

Letter to the Editor

Prophylactic therapy in children with hereditary angioedema

To the Editor:

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is characterized by paroxysms of edema formation in the subcutis and/or the submucosa.¹ In 50% of patients, symptoms first occur during childhood or adolescence. Timely diagnosis and appropriate management are essential because of the severe consequences of edema formation.²

Management comprises therapy of attacks and prevention of their recurrence. Prophylaxis is a challenge for the clinicians, because of the narrow range of suitable medications and their poor safety profile, especially in children.

Only case reports³ and review articles^{4,5} have been published to date on the prophylactic treatment of pediatric patients with HAE, and reports on long-term follow-up studies of larger populations are lacking. International guidelines provide only meager advice on the management of children.⁶ Our objective was to present the algorithm we have designed, in observance of international recommendations, to guide the therapy of HAE.

A prospective analysis was conducted in 48 pediatric patients with HAE aged younger than 18 years. The study design is described (see this article's [Methods](#) section in the Online Repository at www.jacionline.org).

The patient group included 23 boys and 25 girls, 43 with type I and 5 with type II HAE. Their mean age at diagnosis was 7.6 years (range, 1-17 years). In 63% of these cases, the symptoms of HAE first occurred before 6 years of age, both in girls and in boys.

Patients were followed from diagnosis until the age of 18 years. The presented treatment regimen summarizes the experience of 24 years (1986-2010).

During the first year after diagnosis, 29 patients did not receive prophylaxis, 10 patients received intermittent prophylaxis (IMP), and 9 patients underwent long-term prophylaxis (LTP) with antifibrinolytics. The following is a discussion of the therapy since diagnosis.

Twenty-nine of the 48 patients were symptom-free at diagnosis. On reevaluating the frequency and severity of the manifestations 1 year later, 7 of 29 patients needed antifibrinolytic treatment: 4 received IMP and 3 received LTP with tranexamic acid (TXA). During the second year, 2 of the 3 patients who received LTP with TXA were switched to danazol, because of an increased number of attacks ([Fig 1, A](#)).

Compared with before treatment initiation, HAE attacks did not occur or followed a milder course and their duration halved during IMP with TXA initiated in 10 patients at diagnosis. In this group, the mean yearly attack number decreased from 6.8 (range, 2-36) to 4.5 (range, 1-12) after introducing therapy. In the first year, 3 of these patients were switched to LTP (1 to TXA, and 2 to danazol; [Fig 1, B](#)). In the second year, 2 of these 3 patients also received IMP with human plasma-derived C1-INH (hpdC1-INH) concentrate (Berinert; CSL Behring, Marburg, Germany) as described below. Until now, they have not required further prophylactic treatment.

Patient 1: Unwanted pregnancy occurred in a 15-year-old girl on LTP with TXA, which no longer controlled her attacks. We introduced intermittent substitution of hpdC1-INH concentrate

