

Hereditary Angioedema: Long-Term Treatment with One or More Injections of C1 Inhibitor Concentrate per Week

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Key Words

Angioedema · Hereditary angioedema · C1 esterase inhibitor deficiency · C1 inhibitor concentrate · Long-term replacement treatment

Abstract

Background: Hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) is characterized by recurrent edema attacks in various organs. The objective of the present study was to assess the efficacy and safety of weekly long-term replacement treatment with one or more injections of plasma-derived C1-INH concentrate per week (WLTC) in patients with HAE-C1-INH. **Methods:** Nineteen patients with HAE-C1-INH underwent WLTC for 9 years on average. The benefits and risks were determined based on regular recording by the patients of the severity and number of attacks at the beginning and the end of the study. **Results:** All patients reported that all or most of their attacks were much less severe: the percentage of severe attacks was 93.3% without and 3.8% with treatment. In 8 of the 14 patients undergoing WLTC, the monthly number of attacks was lower at the end of the study than before the study, higher in 5 patients, and unchanged in 1 patient. The mean number of attacks per week in 6 patients (1 patient initially received weekly on-demand treatment for 2 years and then shifted to WLTC) with

weekly on-demand treatment was 4.3 (SD 1.9) at the beginning and 8.0 (SD 3.1) at the end of the study. **Conclusions:** HAE-C1-INH can be significantly improved by one or more injections of C1-INH concentrate per week. However, patients have to accept a large number of intravenous injections and, in some cases, an increase in disease activity.

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Introduction

Hereditary angioedema (HAE) is characterized by recurrent edema attacks in various organs. It may be caused by a genetically determined complement C1 inhibitor (C1-INH) deficiency, but sometimes it is not associated with a C1-INH deficiency [1–6]. The patients reported on in the present paper suffered from HAE due to genetic C1-INH deficiency (HAE-C1-INH).

Acute attacks of HAE-C1-INH can be successfully treated with a purified C1-INH concentrate derived from human plasma or with icatibant, a novel bradykinin B2-receptor antagonist [7–13]. Nevertheless, some patients that suffer from numerous attacks prefer receiving prophylactic rather than symptomatic treatment of acute attacks. Attenuated androgens are widely used in HAE patients for prophylactic long-term treatment [14–17], but

various side effects may occur [16, 18, 19]. Tranexamic acid, an antifibrinolytic agent, is also effective in the long-term prophylaxis of HAE [20]; in many patients, however, it is not sufficiently effective to prevent HAE attacks.

At present, the hope of many patients is directed toward a weekly long-term replacement therapy with C1-INH concentrate (WLTC), i.e. intravenous injections of C1-INH concentrate once or several times a week, as first described in 1989 in 2 patients with C1-INH deficiency [21]. In 2006, 10 patients with HAE-C1-INH were reported to have benefited from weekly injections of C1-INH concentrate for a mean period of 3.5 years [22]. Some patients simultaneously received danazol or tranexamic acid for long-term prophylaxis [22]. One patient benefited from regular injections of C1-INH concentrate for 20 weeks during pregnancy [23]. Recently, it was shown that treatment with 500–1,000 U of C1-INH concentrate up to twice a week was superior to a previous danazol prophylaxis in 22 patients who discontinued danazol due to unresponsiveness or severe side effects [24]; however, the duration of treatment with C1-INH concentrate was not reported. In sum, the available evidence about WLTC has been sparse up to now.

We studied the efficacy and safety of WLTC in 19 patients with HAE-C1-INH who received this medication 1–7 days per week for a period of up to 19 years. The following questions were addressed: (a) To what degree can the severity of HAE attacks be reduced? (b) Is it possible to completely avoid HAE attacks by using WLTC? (c) If not, to what degree can the number of attacks be reduced? Furthermore, adverse effects and potential long-term risks should be evaluated to inform patients who are considering this kind of treatment on what they may be confronted with in the future.

Material and Methods

Study Design

The data were collected in the frame of a prospective observational study. The benefits of WLTC were evaluated by comparing the number and severity of attacks at the beginning and the end (December 2008) of the study. Benefits and risks were assessed by reviews of regular recordings made by the patients.

Patients

Patients were surveyed at the Angioedema Outpatient Service of the Department of Dermatology, University of Mainz, Germany. The diagnosis of HAE-C1-INH was based on personal history, family history, and plasma examination of C1-INH function, C1-INH protein, and C4. All diagnoses were performed or confirmed at the Angioedema Outpatient Service. The 19 participants with

HAE-C1-INH received one or more intravenous injections of human plasma-derived C1-INH concentrate (Berinert P, CSL Behring, Marburg, Germany) per week because of frequent attacks. None of these patients simultaneously received another long-term treatment such as attenuated androgens or tranexamic acid. The injections were administered either by the patients themselves (9 patients), relatives (1 patient), the family doctor (7 patients), or at a hospital near the patient's place of residence (2 patients).

Data Collection

Patients were asked when the first clinical symptoms of HAE-C1-INH had occurred. Furthermore, they regularly recorded the time points, severity and location of the attacks before, during, or after WLTC. This reporting was done by means of a structured questionnaire; the weekly doses of C1-INH concentrate, responses to treatment, and possible side effects were recorded as well.

