Real-life Experience of Subcutaneous Plasma Derived C1-Inhibitor as Long-term Prophylaxis in HAE-C1INH

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Palabras clave: Angioedema hereditario por déficit de C1 inhibidor. AEQoL. HAE-QoL. Derivado plasmático de C1 inhibidor subcutáneo.

Hereditary angioedema (HAE) due to C1-inhibitor deficiency (HAE-C1INH) is an incurable and life-threatening disease [1,2]. Angioedema attacks interfere with the patient's daily and work activities and decrease health-related quality of life (HRQOL), even during angioedema-free intervals [3].

Replacement therapy with subcutaneous (SC) plasma-derived C1-inhibitor (pdC1INH) (Berinert, CSL Behring) was shown to be effective as long-term prophylaxis (LTP) in patients with HAE-C1INH [4,5] and is currently one of the first-choice treatments for LTP in this disease [1,2]. It is easier to self-administer and more efficacious than intravenous (IV) pdC1INH [6]. It has recently become available in Spain [7,8].

The aim of our study was to assess efficacy and changes in HRQOL in HAE-C1INH patients treated with SC pdC1INH (Berinert) as LTP under real-world conditions.

We performed a retrospective, cross-sectional study (Ethics Committee approval, PI-4598). All the patients diagnosed with HAE-C1INH who had received SC pdC1INH for at least 6 months until December 2021 were included. Demographic and clinical data were collected retrospectively. Patients prospectively completed a symptom diary, 2 HRQOL questionnaires, and a treatment satisfaction questionnaire at their follow-up visits as part of their routine health care. HRQOL was assessed using the Angioedema Quality of Life questionnaire (AE-QoL), a specific questionnaire for angioedema as a symptom, and the HAE-QoL, which is specific for HAE-C1INH [3] at 2 time points: prior to starting SC pdC1INH LTP and 6 months later. Disease activity was measured as the monthly attack rate (number of attacks/mo) during the 6 months prior to starting SC pdC1INH LTP and during the 6 months after starting this treatment. The degree of satisfaction with SC pdC1INH LTP was assessed using the specific Treatment Satisfaction Questionnaire for Medication (TSQM, v1.4) [9] 6 months after starting the treatment. Statistical analysis was performed using IBM SPSS for Windows, Version 24. 0 (IBM Corp.).

We included 8 patients (5 women [62.5%]) diagnosed with type I or II HAE-C1INH treated with SC pdC1INH LTP. Mean (SD) age was 47.1 (14.7) years and mean weight 83.1 (17.1) kg (Table S1). Six patients had previously undergone LTP (3 with attenuated androgens [AAs] and 3 with IV pdC1INH) (Table S1). The reasons for switching treatment were adverse effects of AA, the lack of effectiveness of previous LTP, and the high emotional burden of IV treatment. Two patients started LTP with SC pdC1INH because of inability to self-administer IV medication.

The protocol followed that suggested by the Spanish Group for the Study of Bradykinin-mediated Angioedema (GEAB) of the Spanish Society of Allergy and Clinical Immunology (SEAIC). SC pdC1INH LTP was initiated with 2000 IU twice per week in most patients (Figure) [10].

The initial SC pdC1INH doses can be seen in Table S1. Six patients received 2000 IU twice weekly. Patient 3 started at a higher dose (4000 IU twice weekly) owing to high disease activity (prior treatment with IV pdC1INH 1000 IU every 2 days). Patient 1 started with a lower dose (1500 IU twice weekly) because the treatment was initiated in 2018, before SC pdC1INH came onto the market in Spain (the patient signed a consent form). Over the first 6 months, the SC pdC1INH dose had to be increased in 3 patients (Patients 4, 6, and 7), reduced in 4 (Patients 1, 2, 3, and 8), and maintained in Patient 5. The initial median (IQR) SC pdC1INH dose was 37.8% (35.19%-54.29%) of the corresponding dose in the summary of product characteristics (SmPC); at 6 months this was 54.9% (53.425-61.95) (Table S1). All the patients received doses lower than that indicated in the SmPC (60 IU/kg) [8] throughout the study.

The median number of attacks per month prior to SC pdC1INH LTP was 1.93 (1.53-2.94), and a nearly significant reduction was observed 6 months after initiation of SC pdC1INH LTP (median, 0.3 [0-1.69]; P=.069) (Table S1 and Table S5). The clinical condition improved in 6 patients, 3 of whom, remarkably, became asymptomatic (0 attacks/mo). Only 2 patients experienced a worsening of their HAE activity 6 months after the beginning of SC pdC1INH: patient 6 achieved a reduction in attacks 3 months after the dose increase (8 months after initiation of SC pdC1INH LTP), and patient 8 did not complete the dose increase as prescribed.

