Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema

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BACKGROUND: C1-esterase inhibitor (C1-INH) replacement therapy is the treatment of choice for acute edema attacks in patients with hereditary angioedema (HAE).

STUDY DESIGN AND METHODS: Our retrospective, observational study assessed the efficacy and safety of home therapy with a human plasma-derived C1-INH concentrate (pC1-INH) in 20 pediatric patients with HAE who had previously been treated with physician-based therapy. While on home therapy, 15 patients received on-demand treatment and five received individual replacement treatment (IRT).

RESULTS: The switch to home therapy did not involve a significant increase in the dose of pC1-INH administered, but there was a significant increase in dosing frequency. Although only two patients were affected, the frequency of laryngeal attacks appeared to decrease on home therapy. All attacks, including laryngeal edema, were treated successfully during home therapy with pC1-INH. The mean annual number of days hospitalized was reduced from 3.8 during physician-based therapy to 0.11 during home therapy. No side effects or injection site complications were reported. The median time from onset of attack to administration of pC1-INH was reduced from 67.5 minutes during physician-based therapy to 15 minutes after switching to home therapy. The corresponding median time to initial symptom relief for all types of attack was reduced from 60 to 40 minutes.

CONCLUSION: As in adults, home therapy with pC1-INH is effective and safe in the treatment of HAE attacks in pediatric patients; a larger, randomized study should ideally confirm our findings before this approach can be considered the standard of care for pediatric patients.

Hereditary angioedema (HAE) is a rare autosomal dominant disease that results from a functional deficiency of C1-esterase inhibitor (C1-INH); this deficiency is either inherited or, in up to 20% of patients, the result of new mutations.[1,2] C1-INH is a serine-protease inhibitor that is important in controlling vascular permeability by acting on the initial phase of activation in the complement, coagulation, contact, and fibrinolytic systems.[3,4] The functional deficiency of C1-INH permits activation of plasma kallikrein and Factor (F)XIIa, with the subsequent release of bradykinin, which is a key mediator of vascular permeability.[5]

There are two main types of HAE: Type I affects approximately 85% of patients and results from a deficiency in functionally intact C1-INH; the less common Type II results from a dysfunctional form of C1-INH circulating at normal or elevated plasma concentrations.[2] A third, extremely rare type of HAE, Type III, is characterized by normal C1-INH levels and mutations in the coagulation FXII gene.[6,7]

The clinical symptoms are similar for all types of HAE. Patients experience recurrent, acute attacks of edema that can affect any body location.[8] The main locations affected are the skin and subcutaneous tissues or mucous

ABBREVIATIONS: C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema; IRT = individual replacement treatment; pC1-INH = plasma-derived C1-INH concentrate.

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membranes, often the gastrointestinal tract with colic attacks, and rarely the upper airways; the latter type of attack (laryngeal edema) can be potentially life-threatening.[8,9] An untreated attack typically lasts for 1 to 7 days, followed by a variable, attack-free interval.[10] Onset of the next attack and its location are unpredictable, but triggering factors can include emotional stress and mechanical trauma, infectious diseases, and intake of estrogens and angiotensin-converting enzyme inhibitors.[8,10]

International consensus documents recommend that patients with HAE who experience severe attacks should be treated at the earliest opportunity with plasma-derived C1-INH concentrate (pC1-INH).[11-13] A recent placebo-controlled study in patients with Type I or II HAE confirmed that pC1-INH administered at a weight-based dose of 20 U/kg induced initial symptom relief from acute abdominal and facial attacks within a median of 30 minutes.[14] In addition, an open-label extension to this study showed that the 20 U/kg dose of pC1-INH also induced initial symptom relief from acute peripheral attacks within a median of 30 minutes.[15] The same extension study showed that life-threatening laryngeal attacks are especially well controlled by this dose of pC1-INH, with initial symptom relief within a median of 15 minutes.[16]

