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Hereditary angioedema with normal C1 inhibitor: clinical characteristics and treatment response with plasma-derived human C1 inhibitor concentrate (Berinert®) in a French cohort

Background: Hereditary angioedema (HAE) is a rare genetic disorder characterised by episodes of swelling without urticaria. Berinert® (CSL Behring) is a plasma-derived human C1 inhibitor (C1-INH) concentrate, approved for the treatment of HAE with C1-INH deficiency (C1-INH-HAE), however, it is often used off-label in Europe to treat HAE with normal C1-INH. *Objectives:* To report the clinical characteristics of patients with HAE with normal C1-INH (with F12 gene mutation; FXII-HAE) or of unknown origin (U-HAE), and their response to Berinert®. *Materials & methods:* Data from 2007 to 2016 (obtained retrospectively from the French *Cohort BeRinert Angiœdème* [COBRA] registry of HAE patients with everyday use of Berinert®) were analysed; no control group was included. Diagnostic criteria for FXII-HAE and U-HAE included a normal C1-INH antigenic level and function and refractoriness to high-dose antihistamines. For FXII-HAE, diagnosis also included *F12* gene mutation, and U-HAE a positive family history for the disease. *Results:* To date, 28 patients with FXII-HAE or U-HAE were identified (mean age: 27 years; first angioedema attack at 19.8 years; 85.7% female) with 78 documented Berinert®-treated attacks, the majority occurring in the laryngeal and abdominal regions. Efficacy assessment of Berinert® was available for 38 of 78 documented Berinert®-treated attacks; 22 improved within 60 minutes of treatment initiation, nine within 60-180 minutes, four after 180 minutes, and three showed no improvement. No severe or serious adverse effects were reported. *Conclusion:* Data to date suggest that Berinert® may be a safe and efficacious treatment option for the majority of HAE patients.

Key words: Berinert®, hereditary angioedema, pharmaco-epidemiological, C1 inhibitor, drug safety, registry, off label

Hereditary angioedema (HAE) is a rare genetic disorder that has a prevalence ranging from an estimated 1 in 10,000 to 1 in 50,000 [1, 2]. This autosomal dominant disease is characterised by transitory and recurrent episodes of localised subcutaneous and/or submucosal swelling that may involve the face, peripheral extremities, abdomen, genitalia, oropharynx or larynx without wheals [3, 4]. It is a potentially deadly disease as patients with laryngeal oedema are at risk of death by asphyxia [3, 4]. HAE with C1 inhibitor (C1-INH) deficiency (C1-INH-HAE) type I or II are the main forms of the disease [3]. These forms are caused by decreased production (HAE-I) or a functional deficiency (HAE-II) of the C1-INH [3, 4]. C1-INH-HAE is associated with mutations in the *SERPING1* gene, which encodes for the C1-INH protein. More recently, HAE with normal C1-INH has been identified, which is associated with normal C1-INH protein expression [3-6], mutations in the *F12* gene that encodes human coagulation factor XII (Hageman factor) (FXII-HAE) [7], and/or a positive family history for the disease (U-HAE) [8, 9].

The majority of patients affected by FXII-HAE or U-HAE are women, particularly pregnant women or those exposed to exogenous oestrogen (*e.g.* oral contraceptives containing oestrogen). All types of HAE are often aggravated by oestrogen and do not respond to antihistamines [10].

The optimal management of HAE includes treatment of acute attacks, short-term prophylaxis to prevent an attack, and long-term prophylaxis to minimise the frequency and severity of recurrent attacks. Several specific therapies for

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the treatment of HAE have recently been made available in the US and Europe, including C1-INH replacement therapy, bradykinin receptor antagonists, and kallikrein inhibitors [1, 3, 4].
Berinert® (CSL Behring) is a human C1-INH concentrate derived from human plasma, which is administered intravenously [11]. Berinert® has been shown to be effective for the acute treatment of patients with C1-INH-HAE [12-14]. Berinert® is currently approved for acute on-demand therapy of C1-INH-HAE [1, 4], but is used off-label in Europe to treat patients with FXII-HAE and U-HAE. Plasma-derived human C1-INH concentrates have demonstrated efficacy in observational studies of patients with FXII-HAE and U-HAE [15-17], and international guidelines have indicated that this treatment option may be used to treat FXII-HAE and U-HAE attacks [1].
The purpose of this report was to describe the clinical characteristics of a French population of patients with FXII-HAE or U-HAE, along with their response to treatment with plasma-derived human C1-INH concentrate (Berinert®).

