Use of Concentrated Plasma-Derived Subcutaneous C1 Inhibitor as Long-Term Prophylaxis in an 8-Year-Old Child With Hereditary Angioedema

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Hereditary angioedema with C1 inhibitor deficiency (C1INH-HAE) is a rare autosomal dominant disorder caused by either deficiency (type 1) or dysfunction (type 2) of the serine protease inhibitor C1 inhibitor (C1INH) [1-6]. It is characterized by recurrent attacks of subcutaneous/submucosal angioedema affecting the skin (91%), gastrointestinal tract (73%), upper airway (48%), or other areas. It can be triggered by physical or psychological stress. The mean age at onset of symptoms is 10 years. Early onset may predict a severe course. The diagnosis, based on evidence of C1INH deficiency or gene mutations, is often delayed for years [1-4]. Management is based on acute treatment of the swelling events with icatibant, plasma-derived C1INH (pdC1INH) or recombinant human C1INH (rhC1INH), and short-term prophylaxis and long-term prophylaxis (LTP). LTP was reported to minimize the impact of C1INH-HAE on patients [1-2], although the development of new drugs has prompted current HAE guidelines to aim for total symptom control [3-6]. LTP agents included antifibrinolytics (tranexamic acid), androgens, and intravenous (IV) pdC1 INH [1-4]. Tranexamic acid was preferred for LTP in children [1], although some authors displaced it owing to its limited efficacy [5]. Androgens are not recommended before Tanner stage V [1-4]; therefore, their use in pediatrics is very limited. New approaches include subcutaneous (SC) pdC1INH, which is licensed for children aged over 6 years in United States but not prescribed until age 12 years in Europe, and lanadelumab and berotralstat, which are not allowed in patients younger than 12 years [3-6].

HAE guidelines recommend follow-up visits to review disease activity and its impact on quality of life [1-6] and to monitor treatment efficacy and adverse effects [1]. The scales used to assess treatment efficacy include the disease-specific Angioedema Activity Score (AAS), which prospectively evaluates disease activity over 1 month [7], and the Hereditary Angioedema Activity score (HAE-AS), which is specific for C1INH-HAE and retrospectively evaluates disease activity in the previous 6 months [8]. These scales have not been validated in children.

We report the case of an 8-year-old girl who debuted with 2 peripheral cutaneous angioedema episodes after taking ibuprofen. Hypersensitivity to this analgesic was ruled out by challenge testing. She subsequently developed 2 new episodes of angioedema. C1INH deficiency and function were demonstrated and confirmed a month later (C1INH protein, 14 mg/dL; C1INH function, 33%; C4, 6 mg/dL; C1q, 26 mg/dL; C1q antibodies, 2.94). Given that acquired C1INH deficiency had been ruled out, she was diagnosed with type 1 C1-INH-HAE 6 months after onset. No mutation was detected when all exons of the SERPING1 gene were studied, although the mutation is not detected in up to 10% of HAE patients. A family history of HAE was demonstrated by screening. The patient's mother (C1INH protein, 15 mg/dL; C1INH function, 48%; C4, 3 mg/dL) and sister (C1INH protein, 13 mg/dL; C1INH function, 51%; C4, 6.7 mg/dL) were affected. Her sister remained asymptomatic, probably because of her age (11 months at diagnosis, 5 years old now), and her mother, who reported undiagnosed episodes of peripheral cutaneous angioedema and abdominal pain, is now treated with tranexamic acid and has experienced no attacks since 2020. The patient, despite LTP with tranexamic acid, experienced multiple attacks. She required multiple visits, emergency department admissions, and on-demand treatment with subcutaneous icatibant, which was gradually reduced starting 12 hours after initiation. pdC1INH was also added, as needed. In August 2020, LTP with off-label SC pdC1INH (Berinert) was requested from our pharmacy department. The treatment was delayed until February 2021. During these months, the patient had 13 attacks, 9 of which were treated with icatibant and 1, which involved laryngeal angioedema, also requiring intravenous pdC1INH and admission to hospital. Pre- and posttreatment clinical and laboratory data can be consulted in the supplementary table (ST 1). The patient's parents gave their informed consent for publication of this case.

Treatment was started at hospital and subsequently administered at home by the parents. After initiation of LTP with pdC1INH (Berinert) 2000 IU (60 IU/kg) every 3 days, the number of attacks decreased to zero. The patient had no further emergency department visits, only regular specialist attendance. C1INH levels and function improved 1 month after starting treatment. At the follow-up visits every 2 months, administration frequency was progressively reduced according to the patient's clinical status, following recommendations published by experts from the Spanish Bradykinin-Induced Angioedema Group (GEAB) [9]. Analytical monitoring was performed 1 month before dose modifications (ST 1). During the 3-4-5 and 6-day administration schedule, the patient remained asymptomatic. However, when the schedule was extended to every 7 days, she had 2 mild peripheral cutaneous attacks the day before administration of pdC1INH. One occurred during COVID-19, although an increase in attacks with this infection has been reported mainly in patients without prophylaxis [10]. Both resolved at home with icatibant. The patient is now receiving pdC1INH in a 6-day schedule, with total disease control. She has presented no adverse events. The HAE-AS scores based on pretreatment disease activity and after 6 and 12 months of treatment decreased from 13 to 0 and 5 points, respectively. The latest scores were recorded after the attacks occurring during extension of the treatment interval to a 7-day schedule. The posttreatment AAS score was 0 points, except for the 2 weeks with attacks, when 6 and 5 points were reported, respectively.

Delayed development of clinical trials in children is hindering young patients' options for new treatments. Publication of case reports helps physicians and pharmacists to find alternatives for children with uncontrolled disease and may facilitate the authorization of treatment, which is often delayed. In the case we report, this delay resulted in 13 angioedema attacks (1 of which was life-threatening) and a hospital admission. HAE questionnaires are useful for follow-up and can help identify disease activity, support the need for new treatments, and monitor their effectiveness, as we have shown.

We demonstrate that LTP with subcutaneous pdC1INH (Berinert) in a pediatric patient is safe and effective, achieving total control with reduced use of health care resources. Although C1INH levels and function increased after initiation of SC pdC1 INH and were maintained afterwards, we found no correlation with recurrence of symptoms. Studies are needed to verify the clinical utility of laboratory monitoring. Specific patient-reported outcome measures for disease activity in HAE must be validated for children.

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Conflicts of Interest

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