A practical limitation of C1-INH replacement therapy is the need for intravenous (IV) administration, which usually involves patients having to travel to a suitable clinic or local physician for treatment. Any time delay incurred in starting treatment can exacerbate the severity of angioedema attacks. As a result, patients may need to be hospitalized, and in the case of laryngeal attacks the risk of asphyxiation can increase with any delay in administering treatment.[9,17]

Self-administration of pC1-INH at home (hereafter referred to as "home therapy") by adults can be a viable alternative to enable treatment of acute attacks at an earlier stage than with physician-based therapy, thereby reducing the severity of attacks and resulting in an improved quality of life.[13,18] However, the feasibility of using home therapy for treating acute attacks in pediatric patients, involving either self-administration of pC1-INH or administration by parents, is still debated.[13,19]

Here we report on our experience of treating acute HAE attacks in pediatric patients with pC1-INH using home therapy under the supervision of our clinic. These patients had previously been treated with pC1-INH using physician-based therapy, for which they first had to travel to our clinic or a local physician to receive their treatment. The objective of our study was therefore to compare the efficacy and safety of C1-INH therapy before and after switching from physician-based therapy to home therapy, thereby providing an assessment of the benefits of home therapy in the treatment of pediatric patients with HAE.

MATERIALS AND METHODS

Our clinic currently cares for 558 patients with HAE, including 113 pediatric patients (as of September 2010), in all cases using individualized therapeutic approaches. In addition to physician-based therapy with pC1-INH for the treatment of angioedema attacks, home therapy with pC1-INH has been practiced by adult patients in our care since 1982. The approach used is similar to that in the home-based treatment of hemophilia.[20] At present, 27 of our pediatric patients (24%) practice home therapy either as on-demand treatment or as individual replacement treatment (IRT; as defined below).

The pediatric patients were eligible for home therapy if they met the following criteria: proven functional C1-INH deficiency, generally more than one severe attack per month, willing and able to learn and perform self-infusion or (for a parent administering the treatment) to apply the infusion, suitable venous access, able to recognize early signs of an evolving attack or edema symptoms in a progressing attack, willing to contact health care professionals at our clinic for advice before administering the infusion at home, able to manage a dedicated stock of pC1-INH at home to ensure continuous product availability.

Patients qualified for home therapy only after they had successfully demonstrated self-administration of pC1-INH in our clinic under the supervision of a health care professional or after their parents had demonstrated that they could administer pC1-INH successfully. In addition, our clinic ensured that a physician was available to provide medical advice to patients on home therapy at all times.

Training for the administration of pC1-INH included providing written instructions and personal training by health care professionals (hemophilia nurses). The aim of the training was to ensure that patients or their parents were familiar with the relevant medical and technical aspects of home therapy, including:

- Drug storage, including the need to maintain sufficient reserve drug for use in case of emergency (e.g., for treating laryngeal attacks);
- Reconstitution of the lyophilized pC1-INH preparation and ability to fill the syringe while maintaining sterile conditions;
- Disinfection of the injection site;
- Peripheral venous puncture technique, including appropriate care of peripheral veins;
- Management of any treatment-associated side effects;
- Documentation in a diary of the date, location, and severity of an HAE attack before starting the infusion, together with documentation of possible triggering factors, side effects, absence from school, and hospitalization;

- Documentation that the recommended dose of pC1-INH was administered, including details of the drug name and batch number.

The patients or their parents were also trained to recognize the early clinical symptoms of laryngeal attacks and to start self-administration of pC1-INH at the earliest opportunity if a laryngeal attack was suspected. The training measures included impressing upon patients or parents that they must then call an emergency medical service and report an "emergency case of potential suffocation due to an HAE attack arising from C1-INH deficiency" at the slightest sign of a lack of treatment effect or worsening of symptoms after treatment for a laryngeal attack. In such a situation, the patients or parents were instructed to take their reserve drug with them to the emergency room.

