LETTER TO THE EDITOR

Transitioning from nonspecific therapy to berotralstat in hereditary angioedema type I: real world data from three patients within the same family

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To the Editor

Hereditary angioedema (HAE) is a rare disorder characterized by recurrent episodes of oedema affecting primarily subcutaneous tissues (face, upper or lower extremities, genitals), abdominal organs (stomach, intestines, bladder), and upper airways (larynx, tongue) (1, 2). The oedema can be life threatening when affecting the upper airways.

The majority of HAE cases are caused by variants of the gene *SERPING1* encoding for C1 inhibitor (C1INH), resulting in deficiency or dysfunction of C1INH (HAE-C1INH-Type 1 or 2 respectively). In HAE-C1INH, angioedema is mediated by dysregulation of the kallikrein-kinin system, resulting in localized overproduction of bradykinin, causing increased vascular permeability.

Disease management is based on the following triad: on-demand treatment of crises, short-term prophylaxis, and long-term prophylaxis (LTP) (3). Historically, non-specific treatments have been employed for LTP such as danazol that promotes increased hepatic synthesis of C1INH, associated with numerous adverse effects (weight gain, hypertension, dyslipidaemia, acne, irregular menstrual cycles, increased CPK enzymes and decreased libido), or tranexamic acid (TXA), an antifibrinolytic agent inhibiting plasmin production that showed limited efficacy (4).

Recently, specific plasma kallikrein inhibitors demonstrated their effectiveness in reducing HAE attacks, 2 of them being indicated as first-line LTP(3), namely lanadelumab, a humanized monoclonal antibody administered subcutaneously every 2-4 weeks, and berotralstat, an oral plasma kallikrein inhibitor administered once daily (5).

Due to the recent availability of berotralstat and the rarity of the disease, real-world data remain limited. Moreover, the transition modalities from previous therapies to berotralstat have not yet been precisely described: in clinical studies, patients underwent a wash-out period before initiating berotralstat therapy (5). In this case series, we describe the transition process in a real-world clinical setting.

Three patients from the same family were transitioned to berostraltat at the same hospital. Written consent was obtained prior to data collection. Clinical monitoring was done during outpatient clinic visits during which number of attacks, possible side effects, quality of life, and therapeutic compliance using the 8-item Morisky Medication Adherence Scale (MMAS-8) (6) were recorded.

The 3 patients (2 women and 1 man) had been diagnosed with HAE-C1INH-Type I 9 years ago, with various disease phenotypes as regards frequency and severity of crises (Table I). Patients 1 and 2 had been treated with danazol as LTP for 3 years. Concerns regarding long-term tolerability and/or persistence of severe attacks led to the decision to switch to berotralstat (Table I). Moreover, Patient 1 wished to avoid injectable treatments. Patient 3 was treated with TXA as on-demand treatment of attacks without LTP. However, its effectiveness had been decreasing since puberty (occurrence of severe attacks requiring icatibant).

Switching modalities are detailed in **Figure 1**.

For Patient 1, switch to berotralstat occurred over a brief period (1 month) since the patient was already receiveing the lowest possible dosage of danazol (200 mg/week). The one-month overlapping period was implemented to reach the berotralstat's steady-state, which typically ranges from 6 to 12 days (7). Patient 2, being on a higher danazol dosage, required a 3-month tapering of danazol while initiating berotralstat concurrently, at the end of which danazol were completely discontinued. Patient 3, solely treated with on-demand treatments, did not require a transition period.

After switch, no attack was reported during 6 (Patient 3) to 9 months (Patients 1 and 2) of follow-up, which was associated to improved patients' satisfaction. Berotralstat exhibited superior tolerability compared to danazol, with no reported side effects. All patients achieved a MMAS-8 score of 8, reflecting a high level of adherence to treatment.

Androgens and TXA are no longer recommended for LTP due to adverse safety profile and insufficient efficacy respectively(3). The international guidelines also highlighted that, on top of achieving complete disease control, the goal of LTP is to normalize patients' lives by minimizing treatment burden and adverse effects (3).

