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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Patient’s parents consent:
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Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disorder caused by either deficiency (type 1) or dysfunction (type 2) of the serine protease inhibitor C1 inhibitor (C1-INH) [1-6]. It is characterized by recurrent attacks of subcutaneous/submucosal angioedema, at the skin (91%), gastrointestinal tract (73%), upper airway (48%) or other areas. They can be triggered by physical or psychological stress. The mean age at onset of symptoms is 10 years old. Early onset may predict a severe course. The diagnosis, based on evidence of C1-INH 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 (pdC1-INH) or recombinant human C1-INH (rhC1-INH), and short-term (STP) and long-term prophylaxis (LTP). LTP was reported to minimize the impact of C1-INH-HAE on patients [1-2] but 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], but some authors displaced it due to its limited efficacy [5]. Androgens are not recommended before Tanner Stage V [1-4], so their use in paediatrics is very limited. New approaches include subcutaneous (sc) pdC1INH, licensed for children over 6 years old in United States but not until 12 years in Europe, and lanadelumab and berotralstat, not allowed in patients younger than 12 years [3-6].
HAE guidelines recommend follow-up visits to review disease activity, its impact on quality of life [1-6] and to monitor treatment efficacy and adverse effects [1]. Different scales are available to assess treatment efficacy as the Angioedema Activity Score (AAS), specific to angioedema, that prospectively evaluates disease activity over 1 month [7] and the Hereditary Angioedema Activity score (HAE-S), a specific tool for HAE-C1-INH that retrospectively evaluates disease activity in the last 6 months [8]. These scales have not been validated in children.

We report an 8-year-old girl who debuted with 2 peripheral cutaneous angioedema episodes after ibuprofen intake. Hypersensitivity to this analgesic was ruled out by challenge testing. She subsequently developed 2 new episodes of angioedema. C1 inhibitor 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). Acquired C1INH deficiency had been ruled out, so she was diagnosed with type 1 C1-INH-HAE 6 months after onset. No mutation was detected when all exons of SERPING1 gene were studied, but the mutation is not detected until 10% of HAE patients. Family history of HAE was demonstrated when screening was performed. Her 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 the diagnostic, 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 no attacks since 2020. The patient, despite LTP with tranexamic acid, presented multiple attacks. She required multiple visits, emergency room admissions and on-demand treatment with subcutaneous icatibant, beginning the reduction of the angioedema 12
hours after its administration. pdC1INH was also added, if needed. In August 2020, LTP with off-label sc pdC1INH (Berinert®) authorization was required to our Pharmacy Department. It was delayed until February 2021. During these months, the patient had 13 attacks. Nine of them were treated with icatibant and one included laryngeal angioedema requiring also intravenous pdC1INH and hospital admission. We present pre- and post-treatment clinical and laboratory data in supplementary table (ST 1).

Treatment was started at hospital and afterwards, administered at home by her parents. After beginning LTP with pdC1INH (Berinert®) 2000 IU (60 IU/kg) every 3 days, the number of attacks reduced to zero. The patient had no further emergency visits, only regular specialist attendance. C1INH levels and function rose one month after starting treatment. In the follow-up visits, every 2 months, drug administration frequency was progressively reduced according to the patient’s clinical status, following recommendations published by GEAB experts [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 but, when it was extended to every 7 days, she had 2 mild peripheral cutaneous attacks the day before pdC1INH administration. One occurred during Covid-19, although increase in attacks with this infection has been reported preferentially in patients without prophylaxis [10]. Both were 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. Scores for HAE-AS retrospectively evaluating pre-treatment disease activity and after 6 and 12 months of treatment ranged from 13 to 0 and 5 points, respectively. Latest scores were recorded after the attacks occurring during treatment interval extension to a 7-day schedule. Post-treatment AAS
scores have been 0 points, except for the 2 weeks with attacks, when 6 and 5 points were reported, respectively.

The delay of 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, often delayed. In our patient, this delay resulted in 13 AE attacks (one of which was life-threatening) and a hospital admission. HAE questionnaires are useful in the follow-up and can help objectify disease activity, support the need for new treatments, and also monitor their effectiveness, as we have shown.

We demonstrate that LTP with subcutaneous pdC1INH (Berinert®) in a paediatric patient is safe and effective, achieving total control with less health resources. Although C1INH levels and function increased after the beginning of sc pdC1 INH and maintained afterwards, we found no correlation with symptoms’ relapse. Studies are needed to verify the clinical utility of laboratory monitoring. Validation of specific patient-reported outcome measures for disease activity in HAE is needed for children.

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