The recommended dose of the pC1-INH preparation used in our study (Berinert P, CSL Behring, Marburg, Germany) to treat each acute attack was 500 or 1000 U, depending on the patient's body weight and clinical history. The pC1-INH was administered IV in a peripheral vein. In case of potentially life-threatening laryngeal edema, a second dose could be given after receiving advice from the clinic.

Depending on the medical need and individual course of HAE, patients who switched to home therapy consistently used either on-demand treatment or IRT for treating their acute attacks. On-demand treatment involved self-administration of pC1-INH at home on presentation of edema or other typical symptoms of an attack after consulting with our clinic. IRT involved self-administration of pC1-INH at home after early signs for the onset of an attack (e.g., pain, nausea, typical skin irritation, croakiness), before the onset of edema. Patients on IRT generally had high rates of severe attacks (one or more per week), while patients using on-demand treatment generally had lower attack rates (maximum of three per month). Each patient was assessed at the clinic at least twice a year. Annual serologic tests were performed for human immunodeficiency virus (HIV) and hepatitis A, B, C, and G.

The population for this retrospective, observational study was drawn from pediatric patients in our care who previously had their HAE attacks treated with pC1-INH using physician-based therapy and had then been switched to home therapy. We identified 27 patients from 7.0 to 17.7 years of age who could potentially provide suitable data for comparing the feasibility, efficacy, and safety of their current home therapy with their earlier physician-based therapy. Twenty of these patients agreed to be included in the study. The remaining seven patients did not respond to our request to participate in the study. Although this was an observational study with no study-specific interventions, according to local regulations ethical approval was obtained for the conduct of study.

After obtaining parental agreement in writing for the children to participate in this study, we gathered information using a questionnaire to be completed by the patients and/or their parents and by consulting our clinic's records based on the patients' HAE diaries. Data obtained included age at start of home therapy, type of regimen (on-demand treatment or IRT), number of treatments (including treatment of laryngeal attacks), dose of pC1-INH, side effects, days hospitalized, and absence from school. For each attack, the times from initial signs (in patients on IRT) or edema symptoms (in patients using on-demand treatment) to start of treatment with pC1-INH, and from start of treatment to initial symptom relief, were recorded.

The data for home therapy, and the corresponding data for the previous physician-based therapy, were summarized using descriptive statistics, and statistical comparisons were made using the Wilcoxon signed rank test. For each comparison, the analyses were also conducted separately for on-demand treatment and IRT.

RESULTS

The median age of the 20 pediatric patients included in our study was 14.0 years (range, 7.0 to 17.7 years) at the time of data collection. Sixteen patients had Type I HAE and four had Type II HAE. After switching to home therapy, 15 patients used on-demand treatment (median age, 13.2 years; range, 7.0 to 17.7 years), 12 with Type I HAE and three with Type II HAE. Five patients used IRT (median age, 14.5 years; range, 10.5 to 16.8 years), four with Type I HAE and one with Type II HAE. Thus the median age at the time of switching to home therapy was comparable between the on-demand therapy and IRT groups. Six of the 20 patients administered the infusions themselves, while in the 14 remaining patients the infusions were administered by the parents.

At the time of data collection, the median duration of all 20 patients on home therapy was 3.0 years (range, 1.1 to 6.7 years). Cumulatively, these 20 patients had received home therapy with pC1-INH for 74.1 patient-years, during which approximately 2400 treatments were administered.

Across all patients, the median number of treatments (reflecting number of attacks) administered on home therapy (0.83 per month) was significantly higher than during the previous physician-based therapy (0.37 per month; Table 1). When analyzed separately for patients using on-demand treatment and IRT, the increases after switching to home therapy were not significant with on-demand treatment; the number of patients on IRT was low but showed a similar trend. With both regimens, there was a high degree of overlap between the ranges before and after switching to home therapy, suggesting that the differences seen may not have been relevant.

