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, nanofiltered 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 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)**

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 *SERPING1* 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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