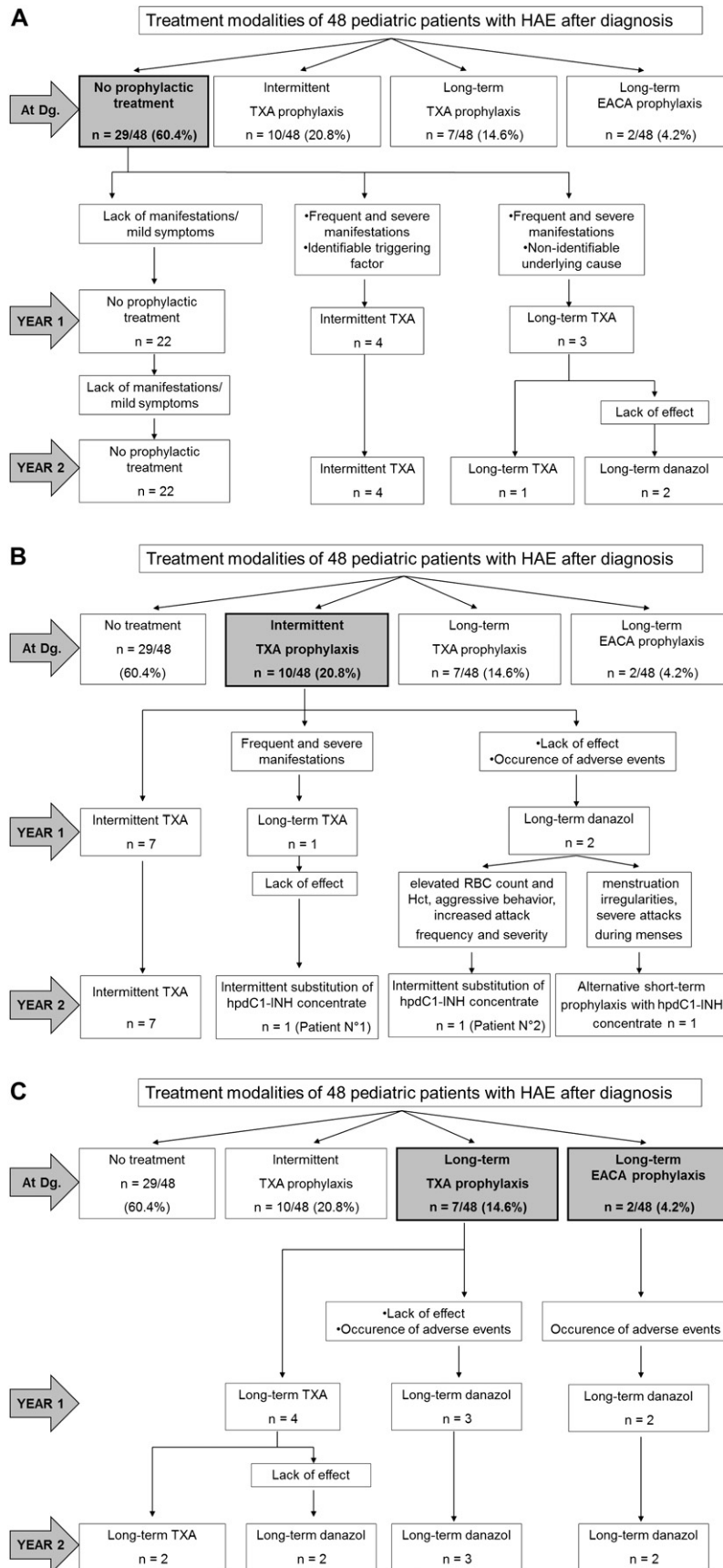
(500 IU given twice weekly) for the first trimester of pregnancy, and, subsequently, attacks occurred less frequently ([Fig 1, B](#)).

Patient 2: Although this patient did not experience attacks initially during LTP with danazol, the number of attacks increased subsequently. In addition, the patient developed erythrocytosis, polycythemia, thrombocytopenia, and became aggressive. We discontinued danazol and introduced IMP with hpdC1-INH concentrate (500 IU once a week) for 2 months. During this period, only mild, cutaneous edema occurred occasionally, and hematologic abnormalities resolved after discontinuation of danazol ([Fig 1, B](#)).

At diagnosis, 9 of the 48 patients were receiving LTP with antifibrinolytics for frequent and severe symptoms: 2 were taking epsilon-aminocaproic acid and 7 were taking TXA. In this group, the mean yearly attack number decreased from 6.2 (range, 3-12) to 3 (range, 1-10) when introducing therapy on diagnosis. One year later, 5 of these 9 patients were switched from antifibrinolytics to long-term danazol therapy, because of adverse effects (2 patients) or an increased frequency of symptoms (3 patients) ([Fig 2](#)). During the second year, TXA was replaced with danazol in an additional 2 patients, because of adverse reactions or unsatisfactory efficacy ([Fig 1, C](#)). Additional results are described (see this article's [Results](#) section in the Online Repository at www.jacionline.org).