TABLE 1. Frequency of treatments, laryngeal attacks, and days hospitalized in pediatric patients on home therapy and during their previous physician-based therapy

	Physician-based therapy			Home therapy		
Parameter	All patients (n = 20)	On-demand treatment* (n = 15)	IRT* (n = 5)	All patients (n = 20)	On-demand treatment (n = 15)	IRT (n = 5)
Number of treatments/month						
Mean (SD)	1.6 (2.45)	0.48 (0.73)	4.8 (3.04)	2.7 (4.27)	0.55 (0.47)	9.2 (3.98)
Median (range)	0.37 (0-10)	0.17 (0-3)	4 (2-10)	0.83 (0.08-15)	0.33 (0.08-1.4)	10 (5-15)
Wilcoxon test				p = 0.003	p = 0.084	p = 0.063†
Number of laryngeal attacks/year‡						
Mean (SD)	0.70 (2.70)	0.80 (3.10)	0.40 (0.89)	0.25 (0.91)	0.27 (1.03)	0.20 (0.45)
Median (range)	0 (0-12)	0 (0-12)	0 (0-2)	0 (0-4)	0 (0-4)	0 (0-1)
Wilcoxon test				p = 0.500	p = 1.000	p = 1.000
Number of hospital days/year						
Mean (SD)	3.8 (12.15)	0.80 (1.08)	12.6 (23.8)	0.11 (0.46)	0.14 (0.53)	0 (0)
Median (range)	0 (0-55)	0 (0-3)	3 (0-55)	0 (0-2)	0 (0-2)	0 (0-0)
Wilcoxon test				p = 0.008	p = 0.063	p = 0.250

* Treatment regimen on home therapy after switching from physician-based therapy.
† The lowest achievable p value for five patients tested with the Wilcoxon signed rank test (p = 0.0625).
‡ Only two patients experienced laryngeal attacks; during home therapy one of these patients used on-demand treatment and the other patient used IRT.

Laryngeal attacks occurred in two patients, one using on-demand treatment and the other using IRT, in both cases while on home therapy and previously while on physician-based therapy. In both patients, the occurrence of laryngeal attacks decreased on home therapy, from 12 to 4 attacks per year in the patient using on-demand treatment and from two attacks to one attack per year in the patient on IRT (Table 1).

The mean number of days in hospital while on home therapy (0.11 days/year) was significantly lower than during the previous physician-based therapy (3.8 days/year), although this difference was exaggerated by the influence of one patient with a hospitalization rate of 55 days per year (Table 1). Mean data are quoted due to more than 50% of the patients reporting no hospitalization. None of the patients receiving IRT while on home therapy were hospitalized. Only nine patients reported having missed school due to HAE attacks while on home therapy, compared to 18 before switching from physician-based therapy.

In patients on home therapy, the median time from initial signs (in patients on IRT) or edema symptoms (in patients using on-demand treatment) to start of treatment with pC1-INH was significantly shorter with home therapy (15 min) than during the previous physician-based therapy (67.5 min; Fig. 1A). This trend was seen in patients using on-demand treatment and IRT (Figs. 1B and 1C). Similarly, the median time from start of treatment to initial symptom relief was significantly shorter with home therapy (40 min) than with physician-based therapy (60 min; Fig. 1A). This trend was also seen in patients using on-demand treatment and IRT (Figs. 1B and 1C). Due to the low number of patients on IRT, the differences compared to physician-based therapy could not reach statistical significance at the $p < 0.05$ level.

During physician-based therapy, the dose of pC1-INH administered per attack was consistently 500 U in 18 patients and 1000 U in two patients. These doses remained unchanged after switching to home therapy in 19 of the 20 patients treated, including the two patients who had laryngeal attacks. In one female patient on IRT, the dose had to be increased from 500 to 1000 U while on home therapy due to a considerable increase in body weight. All attacks, including potentially life-threatening laryngeal attacks, were treated successfully with pC1-INH administered as home therapy, with patients reporting rapid regression of their attacks.

