

Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients

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Abstract

Background: Hereditary angioedema (HAE) due to the deficiency of C1 inhibitor (C1-INH) causes chronically recurrent cutaneous, abdominal and laryngeal angioedema that are disabling and potentially life-threatening.

Objective: We designed a prospective study to quantify the residual disease in patients with HAE treated according to the existing consensus documents.

Methods: Data were collected from diaries recording occurrence, duration, location and treatment of acute angioedema attacks. A total of 386 semesters properly completed were analyzed. Forty-seven of 103 patients were on prophylactic treatment, 41 with attenuated androgens and six with tranexamic acid. A total of 1532 angioedema attacks (one every 45.3 days) were registered.

Results: Peripheral attacks were the most frequent (698), followed by abdominal (503) and combined locations (232), laryngeal edema was less common (99). Patients on prophylaxis with attenuated androgens had 7.7 attacks/year lasting 1.47 days, those on tranexamic acid had 8.1 attacks/year lasting 1.59 days, and those without prophylaxis had 8.9 attacks/year lasting 1.68. Plasma-derived C1-INH was used by 44 patients to treat a total of 376 acute attacks that resolved faster (1.1 day) than those not treated (1.85 day) or treated with tranexamic acid (1.79 day). No adverse events related to C1-INH infusion were reported.

Conclusion: Our data demonstrate that tranexamic acid is not effective in the treatment of acute attacks and indicate that under the current therapeutic approach, the HAE related disability is effectively but partially reduced. Incomplete success does not appear to depend on limited efficacy of the drugs but on their limited use that can be overcome by implementing specific treatment strategies.

Hereditary angioedema (HAE) caused by deficiency of C1 esterase inhibitor (C1-INH) is a rare genetic disorder. The minimum prevalence, documented with a country-based study in Denmark, is 1.41 every 100 000 inhabitants, while the estimated prevalence ranges between one and three every 50 000 (1, 2). The disease has been recognized in almost any ethnic group (3). Patients with HAE suffer from self-limiting, episodic swellings of the extremities. Facial and pharyngeal involvement is frequent, and laryngeal edema with death for asphyxia may occur (4). Characteristic of HAE is recurrent severe abdominal pain, in which edema of the gastrointestinal mucosa may cause temporary bowel occlusion responsible for resulting symptoms (5). Attacks start early in life, mostly before or around puberty, they last between 1 and 5 days with typical progression over the first 24 h, followed by a

plateau and slow regression within 72 (6). It is not unusual for attacks to start at one location and spread to another before resolving. During angioedema bouts, patients are partially or totally unable to perform daily activities. The clinical expression of HAE is extremely variable from patient to patient and even in the same patient from episode to episode. Such variability is not directly related to the genetic defect; even within the same family, there are subjects who develop minimal symptoms, whereas others may present attacks every 5 days (7).

Therapies for HAE have been available for more than 30 years. Attenuated androgens, given long term, are effective in reducing attack frequency and severity (8). Plasma-derived human C1-INH (pdC1-INH) concentrate, widely used in Europe since 1985 and recently approved by FDA, has

proved efficacy in treatment of acute attacks (9). New drugs and new therapeutic approaches for HAE have recently been tested in clinical trials and in some case, received marketing approval (10).

Consensus documents provide indications for the use of existing drugs in patients with HAE, but the benefit of these indications has never been assessed (11–13). Therefore, we planned a prospective study aimed to provide information on angioedema recurrences in Italian patients with HAE to define the residual burden of the disease when effective treatments are available and used within the recommendations of the consensus documents.

Methods

Semestral diaries, prepared by the CSL Behring to record angioedema attacks, were sent each year between 2004 and 2008 by the Italian Association of Patients with Hereditary Angioedema (IAHAE) to all registered patients. HAE diagnosis had been established based on family and/or personal history of recurrent angioedema without major urticaria and evidence of functional C1-INH plasma levels below 50% of normal values. Normal C1-INH values in our laboratory range between 70% and 130% (2.5 and 97.5 percentile) of normal pooled plasma. For those patients without evidence of C1-INH deficiency within the family, the genetic origin of the disease was confirmed by evidence of mutation in C1-INH gene (SERPING1) (14). C1-INH functional levels were measured using a chromogenic assay (Technochrom C1-inhibitor, Technoclone GmbH, Vienna, Austria).