In the whole population of pediatric patients with HAE 60.4% (29/48) did not require prophylaxis after diagnosis, and 17 of 27 patients who received a diagnosis younger than age 6 years did not require prophylaxis; this was in agreement with the literature.⁶ At diagnosis, LTP was introduced in 18.7% (9/48) of patients, in case edematous attacks recurred frequently (≥ 1 attack per month), or the patient's history contained life-threatening episodes. This rate is in contrast with the management of adults, whereby 39% of our patients are receiving LTP. By the age of 18, 13 of 30 patients were receiving LTP (43%), which is similar to the rate seen in adults. According to the guidelines, antifibrinolytics are the agents of choice for prophylaxis in pediatric patients.⁶ Their use is seldom contraindicated; thrombophilia is the primary excluding factor. TXA had a good therapeutic effect in approximately one-third of our patients, similar to the results of Zanichelli et al.⁷ Nevertheless, because TXA is safer than attenuated androgens, the former was chosen to initiate prophylaxis in pediatric patients. Because TXA may not prove sufficiently effective, introducing anabolic androgens may be necessary in a proportion of cases.⁶ When administered at the lowest effective dose, danazol appeared well tolerated. IMP was preferred whenever allowed by the patient's condition. During IMP with TXA in 22.9% (11/48) of our patients, edematous attacks did not occur or their duration and severity decreased.

Considering that HAE is an uncommon disorder, our study is relatively large, because the data contain follow-up information from 48 patients. In our experience, the therapeutic modalities recommended for pediatric patients include the emergency therapy of attacks, as well as IMP with TXA or hpdC1-INH concentrate. We adopted individualized treatment, through many adjustments guided by regular monitoring, with the lowest effective drug doses. To obtain statistically homogeneous



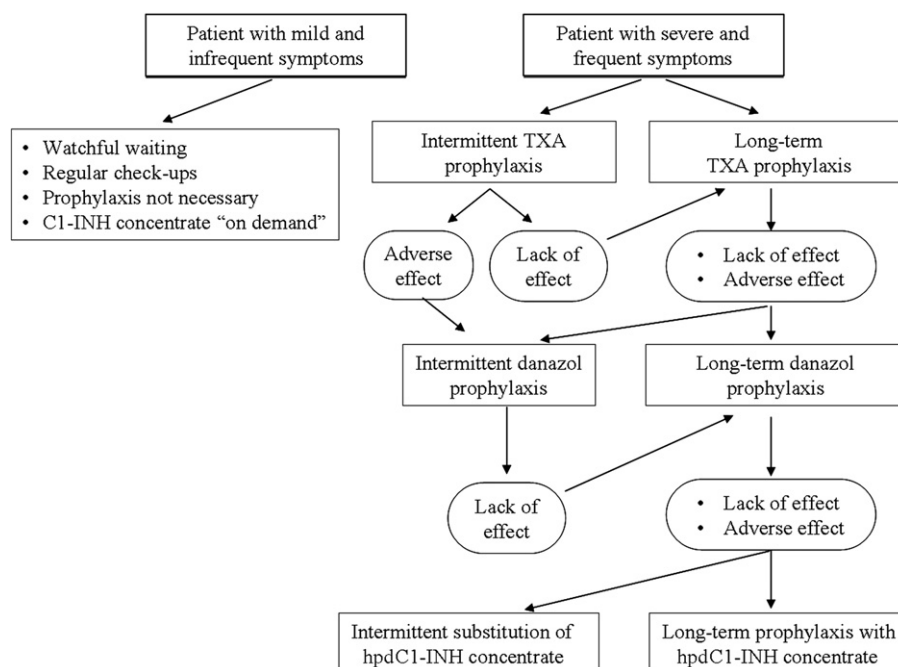


FIG 2. Therapeutic algorithm of prophylaxis in pediatric patients with HAE once the diagnosis had been established. The initial doses were based on a stepwise management strategy, for both the duration of treatment and the dose administered, as follows: intermittent or long-term TXA, 20 mg/kg per day; intermittent or long-term danazol, 100 mg every other day; and intermittent hpdC1-INH concentrate, 500 IU, 1-2 times/week (Berinert; CSL Behring, Marburg, Germany).

patient groups for comparison, these findings need confirmation in a large-scale, multicenter trial. Such a study might yield results that would justify reviewing the current treatment protocols.

Henriette Farkas, MD, PhD, DSc^a
Dorottya Csuka, MSc^a
Zsuzsanna Zotter, MD^a
Lilian Varga, PhD^a
George Füst, MD, PhD, DSc^a

From ^athe 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary. E-mail: farkash@kut.sote.hu.

Supported by the OTKA-NKTH 100886 grant (to H.F.).