In all patients, the administration of pC1-INH was safe and well tolerated while on home therapy as well as during their previous physician-based therapy. No side effects were reported retrospectively by any of the patients, including injection site–related effects. There were no cases of seroconversion for HIV or hepatitis A, B, C, and G.

DISCUSSION

In this retrospective, observational study we assessed the feasibility and effectiveness of home therapy with pC1-INH, given either as on-demand treatment or IRT, for the treatment of acute HAE attacks in pediatric patients. With both regimens, home therapy with pC1-INH under medical supervision was safe and effective. The median time from initial signs (in patients on IRT) or edema symptoms (in patients using on-demand treatment) of an attack to start of treatment was significantly shorter with home therapy (15 min) than before the switch from physician-based therapy (67.5 min). Furthermore, the median time from start of treatment to initial symptom relief was significantly shorter with home therapy (40 min) than before the switch from physician-based therapy (60 min).

Earlier studies have established the feasibility, efficacy, and safety of home therapy with pC1-INH in adults with HAE.[18,21-23] A recent international consensus document recommends consideration of home therapy for the treatment of all patients with HAE, irrespective of the frequency or severity of their angioedema attacks.[13] For pediatric patients, home therapy is recommended if a parent or other responsible adult is available and willing to receive training in the administration of pC1-INH. However, the consensus document also states that reliable data on the efficacy and safety of home therapy in pediatric patients are lacking.

Our observational study expands the positive experience of home therapy with pC1-INH in adults to pediatric patients, showing that home therapy given as on-demand treatment or IRT is also feasible and beneficial in these younger patients. One of the main benefits of home therapy is that the delay in commencing treatment is minimized because no time is lost by having to travel to a suitable clinic or local physician for the administration of pC1-INH. Particularly in the case of laryngeal attacks, any such delay can place patients at risk because an attack then has more opportunity to progress and become more severe.[9] Our data are consistent with observations in earlier studies in adults with HAE demonstrating that prompt treatment (within 2 hr of the onset of initial signs or edema symptoms) reduced the duration of attacks compared to when the start of treatment was delayed.[22,24,25] The median time to initial symptom relief while on home therapy in our

