



Letter

Short-term prophylactic use of C1-inhibitor concentrate in hereditary angioedema

Findings from an international patient registry

Although most hereditary angioedema (HAE) attacks appear to occur spontaneously, they can be precipitated by emotional stressors or physical triggers, including invasive medical or dental procedures or other physical trauma.^{1,2} Short-term prophylaxis (STP) is appropriate for patients anticipating situations that might precipitate an HAE attack.^{1,3–6} HAE guidelines recommend that plasma-derived C1 inhibitor (C1-INH) (10–20 U/kg of Berinert [CSL Behring, King of Prussia, Pennsylvania] or 1,000 to 2,000 U of Cinryze [ViroPharma Biologics, Inc, Lexington, Massachusetts]), administered within 6 hours (within 24 hours for Cinryze) before the stressor event, be used as first-line treatment, if available, in situations in which STP is desired.^{1,5,7} The plasma-derived, pasteurized, nanofiltered C1-INH concentrate (pnfC1-INH) is approved in many

countries for on-demand treatment of HAE attacks and is also approved in the European Union for STP. Few data are currently available regarding the use of pnfC1-INH as STP.

The Berinert Registry (clinicaltrials.gov Identifier: NCT01108848), conducted between 2010 and 2014 at 30 US and 7 European sites, represents the largest clinical research evaluation of pnfC1-INH use and one of few data sets to describe its use for STP.⁸ The registry collected data on individuals using pnfC1-INH regardless of reason for use, and investigators were asked to designate infusions as acute treatment, prophylaxis, or other. During the data analysis phase, classification of STP as the reason for infusion was determined by convention. STP consisted of pnfC1-INH infusions that were investigator designated as prophylaxis and that were administered more than 7 days apart from any other prophylactic infusion. STP also included infusions that were investigator designated as prophylaxis and that were indicated as having been administered for a medical or dental procedure. Details regarding the procedure or event requiring prophylaxis were not typically recorded as part of the registry data collection.

Because the registry was designed to gather data on pnfC1-INH use, only HAE attacks treated with pnfC1-INH were recorded. The frequency of attacks within the first 3 days after STP infusion is of primary clinical interest, although a full observation period of 7 days was evaluated based on an expected washout interval of 5 half-lives after a single pnfC1-INH dose, assuming a mean half-life of 33 hours.⁹ Adverse events (AEs) were identified within 30 days after each pnfC1-INH infusion.

Approximately 1 of 4 patients in the registry (79 of 318 [24.8%]) used pnfC1-INH at least once as STP. Registry patients who used pnfC1-INH as STP were all white, were primarily female (74.7%), and ranged in age from 8 to 76 years (mean [SD], 42.4 [17.56] years). The median pnfC1-INH dose per STP infusion was 14.6 IU/kg (range, 3.6–33.9 IU/kg) or 1,000 IU (range, 500–3,500 IU).

The cumulative HAE attack rates within 1 and 2 days after STP infusion regardless of dose were low at 0.04 (95% confidence interval [CI], 0.015–0.088) and 0.06 (95% CI, 0.028–0.115) attacks per infusion, respectively, and 0.11 (95% CI, 0.061–0.174) attacks per infusion at 3 days. From day 3 to day 4 after infusion, the cumulative attack rate had the largest numerical change (+0.12), increasing to 0.23 (95% CI, 0.158–0.319) attacks per infusion at 4 days. Beyond 4 days, the cumulative attack rates per infusion increased only slightly more (postinfusion day 5: 0.28; 95% CI, 0.198–0.373; day 6: 0.32; 95% CI, 0.238–0.458; and day 7: 0.35; 95% CI, 0.261–0.458). When used for long-term prophylaxis, plasma-derived C1-INH is recommended to be given every 3 to 4 days; thus, an increase in attack frequency beyond 3 days of an STP infusion is not unexpected.