Disclosure of potential conflict of interest: H. Farkas has received research support from OTKA-NKTH; has received consultancy fees and travel support from Shire, Pharming, Viropharma, and CSL Behring; and has received lecture fees from Shire. D. Csuka has received travel grants from CSL Behring, Shire, and Viropharma. L. Varga has received travel support from CSL Behring and Shire. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

- Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 2004;114(3 Suppl):S51-131.
- Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;119:267-74.
- Barakat A, Castaldo AJ. Hereditary angioedema: danazol therapy in a 5-year-old child. *Am J Dis Child* 1993;147:931-2.
- Sardana N, Craig TJ. Recent advances in management and treatment of hereditary angioedema. *Pediatrics* 2011;128:1173-80.
- Farkas H, Varga L, Szeplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. *Pediatrics* 2007;120:e713-22.
- Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;6:24.
- Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;66:192-6.

<http://dx.doi.org/10.1016/j.jaci.2012.08.001>

FIG 1. This flowchart represents our management strategy during the initial 2 years after diagnosis. **A**, Follow-up of patients not receiving treatment at the time of diagnosis. **B**, Follow-up of patients undergoing IMP with antifibrinolytics at the time of diagnosis. **C**, Follow-up of patients undergoing LTP with antifibrinolytics at the time of diagnosis. *Dg*, Diagnosis; *EACA*, epsilon-aminocaproic acid; *Hct*, hematocrit; *hpdC1-INH concentrate*, human plasma-derived C1-INH concentrate; *RBC*, red blood cell.

METHODS

Study design

After diagnosis, we asked the patients and their relatives to record disease symptoms to accumulate clinical information on the frequency, severity, duration, and localization of attacks, as well as on their triggering factors. Data on the symptoms were collected from patient diaries and medical charts. When a new drug was introduced, the patient was requested to record the name and dosage of the medication continuously, in the diary. In addition, patients were asked to record the consumption of hpdC1-inhibitor concentrate (Berinert; CSL Behring, Marburg, Germany) used either during attacks or as prophylaxis. hpdC1-inhibitor concentrate has been available in Hungary since 1986 (authorized for marketing in 1996). The clinical data thus obtained, as well as the findings of laboratory and imaging studies, were entered into the National HAE Registry.

Follow-up visits were scheduled at 6-month to 1-year intervals. Patients on intermittent or long-term prophylaxis were examined as follows.

In case of danazol prophylaxis, laboratory tests (complete blood count, liver and renal function tests, blood coagulation, serum lipid profile, and urinalysis) were repeated initially at 3-month intervals. Abdominal ultrasound scanning was performed semiannually during the first 2 years of treatment. Subsequently, asymptomatic persons or patients with mild symptoms were checked every 6 to 12 months to detect potential liver damage. Anthropometric assessments of growth were repeated every 6 months (comparison of body height and weight development to age-specific reference values and bone age determination with hand x-rays, when necessary). In addition, the development of secondary sexual characteristics, somatic and mental parameters, as well as the time of the onset of puberty, were compared with a control population. The somatic development of children with HAE was monitored regularly by family pediatricians, and the medical professionals employed by educational institutions. The tool used for this purpose was a percentile calculator that was based on reference data from the National Longitudinal Child Development Study conducted in Hungary.

In case of prophylaxis with antifibrinolytics, complete blood count, liver and renal function tests, blood coagulation, creatine kinase level, and urinary parameters were monitored just as with danazol. An ophthalmology review was performed semiannually during the initial 2 years of treatment and annually thereafter.

In case of intermittent prophylaxis with hpdC1-INH concentrate, virus serology tests for blood-borne pathogens (hepatitis B and C, HIV, parvovirus B19) were performed at baseline and during follow-up, at the annual control visits.

Treatment

The national HAE protocol, developed by our center, has been in use since 1992 for the diagnosis, management, and follow-up of patients. The therapeutic strategy was reassessed at the annual control visits.