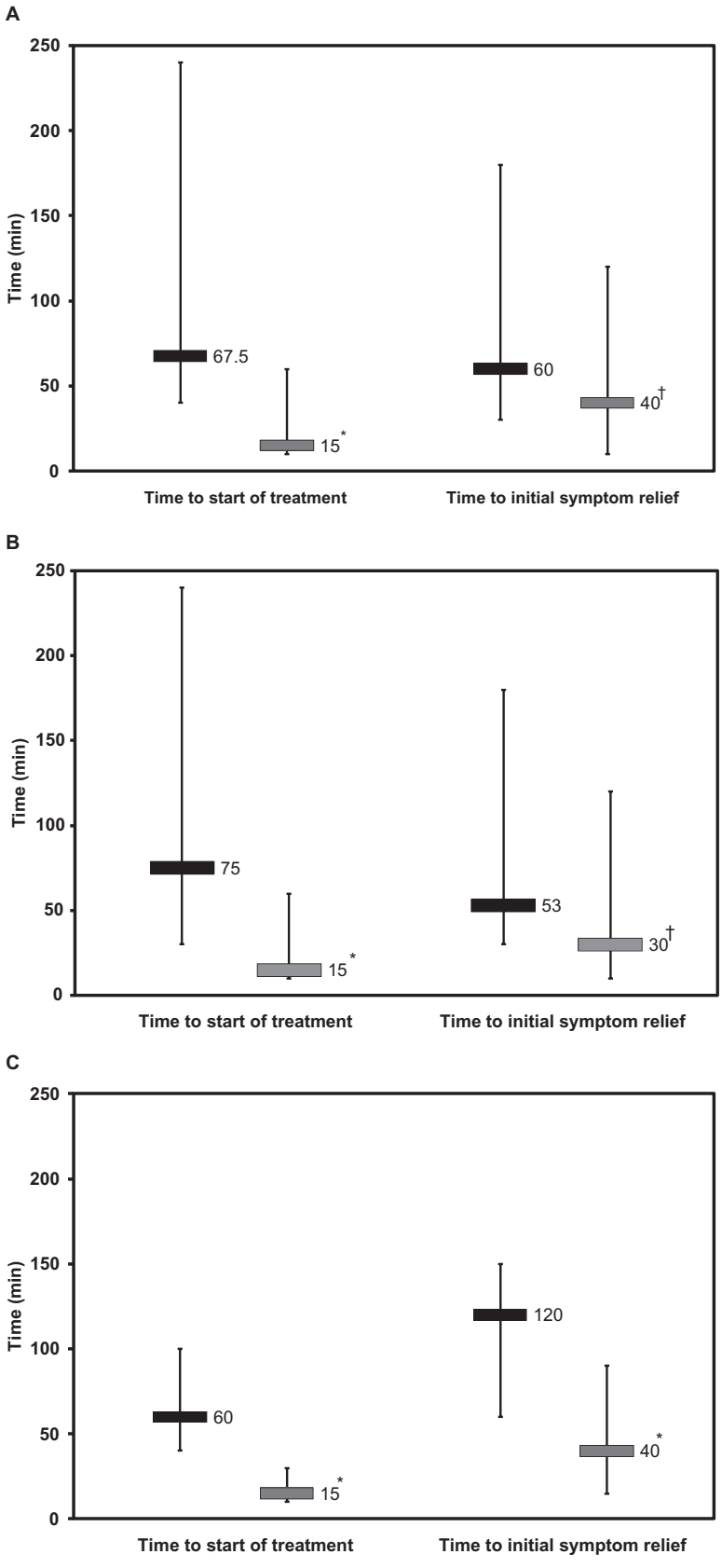

Fig. 1. (A) Median (range) time from initial signs or edema symptoms to start of treatment, and from start of treatment to initial symptom relief, in pediatric patients on home therapy (gray bars) and during their previous physician-based therapy (black bars; n = 20). (B) Median (range) time from initial edema symptoms to start of treatment, and from start of treatment to initial symptom relief, in pediatric patients using on-demand home therapy (gray bars) and during their previous physician-based therapy (black bars; n = 15). (C) Median (range) time from initial signs to start of treatment, and from start of treatment to initial symptom relief, in pediatric patients on IRT home therapy (gray bars) and during their previous physician-based therapy (black bars; n = 5).

observational study (40 min) was slightly longer than in a recent placebo-controlled study on the efficacy of the same pC1-INH preparation (30 min).[14] This difference may be due to the different methods used for collecting data in these two studies. The controlled study involved frequent questioning of the patients during an attack to establish the time of initial symptom relief, whereas our observational study involved a combination of consulting clinic records and retrospective questioning of the patients and/or their parents. In addition, a further limitation of our study is the relatively small number of patients providing data, which can result in a high degree of variability in the data obtained.

A recent review indicates that laryngeal attacks in pediatric patients with HAE should be treated immediately with pC1-INH, followed by hospitalization due to their potentially life-threatening nature.[17] Furthermore, the international consensus document recommends that patients with laryngeal attacks should self-administer pC1-INH at home while awaiting transfer to the hospital.[13] Based on our experience with home-based therapy of HAE, including treatment of laryngeal angioedema in adult patients since 1982, the training given to our pediatric patients on home therapy or their parents includes contingency measures in case of a lack of treatment effect or worsening of symptoms after treatment of a laryngeal attack (as described above). In practice, our experience has shown that the effective treatment of laryngeal attacks with pC1-INH administered at home has meant that subsequent hospitalization is not always necessary. Indeed, in our study, while only two patients experienced laryngeal attacks, neither needed to be hospitalized after treatment with pC1-INH.