Materials and methods

To collect data on the everyday use of plasma-derived human C1-INH concentrate (Berinert®) in France, the National Angioedema Reference Centre (CREAK) created the *Cohort BeRinert Angiœdème* (COBRA) registry in 2010. This registry aims to enrol all patients with HAE who have received at least one dose of human C1-INH concentrate. The primary objective of the COBRA registry is to describe the long-term efficacy and safety of human C1-INH concentrate. Patients are followed for up to 10 years and enrolment in the COBRA registry is ongoing. To collect data, physicians are provided with electronic case report forms for each patient and are encouraged to update the registry every six months. If a patient is receiving human C1-INH concentrate for the first time, the patient is prospectively followed, however, if a patient has already received human C1-INH concentrate prior to the registry being set up, retrospective data collection is carried out and then the patient is followed prospectively.
Each electronic case report allows the collection of the following data:

– Sociodemographic and clinical characteristics of each patient (age, sex, age of patient at first angioedema attack, age at diagnosis of HAE, concomitant diseases, hormonal status, family history, *etc*.).
– The characteristics of angioedema attacks (number of attacks, length of attacks, time between attacks, *etc*.).
– Treatment details (number of previous human C1-INH concentrate treatments, background HAE treatments, number of vials of human C1-INH concentrate infused, who administered the product [self-administration, nurse, physician, or family], place where the patients received treatment, *etc*.).
– Quality of life.
– Safety of human C1-INH concentrate.
– Efficacy (the time between receiving the human C1-INH concentrate injection and the onset of disease improvement, the rate of complete resolution of symptoms, *etc*.).

Data from 2007 to February 2016, from patients with FXII-HAE or U-HAE, were analysed to demonstrate the sociodemographic and clinical characteristics of patients and the long-term efficacy and safety of human C1-INH concentrate in this patient population.
FXII-HAE was diagnosed based on normal C1-INH concentrations and function, failure of antihistamine and corticosteroids, and either a confirmed *F12* mutation or family history of HAE for U-HAE, as previously described [8]. The disease was refractory to high-dose antihistamines. Mutations in exon 9 of the *F12* gene were investigated by PCR-Sanger sequencing. The efficacy analysis set included all patients with FXII-HAE or U-HAE who received human C1-INH concentrate and had documented efficacy parameters. The safety analysis set included all patients with FXII-HAE or U-HAE in the COBRA registry and adverse events were collected based on reports by the patient and/or the physician.
Descriptive statistics were applied to the data and included the usual parameters: mean and standard deviation (SD) for quantitative variables, and numbers and percentages for qualitative variables.
The registry was approved by the CNIL (the French commission for informatics and freedom) and the Ethics Committee.
Written information was given to patients when their information was entered into the COBRA registry. Oral consent was collected.

Results

Patients

To date, the COBRA registry includes efficacy and safety data for 233 patients with C1-INH-HAE, with a total of 483 documented human C1-INH concentrate-treated attacks. Of these patients, 28 were from nine French centres; 11 patients (39.3%) were diagnosed with FXII-HAE and the 17 remaining patients (60.7%) with U-HAE.
The majority of patients were women (85.7%) with a mean age of 27.0 years (*table 1*). The mean age of patients when they presented their first angioedema attack was 19.8 years and the mean age of patients at FXII-HAE or U-HAE diagnosis was 23.7 years (*table 1*).
Twenty-one patients (75.0%) had documented efficacy parameters which were included in the efficacy analysis set. Nineteen were female (90.5%), mean age was 27.6 years, and the mean age of patients at their first angioedema attack was 20.7 years old (*table 1*).
The majority of patients had 1-5 angioedema attacks in the previous year and approximately 38.5% of patients were receiving another concomitant HAE treatment (*table 2*).

Characteristics of attacks

In the 21 patients included in the efficacy analysis set treated with human C1-INH concentrate, 78 documented FXII-HAE or U-HAE attacks were reported; the majority in the laryngeal and abdominal regions (*table 3*, *figure 1*). Fifteen of the attacks were associated with angioedema

Table 1. Characteristics of all FXII-HAE and U-HAE patients in the COBRA (n = 28) and EAS (n = 21).