The study protocol was approved by our Institutional Review Board, and patients gave their informed consent before participating in the study. Diaries were mailed to 570 patients and returned, properly completed, by 103. Forty-four were men and 59 women, median age 39.2 (range 11–83), 98 had HAE type I (low C1-INH antigenic and functional levels) and five had HAE type II (normal C1-INH antigenic levels, but low function) (Table 1).

Total number of semesters completed for analysis was 386. Patients were asked to provide information on their long-term treatment and fill in, at the occurrence of each angioedema attack, the date of beginning and end, location, severity, treatment and degree of impairment of daily activities.

All patients had 2000 units of pdC1-INH available at home (Berinert P, CSL Behring Marburg) for treatment of angioedema attacks. According to the treatment consensus attacks to be treated were those involving face, neck and oral/upper airways mucosa and those abdominal attacks with moderate to severe pain. For peripheral and mild abdominal attacks, the recommendation was to start tranexamic acid

(1 g, 20 mg/kg for children, every 4 h orally) or use pdC1-INH, based on the attack-related inability (13). PdC1-INH infusions were performed by medical personnel (family physician or local hospital) in 100 patients; three patients adopted the practice of self-infusion. The suggested dose was 1000 units, 500 for children below 40 kg, given i.v. with the possibility to be repeated if needed. At this writing, doses of Berinert P for treatment of attacks in HAE patients have been increased to 20 U/kg based on the evidence provided by Craig et al. (9) in a recent controlled study.

Long-term prophylaxis was considered for patients older than 4 years of age, and not pregnant, with more than one severely disabling angioedema attack per month. For women in reproductive age and patients under 18, the first choice was tranexamic acid, and for adult men, attenuated androgens that represented the second choice for adult women and patients above 14 not responding to tranexamic acid. None of our patient was on long-term prophylaxis with pdC1-INH.

Statistical analysis

Data are reported as median and interquartile range (25th and 75th percentiles). Differences between groups were evaluated by Mann–Whitney nonparametric test. Significance level was set at $P < 0.05$.

Results

Forty-seven of 103 patients were on prophylactic treatment, six with tranexamic acid and 41 with attenuated androgens (Table 2).

During the 386 semesters analyzed, a total of 1532 HAE acute attacks (one every 45.3 days of observation) were documented. Peripheral attacks were the most frequent (698), followed by abdominal (503) and combined locations (232). Laryngeal involvement was present in 6% of attacks (Table 3).

The distribution of patients, according to the frequency of attacks is reported in Table 4.

Patients on prophylaxis with attenuated androgens had less attacks (7.7/year) and slightly shorter (1.47 days) than those on tranexamic acid (8.1/year, lasting 1.59 days) and those without prophylaxis (8.9/year lasting 1.68), but none of these differences was statistically significant. Hence, in patients on attenuated androgens, we compared the number of attacks registered during the study period (7.7) with the average number of yearly attacks that the same patients had before

Table 1 Descriptive data of the patients

Number of patients	103
Median age (range)	39.2 (5–93)
Male/Female	44 (42.7%)/59 (57.3%)
HAE type I/II	98 (95.1%)/5 (4.9%)

Table 2 Frequency of hereditary angioedema attacks in patients with and without prophylactic treatment

Prophylactic treatment	Daily dosage range	Number of patients	Median number of attacks per year
Danazol	50–200 mg	37	7.6
Stanozolol	2–4 mg	4	7.9
Tranexamic acid	1.5–3 g	6	8.1
No prophylaxis		56	8.9

Table 3 Characteristics of hereditary angioedema attacks

Total number of attacks	1532
Days of duration	Median: 1.58 days (range: 1–8)
Duration of attacks without prophylaxis	Median: 1.68 days (range: 1–8)
Duration of attacks with prophylaxis	
Attenuated androgens	Median: 1.47 days (range: 1–7)
Antifibrinolytics	Median: 1.59 days (range: 1–5)
Location of attacks	
Peripheral	698
Abdominal	503
Laryngeal	99
Mixed	232

Table 4 Distribution of patients according to the frequency of attacks

Number of attacks per year	Number of patients (%)
>12	23 (22.3)
6–12 attacks/year	24 (23.3)
1–5 attacks/year	38 (36.9)
<1 attack/year	13 (12.6)
No attacks	5 (4.9)

treatment (14.3), as reported in their files, and found that this difference was highly statistically significant ($P < 0.01$).

