Real-life experience of subcutaneous (SC) plasma derived C1-inhibitor (pdC1INH) as long-term prophylaxis (LTP) in HAE-C1INH

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Palabras clave: Angioedema hereditario debido a deficiencia de C1-inhibidor. Calidad de vida relacionada con la salud. AE-QoL. HAE-QoL Profilaxis a largo plazo.

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

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

The aim of our study was to assess efficacy and changes in the HRQoL in HAE-C1INH patients treated with SC pdC1INH (Berinert®) as LTP in real-life.

We performed a retrospective, cross-sectional study (Ethics committee approval PI-4598). All the patients diagnosed with HAE-C1INH that had received SC pdC1INH (Berinert®, CSL-Behring) for at least 6 months until December 2021 were included. Demographic and clinical data were collected retrospectively. Patients completed prospectively a symptom diary, two HRQoL questionnaires and a treatment satisfaction questionnarie at their follow-up visits as part of their routine health care. HRQoL was assessed with the Angioedema Quality of Life questionnaire (AE-QoL), a specific questionnaire for angioedema as a symptom, and the HAE-QoL, specific for HAE-C1INH [3] at 2 time points: prior to starting SC pdC1INH LTP and 6 months after. Disease activity was measured by monthly attack rate (attacks/month) the six months prior to

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starting SC pdC1INH LTP and during the six months after starting this treatment. The degree of satisfaction with SC pdC1INH LTP was assessed using the specific Treatment Satisfaction and Medical Outcomes (TSQM) v1.4 questionnaire 6 months after starting the treatment. Statistical analysis was performed using SPSS.2 software.

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

The protocol suggested by the Spanish Group for the Study of Bradykinin-mediated Angioedema (GEAB) of the Spanish Society of Allergy and Clinical Immunology (SEAIC) to initiate SC pdC1INH LTP was followed, beginning with a 2,000 IU twice per week dose in most patients (**Figure 1**) [9].

Starting SC pdC1INH doses can be seen in **Table S1.** A 2,000 IU twice weekly dose was initiated in 6 patients. Patient 3 started with a higher dose (4,000 IU twice weekly) due to high disease activity (prior treatment with IV pdC1INH 1,000 IU every 2 days). Patient 1 started with a lower dose (1,500 IU twice weekly) because the treatment was initiated in 2018 before SC pdC1INH was commercialized 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 SC pdC1INH dose was a median of 37.8 % (IQ_{25-75} 35.19 - 54.29) and at 6 months a median of 54.9% (IQ_{25-75} 53.425-61.95) of the corresponding dose according to the SmPC (**Table S1**). All patients received doses lower than that indicated in the SmPC (60 IU per kg of body weight) [8] throughout the entire study.

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The median number of attacks per month prior to SC pdC1INH LTP was 1.93 (IQ_{25-75} 1.53 - 2.94) and a nearly significant reduction was observed 6 months after the initiation of SC pdC1INH LTP (median 0.3 IQ_{25-75} 0 - 1.69) (*p = 0.069*) **(Table S1** and **Table S5)**. Six patients managed to improve and, remarkably, 3 of them became asymptomatic (0 attacks/month). Only 2 patients experienced a worsening in 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 the start with SC pdC1INH LTP), patient 8 did not complete the dose increase as prescribed.

Regarding HRQoL, an improvement was observed 6 months after treatment initiation as measured by both questionnaires, AE-QoL and HAE-QoL.

The AE-QoL total 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 non-significant improvement in all the dimensions scores (**Table S2**), except in the Fatigue/Mood domain. Individual scores are shown in Figure 1.

The HAE-QoL results also showed an improvement in the total score (nearly significant, p=0.093) (Table S5) and all the dimension scores, except for the Disease-related stigma domain (**Table S3**). Statistical significance was achieved in two dimensions: Perceived Control over Illness (*p = 0.031*) and Mental Health (*p = 0.020*). Individual scores are shown in Figure 1.

With regard 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 has proven to be effective, even in patients with high body weight with a decrease in HAE activity, an increase in HRQoL and a 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/week) in real-life with good results [10]. The lower SC pdC1INH

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doses imply a reduction in direct costs and the possibility to prescribe this treatment to more patients.

In conclusion, the GEAB protocol for starting LTP with SC pdC1INH in HAE-C1INH has been useful to individualize treatment in our case series.

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

Conflicts of interest

This work received the first PUBLI-Scholarship award granted by CSL-Behring at the National Congress of the Spanish Society of Allergology and Clinical Immunology in 2021.

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

R. Cabañas has received grant research support and/or speaker/consultancy fees from Novartis and Pharming NV and. She has also received funding to attend conferences/educational events from CSL-Behring, Novartis and Takeda.

T. Caballero has received grant research support and/or speaker/consultancy fees from Astria, Biocryst, CSL-Behring, Novartis, Pharming NV and Takeda. She has also received funding to attend conferences/educational events from BioCryst, CSL-Behring, Novartis, Pharming and Takeda. T Caballero is/has been a clinical trial/registry investigator for Biocryst, CSL-Behring, IONIS, Novartis, Pharming NV abd Takeda. She is a researcher in the IdiPaz research program.

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Figure. GEAB SC pdC1INH LTP Protocol.