Characteristic	All patients[a] (n = 28)	EAS[b] (n = 21)
Sex, n (%)		
Female	24 (85.7)	19 (90.5)
Male	4 (14.3)	2 (9.5)
Age (years)	27.0 ± 10.7	27.6 ± 10.0
Range	8.0-48.7	8.0-46.3
Bodyweight (kg)	60.1 ± 16.1[c]	59.7 ± 12.6
Body mass index (n)		
<18.5 kg/m^2	2	1
18.5-24.9 kg/m^2	13	9
25.0-29.9 kg/m^2	5	5
≥30.0 kg/m^2	1	0
Data missing	7	6
Age at first attack (years)	19.8 ± 9.8[d]	20.7 ± 8.7
Age at diagnosis (years)	23.7 ± 9.9[e]	24.1 ± 9.0
Family history of HAE (n)	24	18
Females receiving OC (n)	16	12
Combined OC (oestrogen/progestin)	8	8
Progestin	12	10
Oestrogen + progestin	3	2
Intrauterine device	1	1
Data missing	0	0

All values are mean ± standard deviation unless otherwise stated. EAS: efficacy analysis set; HAE: hereditary angioedema; OC: oral contraceptive. [a] The safety analysis set included all patients enrolled in the COBRA registry. [b] The efficacy analysis set included all patients who had documented efficacy parameters. [c] Data missing for 7 patients. [d] Data missing for 2 patients. [e] Data missing for 1 patient.

symptoms including asthenia, dyspnoea, headache, dysphonia, diarrhoea, abdominal pain, tiredness, hyperalgesia, hypovolaemia, compressing sensation, and vomiting. Eighteen of the events were considered to be related to trigger events including: stress; ear, nose and throat infections; surgery; tiredness; gastroenteritis; physical effort; or a cold.

Efficacy

Treatment response data was available for 38 out of the 78 documented FXII-HAE or U-HAE attacks. Of these 38 attacks, 22 showed symptom improvement within 60 minutes of treatment initiation, five improved within 60-120 minutes, four improved between 120 and 180 minutes, four improved after 180 minutes, and three showed no improvement (*table 3*). The majority of attacks were completely resolved within 12 hours, with four attacks completely resolved within 60 minutes of treatment initiation (*table 3*).

Safety and tolerability

No severe or serious adverse effects were reported.

Table 2. Details of FXII-HAE and U-HAE patients in the COBRA (n = 28) and EAS (n = 21).1

Parameter	All patients[a] (n = 28)	EAS[b] (n = 21)
Age at initiation of Berinert® treatment (years)	24.9 ± 10.5	25.3 ± 9.9
Duration of Berinert® treatment (years)	1.8 ± 1.4	1.9 ± 1.5
Background HAE treatment (n)	9	7
Tranexamic acid	7	5
Danazol	2	2
Other	1	0
Data missing	2	2
HAE attacks in the previous year (n)		
None	9	4
1-5	6	5
6-10	4	3
>10	1	1
Data missing	8	8
HAE attacks in the previous year	5.8 ± 13.6[c]	11.6 ± 18.3
HAE attacks in the year prior to treatment with Berinert®, (n)		
None	14	7
1	2	2
2	0	0
>3	4	4
Data missing	9	8
Mean number of HAE attacks in the year prior to treatment with Berinert®	0.9 ± 1.5[c]	1.3 ± 1.8
Prophylactic Berinert® in the last year	7[d]	2
Mean number of prophylactic Berinert® treatments in the previous year	0.3 ± 0.5[d]	0.1 ± 0.4[e]

All values are mean ± standard deviation unless otherwise stated. EAS: efficacy analysis set; HAE: hereditary angioedema. [a] The safety analysis set included all patients enrolled in the COBRA registry. [b] The efficacy analysis set included all patients who had documented efficacy parameters. [c] Data missing for 8 patients. [d] Data missing for 6 patients. [e] Data missing for 6 patients.

Discussion

This is the first analysis of patients with FXII-HAE or U-HAE enrolled in the observational COBRA registry to investigate the clinical characteristics of a French population of patients with HAE, along with their response to treatment with human C1-INH concentrate.

The clinical characteristics of the patients with FXII-HAE or U-HAE in the COBRA registry support and validate previous findings suggesting that oestrogens may play an important role in the development of FXII-HAE and U-HAE. Firstly, the majority of patients identified in the COBRA registry with FXII-HAE or U-HAE were women. This is similar to previous studies of FXII-HAE and U-HAE in which very few men have been diagnosed with this form of HAE [5, 6, 18-21]. Furthermore, the mean age at disease onset in this study was some time after the onset of

Table 3. Angioedema attacks and Berinert® response in FXII-HAE and U-HAE patients.