Although our study included only two patients who experienced laryngeal attacks, a decrease was nevertheless seen in the frequency of laryngeal attacks in both of these patients while on home therapy, compared to the frequency reported during their previous physician-based therapy. This decrease in attack frequency suggests that administration of pC1-INH in the early stages of an attack while on home therapy, especially with IRT, may reduce any possible progression to laryngeal edema, which in turn would reduce the need for hospitalization without compromising patient safety. A further benefit of treatment with pC1-INH is that it provides particularly rapid relief from the symptoms of laryngeal edema; in a recent open-label study using the same pC1-INH preparation as our study, initial symptom relief occurred within a median of 15 minutes.[16] We therefore surmise that the early administration of pC1-INH with home therapy may be especially beneficial in the treatment of this potentially life-threatening type of attack.

After switching from physician-based therapy to home therapy, there was an increase in the median treatment frequency, from 0.37 treatments per month while on physician-based therapy to 0.83 treatments per month after switching to home therapy. This trend has also been reported in an earlier study in adults comparing home therapy with pC1-INH to physician-based therapy, although no explanation for this observation was proposed.[23] One explanation for this increase in treatment frequency in our study may lie with the effect of puberty in a majority of the patients in our study, who had a median age of 14.0 years. Puberty in pediatric patients with HAE may be associated with substantial changes in the course of the disease, such as clustering of edematous attacks, particularly in girls.[26] Consistent with this possible explanation, the majority of the patients in our study (13 of 20 patients) were girls, with a median age of 15.1 years (range, 7.0 to 17.7 years). Patients on IRT have the more severe disease compared to patients using on-demand treatment. It is therefore plausible that the hormonal changes associated with puberty have a greater effect on patients on IRT, which may explain why the increase in treatment frequency was particularly noticeable in this subgroup (comprising three girls and two boys).

The dose of pC1-INH administered per attack (500 or 1000 U) remained unchanged in 19 of the 20 patients after switching to home-based therapy. This observation concurs with previous studies on the benefits of home therapy with pC1-INH in adults, although in one study home therapy was associated with increased doses; this was attributed to previous undertreatment during physician-based treatment due to difficulties in accessing the emergency treatment required.[18]

Improvements in the quality of life of adults when switched to home therapy with pC1-INH, whether as on-demand treatment or IRT, have been reported in several studies.[18,25] Although quality of life was not formally assessed in our study, when switched to home therapy the pediatric patients in our study did experience decreases in time to initial symptom relief as well as decreases in extent of hospitalization and absence from school. These benefits, together with the lack of delay and inconvenience caused by having to travel to a suitable

clinic or local physician for treatment, indicate that the pediatric patients in our study should have experienced a clear improvement in their quality of life after switching from physician-based therapy to home therapy.

Home therapy with pC1-INH in adults has been reported to be as safe as when pC1-INH is administered in a hospital.[18] In agreement, no side effects were reported in our study by the patients or their parents while the patients were on home therapy or during their previous physician-based therapy. Side effects are rare during routine treatment with pC1-INH and are generally comparable to the side effects observed during placebo treatment.[27,28] This favorable safety profile has also been reported for adults on home therapy.[21] Technical problems when self-administering IV infusions were reported by fewer than 2% of adult patients on home therapy.[22] Thus, home therapy with pC1-INH has an excellent safety profile with no obvious disadvantages compared to physician-based therapy.

In conclusion, our findings suggest that home therapy of HAE attacks with pC1-INH is a safe and effective option in pediatric patients on condition that appropriate training is given to patients and their parents, and appropriate medical advice is available at all times. While our studies provide promising evidence in support of home therapy, a larger, randomized study should ideally confirm our findings before this approach can be considered the standard of care for treating acute attacks in pediatric patients with HAE.

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CONFLICT OF INTEREST

This study was supported by unrestricted grants from CSL Behring (Hattersheim, Germany). The authors have no conflicts of interest to disclose.

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