There is no precise recommendation on how transitioning from danazol to berotralstat, but abrupt discontinuation of androgens should be avoided (7). Three options have been described (8): tapering danazol after initiation of new treatment, tapering danazol followed by a washout period, or initiating new therapy while tapering danazol. We chose the third option to avoid attacks during the transition period, which may have deleterious psychological impact in patients. Following this method, we observed successful transitions from danazol and TXA to berotralstat in our 3 patients.

Close monitoring and regular communication with patients during the transition period were instrumental in achieving optimal outcomes. HAE is characterized by the absence of validated biomarkers for disease monitoring. Consequently, disease evaluation solely relies on clinical examination and patient's testimonies. Hence, it is crucial to involve the patient in therapeutic decisions and to foster an environment of discussion during or outside of consultations.

Berotralstat therapy requires daily tablet intake. Therapeutic adherence represents a significant public health challenge. The JALMA study indicated that 25% of prescribed medications are not taken by patients, a common negligence among individuals with life-threatening conditions, leading to 12,000 deaths and 100,000 hospitalizations each year (9). Therefore, every effort should be made to improve compliance including therapeutic education, in-depth discussions with patients to understand reasons for poor compliance (fear of side-effects, poor understanding of the disease, erroneous beliefs on drugs), detection and early management of possible side-effects. It is essential to create a relationship of trust with the patient to ensure straightforward communication. Patients' preferences and constraints should be questioned to choose treatment, in particular administration route and frequency of administration. In HAE, it has been made possible thanks to the availability of new options

for LTP. In our series, all three patients reported a high level of treatment adherence according to the MMAS-8 questionnaire.

This publication has several limitations, namely the small sample size, the absence of validated scales to assess quality of life and disease control, and the short duration of follow-up.

This case series highlights the benefits of new treatments such as berotralstat in the management of HAE, providing improved tolerability and effective disease control. It emphasizes the importance of patient-centered care throughout the transition process. Further research and long-term studies are needed to validate these findings and optimize HAE management strategies.

Compliance with Ethical Standards

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Table 1. Demographic characteristics and previous treatments

	Patient 1 (index case's cousin)	**Patient 2 (index case)**	**Patient 3 (index case's daughter)**
Sex	Female	Male	Female
Age at transition to berostraltat (years)	46	58	20
Weight (kgs)	61	72	57
Comorbidities	Hashimoto's thyroiditis	None	None
Concomitant therapies	None	None	Desogestrel
Age at HAE diagnosis	37 years	49 years	11 years
Mutation	*SERPING1* c.1353_1354delGA delGA/wt		
C1INH (antigenic level // function)	47 mg/L // 3.8 U/mL	37 mg/L // 2.5 U/mL	52 mg/L // < 2 U/mL
Attacks description*	Extremities (arm, hand, foot). Not severe, disappear spontaneously.	Laryngeal oedema triggered by local trauma	Mainly facial oedema and abdominal pain.
Attack rate before switch	0 (controlled with danazol)	1.5/year (severe attacks)	1 severe attack every 1 or 2 years
Treatment before switch **LTP** **Treatment of attacks**	Danazol Icatibant	Danazol Icatibant	None Tranexamic acid (TXA) ± icatibant
Dosage	200 mg/week	600 mg/week	2 g orally during attacks
Reason for the switch	Poor tolerance Concerns about long-term use in a woman and wish not to use injectables	Poor efficacy, burden of treatment and poor tolerance **(**muscular pain, increased CPK and liver transaminases)	Lack of efficacy TXA efficacy deteriorated during puberty, with recurrent oedema and fainting.
Therapeutic goals	1- Maintain disease control 2- Avoid side effects of danazol	1- Avoid side effects of danazol 2- Maintain disease control 3- Improve quality of life	1- Maintain disease control

*Under danazol LTP for patients 1 and 2, under ODT by TXA for patient 3

Figure 1: Switching modalities from previous treatment to berotralstat