Parameter	Efficacy analysis set (n = 21)
Number of attacks treated	78
Mean time between attacks (weeks)	17.3 ± 3.2
Number of attacks per patient, *n* (%)	
1	8 (38.1)
2	6 (28.6)
3	2 (9.5)
4	2 (9.5)
≥5	3 (14.3)
Median number of attacks treated per anatomical location[a]	
Abdominal	25
Laryngeal	12
Facial	6
Multiple locations	25
Peripheral	1
Other regions	6
Number of attacks with symptomatic improvement[b] according to the length of time from treatment initiation to demonstration of improvement or no improvement	
<30 min	9
30-60 min	13
60-120 min	5
120-180 min	4
>180 min	4
No improvement	3
Data missing	40
Number of attacks with symptomatic improvement[b] according to the length of time from treatment initiation to disappearance of symptoms or no improvement	
<1 hour	4
1-6 hours	13
6-12 hours	2
12-24 hours	0
>24 hours	4
No improvement	3
Data missing	52

EAS: efficacy analysis set. [a] Attacks could be experienced at more than one location. [b] Symptomatic improvement was considered as a ≥50% improvement of symptoms.

puberty and it has been suggested that the natural increase of oestrogens after puberty may influence the development of FXII-HAE and U-HAE [16].

To our knowledge, no formal studies investigating the efficacy and safety of human C1-INH concentrate in patients with FXII-HAE or U-HAE have been conducted, however, a few observational studies have described the efficacy of human C1-INH concentrates in patients with FXII-HAE or U-HAE [16, 17]. The results of the current observational analysis demonstrate that human C1-INH concentrate may be an effective treatment for acute attacks of angioedema

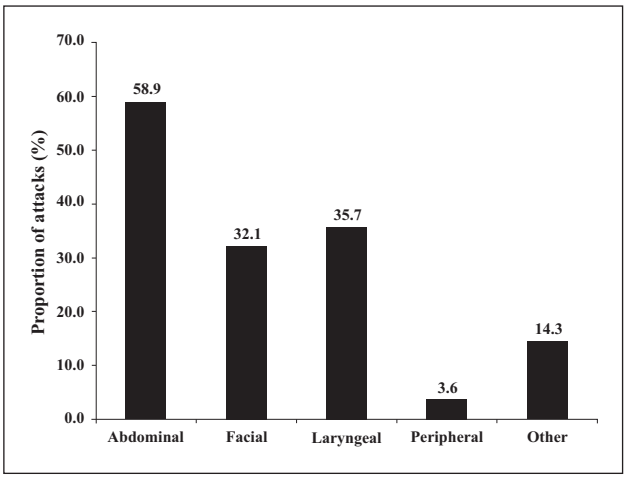

Figure 1. Proportion of C1-INH-HAE attacks treated with human C1-INH concentrate (Berinert®) in the efficacy analysis set (n = 17) stratified by anatomical location; 56 attacks occurred at a defined location and some patients experienced attacks that occurred at more than one location.

in patients with FXII-HAE and U-HAE. Of the 38 documented human C1-INH concentrate-treated attacks for which response data was available, a treatment response occurred within 60 minutes in the majority of patients. Only, two angioedema attacks required additional administration of Berinert®. These findings are consistent with previous reports of patients with FXII-HAE or U-HAE [16, 17] and the efficacy observed in this study is also similar to that seen in patients with C1-INH-HAE [12, 13]. Furthermore, no additional safety concerns were identified in this study.

Currently, there is no consensus on how to treat FXII-HAE and U-HAE, as international guidelines largely rely on experience with C1-INH-HAE [1]. Tranexamic acid could be used to prevent or improve angioedema attacks [22, 23]. The bradykinin β2 receptor antagonist, icatibant, and human C1-INH concentrate have been shown to be effective in C1-INH-HAE patients [13, 24-26] and this combination is approved in such patients in the European Union [1]. Icatibant has also demonstrated preliminary efficacy in three cases of women with FXII-HAE or U-HAE [27]. Nevertheless, the safety and efficacy of icatibant needs to be further examined.

There are a few limitations to this study. Only a small number of patients were investigated and not all of these were prospectively analysed for treatment response. However, as FXII-HAE and U-HAE are rare forms of HAE, it is unlikely that many patients in France will be identified. As such, we believe this study provides important information on the feasibility of treatment of FXII-HAE and U-HAE with human C1-INH concentrate.

In conclusion, although data on treatment response are currently limited, the COBRA registry offers the opportunity to systematically evaluate the long-term efficacy and safety of plasma-derived human C1-INH concentrate in patients with FXII-HAE or U-HAE, and our results suggest that human C1-INH concentrate may be a safe and efficacious treatment option in this patient population. ■

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