Treatment of angioedema attacks was performed with pdC1-INH (376) or tranexamic acid (212), but the majority, 944, remained untreated. The choice of treatment varied depending on the location of the attacks: nearly all laryngeal attacks, and a relevant number of abdominal attacks, were treated with pdC1-INH. Peripheral attacks were mostly not treated or treated with tranexamic acid (Table 5a,b).

Duration of attacks was significantly shorter when pdC1-INH was used compared to no treatment or treatment with tranexamic acid ($P < 0.01$) (Table 6a–c).

Furthermore, attacks treated with tranexamic acid were not significantly shorter than untreated attacks.

No adverse event related to pdC1-INH or to tranexamic acid was reported.

Discussion

Physicians treating HAE can rely on established diagnostic criteria and therapies (7, 11–13), but not on the actual effect that these therapies have in reducing the burden of the disease. HAE is a periodic disorder where potentially life-threatening episodes of angioedema alternate with perfect well-being. Absence of data documenting how these episodes impact in patients' life, and how therapy modifies such an impact, prevents from establishing a therapeutic plan with prognostic prospective. Furthermore, the economic value of a treatment for HAE is undefined and prevent planning for both, pharma-

Table 5 Characteristics of hereditary angioedema attacks treated with (a) C1-INH concentrate (b) tranexamic acid

(a)	
Total number of attacks treated with Berinert P	376
Total number of patients treated with Berinert P	44
Total number of patients home infused with Berinert P	3
Duration of treated attacks (Median)	1.10 days
Duration of attacks not treated with C1-INH concentrate (Median)	1.85 days
Duration of treated attacks home infused (Median)	1.02 days
Location of treated attacks	
Peripheral	60
Abdominal	164
Laryngeal	94
Mixed	58
(b)	
Total number of attacks treated with Tranexamic acid	212
Total number of patients treated with Tranexamic acid	29
Duration of attacks treated with Tranexamic acid	1.79 days
Location of treated attacks (%)	
Peripheral	88 (41.50)
Abdominal	76 (35.84)
Laryngeal	2 (0.94)
Mixed	46 (21.69)

ceutical companies that develop therapies for HAE and health care providers that support coverage of expenses (15).

The results of our study demonstrate that an Italian population of patients with HAE, who has access to established treatments, has an average frequency of eight angioedema attacks per year. Considering the mean length of each attack, this represents 13 days each year with angioedema. This number is influenced by the treatments, both prophylactic and acute, that significantly reduce the days with symptoms. Patients on attenuated androgens have 11.2 days of angioedema per year. But because just patients with at least two severe, i.e., disabling, attacks per month are on attenuated androgens, they start from a minimum of 48 days of disabling angioedema each year pointing to an unquestionable efficacy of the treatment. Nevertheless, 1 day of angioedema per month is not negligible. Increasing the doses would probably further reduce the days with angioedema, but these drugs have important side-effects that are in part dose dependent, higher doses would further increase the existing concerns on the long-term safety of these products, and such an increase cannot be recommended (16).

The use of tranexamic acid to prevent attacks can be effective, but only in a small number of patients and therefore, we cannot rely on this drug to further reduce angioedema attacks in HAE.

Analyzing the treatment of acute attacks, two apparently contrasting facts are observed: pdC1-INH is effective and safe, but it is used only in a minority of attacks. Use of pdC1-INH, but not of tranexamic acid, provides, in fact, a significant reduction in duration of angioedema symptoms

Table 6 Duration of 376 acute attacks treated with (a) C1-INH and of 944 untreated acute attacks (b) C1-INH and of 212 acute attacks treated with tranexamic acid (c) tranexamic acid and of 944 untreated attacks

Treatment	Median (days)	25th percentile	75th percentile	P
(a)				
pdC1-INH	1.10	1	1.12	<0.01
No treatment	1.85	1.73	2.10	
(b)				
pdC1-INH	1.10	1	1.12	<0.01
Tranexamic acid	1.79	1.55	2.00	
(c)				
Tranexamic acid	1.79	1.55	2.00	>0.05
No treatment	1.85	1.73	2.10	

that shorten of 40% shorter, from 1.85 to 1.1 days, without significant side-effect.