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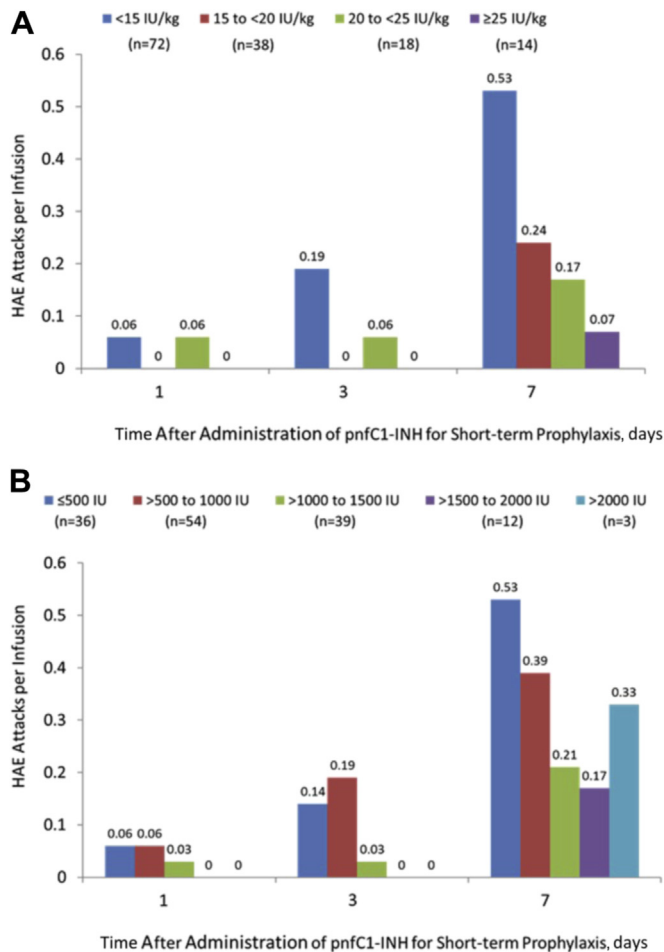


Figure 1. Dose-response analysis of cumulative hereditary angioedema (HAE) attack rates after plasma-derived, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH) short-term prophylaxis (STP) infusion according to pnfC1-INH dose by body weight (A) and absolute dose (B). Cumulative rates were based on attacks treated with pnfC1-INH that occurred within indicated periods after pnfC1-INH administration for STP. Comparisons between dose groups at each time point were not statistically significant based on overlapping confidence intervals.

Dose-response analyses of HAE attack rates 1, 3, and 7 days after STP infusions of pnfC1-INH are presented in Figure 1, according to weight-based dosing (Fig 1A) and absolute pnfC1-INH dose (Fig 1B). Despite small numbers of infusions reflected in some dose groups, these analyses revealed numerical trends that suggested higher efficacy with weight-based doses of 15 IU/kg and higher and absolute doses of at least 1,500 IU, although the CIs overlapped, caused in several cases by a small number of events. These trends were most apparent at 7 days after infusion, given the small number of attacks recorded during the first 3 days after infusion.

There were 6 AEs reported in 5 of 79 patients (6.3%). With the exception of 2 events of headache, all AEs were considered not related to pnfC1-INH.

Despite the limitation of small numbers of infusions for some dose groups and lack of observed statistical significance, the registry data suggest a trend toward greater efficacy with higher doses of pnfC1-INH for STP. Larger series with more complete data would be required to further clarify these findings, although an apparent dose-response effect is consistent with prior experience.¹⁰ Use of adequate STP doses to provide the highest possible degree of attack prevention is medically important and also may avoid the added expenses of subsequent attack treatment.

Limits of these data include the racial homogeneity of the patients and the observational nature and lack of a control group or

baseline attack information in the study. Only attacks treated with pnfC1-INH were recorded in the registry. Thus, attacks that were treated with other HAE therapies or were mild enough to not require any treatment were not captured for analysis, and it is therefore possible that the numerical post-STP attack rates presented here are an underestimation. However, the analyses that suggest a possible dose-response phenomenon and the lowest cumulative attack rates during the first 3 days after infusion were founded on uniform attack definitions for each visit; thus, the observed patterns should not have been affected greatly by this limitation. In addition, reasons for STP or any other use were not solicited in a proactive, mandatory fashion, which precluded analysis of pnfC1-INH efficacy for STP for specific types of procedures or events or timing of administration relative to the prophylaxis event. Despite these limitations, data from this large, international registry suggest that pnfC1-INH is effective and safe when used for STP in patients with HAE. A possible dose-response phenomenon was observed with regard to the rate of HAE attacks after infusion of pnfC1-INH for STP.

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