intracranial abnormalities, including infarction, hemorrhage, or mass lesion, and no apparent changes compared with a previous magnetic resonance imaging of the head from January 2009. She received an additional postprocedure prophylactic dose of C1-INH on day 2 after the surgery and was discharged from the hospital with no change in C1-INH therapy plan. She had 1 more recorded on-demand administration of C1-INH 7 months later.

There were no seroconversions observed in the registry data and no evidence of viral transmission.

DISCUSSION

The data gathered from this large, multinational, ongoing patient registry reflect the real-world use of C1-INH in 135 patients with HAE, with almost 3200 individual infusions, which makes this the largest Berinert and C1-INH registry to date. The nonrestrictive inclusion criteria and impressive number of infusions impart a level of clinical validity and generalizability of the data. Patterns of HAE attacks are of interest in this patient population. Overall, our findings are consistent with previously reported data, despite the caveat that we only captured data on attacks that were treated with C1-INH. Abdominal attacks were most common (53.1%); potentially fatal laryngeal attacks were rare, overall, as a percentage of all attacks (3.6%), but approximately 1 in 5 patients experienced at least 1 laryngeal attack over the roughly 3-year data collection period. For the majority of attacks, a triggering event was not identified. Analysis of our data confirmed a high rate of home or self-administration of C1-INH, which is an encouraging trend, given the high degree of consensus on this issue by all recent major HAE guidelines.¹²⁻¹⁹ Interestingly, nearly half of C1-INH infusions recorded in the registry were given for the purpose of prophylaxis despite this being off label in the United States for Berinert. The present analysis was not designed to evaluate efficacy outcomes.

Mean C1-INH dosages reported prospectively were higher than those reported retrospectively, which is likely explained most readily by geographic and historic differences in dosing recommendations. Most of the retrospectively collected data came from European sites, where C1-INH was initially approved at a set dose of 500 to 1000 IU per infusion, which translates into doses lower than 20 IU/kg for patients with body weight of more than 50 kg. Within the past several years, dosing

recommendations for C1-INH in the EU have been revised and are now consistent with the US Food and Drug Administration recommended dose of 20 IU/kg. Most of the prospectively collected doses were from US sites, where 20 IU/kg has been the dosing recommendation since Food and Drug Administration approval of C1-INH in 2009. The registry findings confirm a high level of safety with C1-INH use for the indication of HAE for either acute treatment or prophylaxis, regardless of dose or administration setting. Although off-label use of C1-INH for indications other than HAE was not an exclusion for registry participation, no such cases were reported. The overall AE rate per infusion was very low (0.09), and there were no unusual or unexpected findings, which corroborated more than 30 years of global experience.

One of the primary goals of this registry was to provide a surveillance mechanism to monitor for potential thrombotic risks with C1-INH administration. There were 2 TEEs reported out of 3196 infusions, and both occurred in patients with other clear prothrombotic risk factors. Concern about potential thrombogenesis with C1-INH administration became heightened subsequent to a report published in 2000 that described 13 neonates and babies without HAE who developed thrombus formation while receiving C1-INH at very high doses to prevent capillary leak syndrome after cardiopulmonary bypass surgery, 9 of whom died.²⁵ These young children with severe congenital heart defects were receiving extremely high doses of C1-INH (up to 500 IU/kg) for an indication that had never been studied in a controlled clinical setting. Although these children who were seriously ill had other potentially contributing factors for thrombosis, including lengthy extracorporeal circulation, foreign body surface contact or possible infectious processes, the causal role of C1-INH was deemed at least "possible" in these cases, especially because some of the cases involved patients who developed bilateral upper extremity venous thrombus formation. Five serious thrombotic events were reported during an open label trial of Cinryze (plasma-driven, nanofiltered C1-INH) used for HAE prophylaxis in 146 patients; all 5 affected subjects had underlying risk factors for these events.²⁷ Thrombotic events have been reported voluntarily in association with C1-INH administration at recommended doses in patients with HAE, and the official product labeling for such products includes a precaution to closely monitor patients with known risk factors for thrombotic events.^{27,29} A retrospective analysis of the Food and Drug Administration's Adverse Event Reporting System database, which gathers spontaneous AE cases in the United States, was conducted in 2011 to identify reports of thrombotic events in patients who used C1-INH and ecallantide (Kalbitor; Dyax Corp, Burlington, Mass).²⁶ This analysis identified 10 thrombotic event cases associated with the use of Cinryze; there were no cases associated with Berinert or Kalbitor. In the cases identified in the Adverse Event Reporting System database, Cinryze was being administered at the recommended dose of 1000 units every 3 to 4 days. The Adverse Event Reporting System database is not designed to establish causality, and continued surveillance of this issue has been recommended.

Animal studies have produced conflicting findings with regard to possible thrombotic risks with C1-INH. In a pig model of coronary ischemia, very high doses of C1-INH (up to 200 IU/kg) were reported to provoke coagulation disorders.³⁰ Conversely, a recent study that investigated the potential benefits of C1-INH in a rat model of ischemic stroke found C1-INH to have strong

antithrombotic effects when given at a much lower dose of 20 IU/kg.³¹ A study that evaluated thrombin and plasmin generation measurements in plasma taken from patients with HAE during an acute attack found increased thrombin generation compared with plasma from controls without HAE.³² These findings are consistent with other published observations that reported activation of FXII and FVII during acute HAE attacks.^{33,34} In light of the observed inverse correlation between thrombin generation and C1-INH levels noted in this study, the investigators suggested that C1-INH may be antithrombogenic, rather than prothrombogenic.

The limitations of our analysis are typical of any registry-based study. Data were collected in the real world without any governance over C1-INH usage or dosing patterns. As such, the use of C1-INH varied according to local standards of care in the different countries with participating sites. For the same reasons, patterns of individual usage varied widely, including the number of infusions per subject, given that there was no mandatory duration for registry participation. Data collection methods included both retrospective and prospective methods; however, approximately two-thirds of the subjects had data collected by both methods, and only 6 subjects had retrospective data only. In spite of the international setting of the registry, the patient population was not very ethnically diverse. Although there is no reason to suspect differences in treatment patterns or outcomes based on ethnicity, this limitation should be acknowledged when interpreting the findings.

CONCLUSIONS

These data reflect a large experience pool with a widely used formulation of C1-INH, Berinert, and reveal real-world usage patterns and safety outcomes. The findings confirm that self-administration of Berinert is feasible and safe, and is being widely implemented, which shows an encouraging trend that is consistent with consensus recommendations. Although the issue of potential thrombotic risk with C1-INH administration requires further evaluation, the registry data found no evidence to suggest that Berinert in dosages commonly used in patients with HAE is an independent causative factor for such events.

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