HRQOL improved 6 months after initiation of treatment according to both the AE-QoL and HAE-QoL.

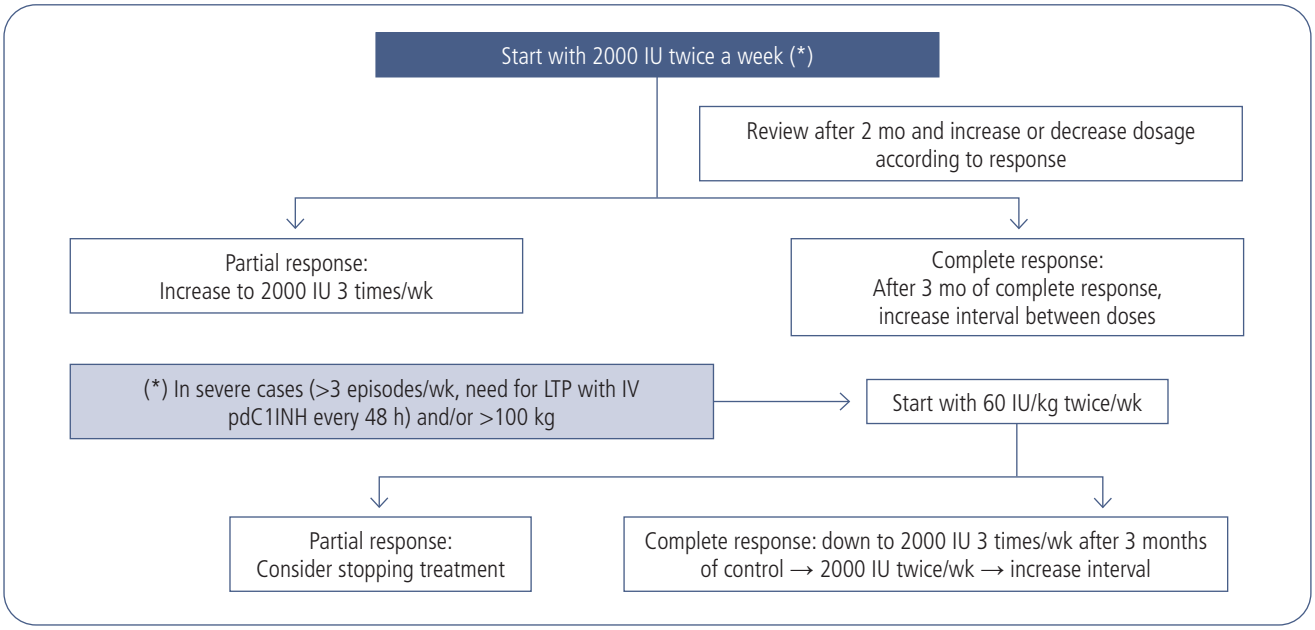

Figure. Subcutaneous pdC1INH LTP protocol of the Spanish Group for the Study of Bradykinin-mediated Angioedema.

The total AE-QoL score improved, and the difference was higher than the minimal clinically important difference (6 points) [3], although it was not statistically significant (Table S5). There was also a nonsignificant improvement in all the dimension scores (Table S2), except in the Fatigue/Mood domain. Individual scores are shown in Table S5.

The total HAE-QoL score also improved (nearly significant, *P*=.093) (Table S5), as did all the dimension scores, except for the Disease-related Stigma domain (Table S3). Statistical significance was achieved in 2 dimensions: Perceived Control over Illness (*P*=.031) and Mental Health (*P*=.020). Individual scores are shown in Table S5.

According to the TSQM questionnaire, the mean satisfaction rate was 77.7% (Table S4). Only 2 patients had adverse effects, mainly local discomfort at the injection site (itching and stinging).

In our series, the use of lower doses of SC pdC1INH than those approved in the SmPC and even lower than those proposed in the GEAB protocol proved to be effective, even in patients with high body weight and decreased HAE activity, increased HRQOL, and high overall satisfaction. Other authors also used SC pdC1INH as LTP at doses lower than those approved in the SmPC (42.86-65.22 IU/kg/wk) in real life, with good results [11]. The lower SC pdC1INH doses imply a reduction in direct costs and the possibility of prescribing this treatment to more patients.

In conclusion, the GEAB protocol for starting LTP with SC pdC1INH in HAE-C1INH proved useful for individualizing treatment in our case series.

Since the present study is limited by the small number of patients and the short observation period, further studies are needed.

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Conflicts of Interest

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A. Entrala has received funding to attend conferences/educational events from CSL-Behring and Novartis.

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Previous Presentations

These data were presented as an oral communication at the National Congress of the Spanish Society of Allergology and Clinical Immunology in 2021.

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