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. Short-term prophylaxis (STP) is appropriate for patients anticipating situations that might precipitate an HAE attack. 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. 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. 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. 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.

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. 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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References

Anaphylaxis induced by ingested molds

We present the case of a 22-year-old Spanish woman residing in Madrid with a personal history of milk and egg allergy, which she overcame in her childhood, and seasonal allergic rhinitis and asthma attributable to pollen allergy. No history of β-lactam allergy was recorded. She developed 5 mild to moderate anaphylactic reactions with generalized urticularia and angioedema in the eyelids together with dyspnea and wheezing, nausea, and occasional vomiting, with all symptoms appearing shortly after eating dry cured meat products or blue cheeses, both of which she tolerated in the past. Neither physical exercise nor the use of any drug preceded any of the anaphylactic reactions. All 5 reactions were treated in the same emergency unit with intravenous corticosteroids, histamine-1-antihistamines, and inhaled salbutamol. None of the patients received treatment with epinephrine.

The patient currently tolerates all the ingredients listed in these foods (pork, beef, milk, sugar, spices, pepper, garlic, ascorbic acid, sodium nitrite, and potassium nitrite). Skin prick tests (SPTs) with standard food allergen extracts (Alk-Abelló, Hørsholm, Denmark) to pork, beef, milk, egg, and spices (parsley, mustard, oregano, pepper, garlic, sesame, and paprika) were performed, with negative results. A complete battery of test inhalant allergens was performed, yielding a positive result with various pollens and fungi, whereas the SPT results were negative for house dust mites and cat and dog dander. Phosphate-buffered saline and histamine diphosphate (100 μg/mL) were used as negative and positive (5 × 5 mm) controls, respectively. The wheals obtained with the fungal extracts were 13 × 11 mm with Alternaria, 4 × 4 mm with Aspergillus, 3 × 4 mm with Cladosporium, and 10 × 8 mm with Penicillium. The serum total IgE concentration was slightly elevated (225 kU/L), consistent with her atopic diathesis. In addition, serum mold specific IgE levels using the commercial CAP-FEIA system and serum basal tryptase (Thermo-Fisher Scientific Inc, Waltham, Massachusetts) were measured: tryptase values were in the reference range (5 ng/mL) and specific IgE levels were 31.00 kU/L for Penicillium notatum (positive cutoff limit, 0.35 kU/L), 1.22 kU/L for Aspergillus fumigatus, 47.10 kU/L for Alternaria alternata, and 15.30 kU/L for Penicillium frequentans. Specific IgE antibodies to P notatum and Alternaria tenuis allergens (32100412-PT and 32100400 — NL, Allergopharma, Reinbek, Germany) were determined by enzyme-linked immunosorbent assay using a commercial kit (Costar 3590; Corning, New York, New York) according to the manufacturer’s instructions. Absorbance was measured at 405 nm using a spectrophotometer and expressed as optical density (OD) units. Samples were assayed in duplicate, and levels of specific IgE above 0.145 OD were considered a positive result. Mean levels of specific IgE to A tenuis were more than 1.400 OD units, and results were negative (<0.145 OD units) in the case of P notatum. Both extracts were analyzed by sodium dodecyl sulfate—polyacrylamide gel electrophoresis (SDS-PAGE) as described by Laemmli, with protein bands ranging from 11 to 97 kDa. An SDS-PAGE IgE-immunoblot assay revealed IgE reactivity with 26-kDa and 57-kDa proteins in the Alternaria extract, with no IgE binding in the Penicillium extract (Fig 1).

Fungal allergen exposure can induce allergic symptoms in the respiratory tract and skin, whereas generalized reactions are rare. Few cases of anaphylaxis have been described with the ingestion of molds and yeasts in patients sensitized to fungi.

Certain cured meats and cheeses (soft-ripened, washed-rind, and blue cheeses) require molds as a part of their elaboration. The application of a mold starter attempts to promote flavor and prevent pathogenic bacteria from multiplying through proteolytic, lipolytic, and antioxidant processes. These molds are applied on the skins and rinds or directly inoculated in the cheese for both preservation and to add certain tastes and textures. However, undesirable fungal species may also grow and spoil a food or produce contamination via mycotoxins. Normally, the products are inoculated with starters of the Penicillium genus, such as Penicillium nalgiovense, Penicillium camemberti, Penicillium glaucum, and Penicillium roqueforti, the type of mold used being different depending on the production regions, but other genera, such as Aspergillus, Eurotium, Mucor, Rhizopus, Cladosporium, Geotrichum, and

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