1. Long-term prophylaxis (LTP)

We recommended LTP if the edematous attacks recurred frequently (≥ 1 attack per month), or the patient's history contained life-threatening episodes. An antifibrinolytic was proposed as the initial choice, unless the use of this agent was contraindicated.

a) Tranexamic acid (TXA)

TXA (Exacyl; Sanofi-Synthelabo Produtos Farmaceuticos SA, Porto Salvo, Portugal) 20 to 40 mg/kg initial daily was administered in 2 or 3 divided doses (maximum of 3 g/day). Epsilon-aminocaproic acid (EACA; 0.17–0.43 g/kg daily) had been used previously, when TXA was not yet available. The efficacy of these drugs was similar; however, EACA was not tolerable by the patients because of gastrointestinal side effects. Antifibrinolytics were avoided in suspected, active thromboembolic disease, or if the family history was positive for thrombophilia.

b) Danazol (Danoval; KRKA, Novo Mesto, Slovenia)

If antifibrinolytics failed to mitigate the frequency and severity of symptoms or caused serious adverse effects, we introduced an attenuated

androgen. Treatment was initiated with the lowest available dose of danazol (100 mg) taken every other day and titrated to the lowest effective maintenance dose (range, 33–200 mg/day, administered every 1–3 days). Potential adverse effects, such as decreased growth rate, hirsutism, behavioral disturbances, menstruation irregularities during puberty, myalgia, headache, elevation of serum transaminase levels, and changes of the lipid profile, were monitored.

2. We chose intermittent prophylaxis (IMP)

- in cases, with an increasing number and severity of edematous attacks (in comparison with that experienced previously), where the suspected underlying cause of this change was transient or could not be eliminated immediately; as well as
- when the patient was entering a period of increased attack frequency (examinations, flu season, wintertime, family crises, puberty, pregnancy). Medicinal products conventionally used for LTP were administered but for shorter periods of time (the median duration of IMP was 2 weeks and the range was 1–12 weeks) occasionally in combination with intermittent hpdC1-INH concentrate substitution (500 IU 1–2 times/week; maximum, 1000 IU 2 times/week). In addition, IMP with hpdC1-INH concentrate was introduced when the discontinuation of danazol became necessary because of the lack of effect or the occurrence of undesirable effects.

IMP is not mentioned in the international guidelines, although this term was used in relation to danazol treatment by Agostoni et al in 1978.^{E1}

- Alternative short-term prophylaxis was started 1 to 2 days before the expected date of each menses and continued for a week.

RESULTS

In the case of 30 patients, the observation period ended because these subjects turned 18 years of age. At this time, 3 of them were receiving an antifibrinolytic, and 10 were taking danazol for LTP. In our pediatric patient population, the mean age of patients starting prophylactic treatment with androgens was 11.4 years (range, 5–18 years).

These 10 patients received danazol for an average of 5.8 years, in a mean dose of 86 mg/day, whereas the 3 other patients received antifibrinolytics for 2.5 years on average, in a mean dose of 1262 mg/day.

The patients were followed for 6 years (range, 1–12 years) on average (median duration of follow-up was 7 years [interquartile range, 4–9 years]) from diagnosis until they turned 18 years of age. Nine patients had never received IMP/LTP during follow-up. The distribution of therapies in the individual age groups is shown in Table E1.

In regard to the safety profile of the medicinal products administered, some patients taking antifibrinolytics experienced gastrointestinal symptoms (such as abdominal discomfort, diarrhea, stomach ache, nausea), whereas irregular menstruation, erythrocytosis, polycythemia, and thrombocytopenia occurred in subjects who received danazol. Two of 17 patients (12%) taking TXA, 2 of 2 patients (100%) on EACA, and 2 of 11 patients (18%) receiving danazol experienced adverse events.

Compared with the age-specific percentiles of the Hungarian population, the somatic and mental development, the time of the appearance of secondary sexual characteristics, and the onset of puberty were normal in all patients taking danazol for LTP. Adverse events or seroconversion (regarding the viruses listed earlier) did not occur after treatment with hpdC1-INH concentrate.

REFERENCE

- Agostoni A, Marasini B, Cicardi M, Martignoni GC. Intermittent therapy with danazol in hereditary angioedema. *Lancet* 1978;1:453.

TABLE E1. Distribution of therapies administered at specific ages

	6 Years of age, no.	12 Years of age, no.	18 Years of age, no.
LTP with danazol	3	8	10
LTP with TXA	2	4	3
IMP with danazol	0	0	4
IMP with TXA	5	12	9
No prophylactic therapy	17	6	4