There are several reasons that can explain the infrequent use of this effective therapy. First of all, the indication that was given in 1985 when this drug started to be used, as treatment for moderate to severe attacks, has frequently been elaborated by the patients as a wait and see policy aimed to treat attacks only when they are proved severe or life-threatening. Accordingly, 94 of 99 laryngeal attacks received this treatment compared to 33% of abdominal and <10% of cutaneous. Another cause for low use of pdC1-INH is the need, for the majority of patients, to be treated in the hospital emergency departments where physicians rotate. The uneasiness of having good chance for finding physicians not familiar with the disease patients from going to the hospital to receive pdC1-INH. Tendency to be very conservative in using pdC1-INH originates, in some patients, from a persistent idea, built on the history of HIV epidemics in Italian patients with hemophilia (17) and the transmission of HCV with an early nonviral inactivated preparation of pdC1-INH (18), that blood products still carry a significant infectious risk. Presence or absence of the problem of hospital treatment and the fear of infections end up creating two population of patients with HAE: one who frequently infuses pdC1-INH and one who never experiences such treatment even when needed (Table 7). The three patients who perform self-infusion at home account for 55.3% of all pdC1-INH infusions, and the 59 patients who never used pdC1-INH concentrate suffered from a total of 529 angioedema attacks, 170 of them abdominal. Nonetheless, over the years we found a progressive change in the approach to the acute treatment with pdC1-INH. In a survey that we made considering anamnistically the total use of pdC1-INH concentrate in our patients from 1980 to 2002, we found an average of 0.2 treatments per patient per year (19). This number has changed to 3.6 in this study, which constitutes a difference of almost 20 times. This finding cannot be justified only by taking into account the lower reliability of retrospective compared to prospective data. Advances in the manufacturing of plasma products that drastically improved safety and evidence that over several millions of treatments performed in 30 years, no

Table 7 Number of attacks and of pdC1-INH infusions in 103 patients with and without prophylaxis

Range of attacks	Number of patients in each range of attacks	Total number of attacks	Total number of pdC1-INH infusions
<1	4	0	0
1–5	37	104	13
6–15	32	329	37
16–30	14	296	28
31–60	13	497	90
61–90	2	154	56
>90	1	152	152

infection has ever been related to the pdC1-INH available in Italy (20), increase the use of pdC1-INH concentrate convincing patients previously reluctant because of the HIV/HCV epidemics of the 80's.

Our data documented for the first time that tranexamic acid is not effective in the treatment of acute attacks; median duration of angioedema is not modified by its use.

Based on these data, we conclude that in our patients who have access to the best standard of therapies, the burden of HAE is clearly reduced, but the disease still remains partially disabling. The reason for the persistent degree of disability cannot be directly related to a problem of efficacy of the available treatments and documented side-effects limit the use of attenuated androgen but not of pdC1-INH. Limiting factor for using this drug is logistic and in part cultural. Looking to the near future of patients with HAE, we see a larger use of early on demand therapy as the most promising tool for reducing the disease-related disability. Such a target can be reached implementing the home treatments by educating patients to perform self-infusion. A further improvement in this direction may also come from the new drugs that are accessing the market with administration routes that favor the use at home. Safety of this home treatment is now under evaluation. The policy of increasing early on demand treatments will certainly increase the cost for treatment and improve the quality of life of HAE. A pharmacoeconomic evaluation of this policy was outside the scope of this study but is needed to plan a more effective HAE treatment strategy for the future.

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Conflict of interest

MC has a consultancy agreement with Dyax, Jerini, Pharming, is on the advisory board for Jerini-Shire, Pharming, CSL Behring, Viro Pharma, Dyax and was an invited speaker for Jerini-Shire, Dyax, CSL Behring, Pharming, Viro Pharma. AZ was an invited speaker for Shire, CSL Behring and has a consultancy agreement for CSL Behring.

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