Laboratory

The laboratory diagnosis of C1-INH deficiency was made on the basis of plasma levels of functionally active C1-INH and C4 antigen. Plasma levels of C1-INH and C4 antigens were assayed by radial immunodiffusion (NOR Partigen C1-INH and C4, Dade-Behring, Marburg, Germany); C1-INH activity was determined using the chromogenic substrate C₂H₅CO-Lys(ε-Cbo)-Gly-Arg-pNA (Technochrom C1-Inhibitor, Technoclone, Vienna, Austria). Antibodies to C1-INH were determined according to the method described by Alsenz et al. [25].

Results

Nineteen patients – 17 women and 2 men – with HAE-C1-INH received WLTC for 9 years on average (SD 4.2 years, range 4–19 years). The total number of years of treatment was 175. Patient characteristics are listed in table 1. WLTC was performed in two ways: either as a weekly long-term replacement treatment with C1-INH concentrate (LRT) or as a treatment as soon as the first signs of attacks occurred (weekly treatment on demand with C1-INH concentrate, WTD).

The LRT group comprised 14 patients. In 10 of those 14 patients, treatment commenced within several months after the end of a long-term prophylaxis with danazol. In 9 patients, danazol was discontinued because of liver adenoma or other adverse effects. One patient switched from danazol to LRT because she feared adverse effects. Four other patients refused long-term prophylaxis with androgens because they feared adverse effects.

Six patients were included in the WTD group. Initially, those patients' attacks occurred less frequently than once per week. The patients then underwent WTD with C1-INH concentrate for 17 years on average (SD 6.4 years, range 10–29 years). During this time, the number of attacks kept increasing (see below), so that at a certain

point, a weekly occurrence was reached. At that time, WLTC was started, and patients were enrolled into our study. The period of WTD lasted 6.3 years on average (SD 3.2 years, range 2–12 years). One patient initially received WTD for 2 years and then shifted to LRT. Three of the six patients of this group (patients 16, 17, and 18) have been described earlier [26].

No patient received a concurrent medication with an angiotensin-converting enzyme inhibitor (ACE-I) or an estrogen; none had other risk factors, such as increased exposure to trauma or increased emotional stress, for an increased number of HAE attacks.

Weekly Dose

Initially, the weekly dose of LRT (table 2) was chosen according to the frequency of previous attacks and/or the previous response to treatment with C1-INH concentrate, as well as body weight. In 2 out of 14 patients, the weekly dose was lower at the end than at the beginning. In 4 patients, the weekly dose remained constant. Two of those 4 patients received only 500 U C1-INH concentrate weekly. In 8 patients, the weekly dose had to be increased during the course of LRT to maintain the therapeutic effect. The mean weekly doses were 1,253 U (SD 641 U, range 500–2,300 U) at the onset of treatment and 2,564 U (SD 1,835, range 500–7,000 U) at the end. The mean intervals between the days of injection per week were 4.4 (SD 2.1 days) at the beginning and 3.0 (SD 1.9 days) at the end of LRT. The number of days of injection per week ranged from 1 to 7. The total numbers of injection days per week in all LRT patients were 25.8 at the beginning and 44.6 at the end of LRT. At the end of the study, 2 patients needed the concentrate every 24 h, and 5 other patients, between 36 and 48 h to prevent the next HAE attack. The final weekly dose remained unchanged for 1–12 years among the 14 patients.

In the WTD patients, a dose of 500 U of C1-INH concentrate was effective in all 6 patients. Only patient 17 needed 1,000 U C1-inhibitor concentrate for 5 attacks per year during the last 3 years of the treatment period. Overall, the number of injections increased over time with the number of attacks. The mean weekly dose in patients on WTD was 500 U at the beginning (per definition) and increased up to 1,041 U (SD 307, range 500–1,400 U) by the end of the study.

Severity of Attacks

Patients reported that either all or most of their attacks became considerably less severe than before WLTC (fig. 1). Before treatment, the percentage of severe attacks

Table 1. Characteristics of 19 patients with HAE-C1-INH who received WLTC

Patients, n	19
Patients with HAE type I, n	18
Patient with HAE type II, n	1
Families, n	17
Age at the end of the study, years	51.8 ± 11.2 (range 35–78)
Gender, M/F	2/17
Age at onset of the first clinical symptoms of HAE, years	8.8 ± 6.1 (range 1–19)
<i>Laboratory results¹</i>	
Patients with HAE type I	
C1-INH protein, g/l	0.06 ± 0.02
C1-INH activity, %	8.0 ± 7.5
C4, g/l	0.07 ± 0.04
Patient with HAE type II	
C1-INH protein, g/l	0.59
C1-INH activity, %	7.0
C4, g/l	0.11

¹ Normal range for C1-INH protein: 0.15–0.35 g/l; normal range for C1-INH activity: 70–130%; normal range for C4, 0.20–0.50 g/l.

was 93.3%; at the end of the study, it was 3.8%. In the LRT group, 2 patients were free from attacks, 6 patients had only mild or very mild attacks, and 6 had mainly mild attacks but a few severe, sudden attacks. In the WTD group, patients mainly had mild or very mild attacks, and a few severe ones.

No patient reported a loss of effectiveness of the C1-INH concentrate during the course of WLTC. Any additional acute attacks in both subgroups were successfully treated with C1-INH concentrate.

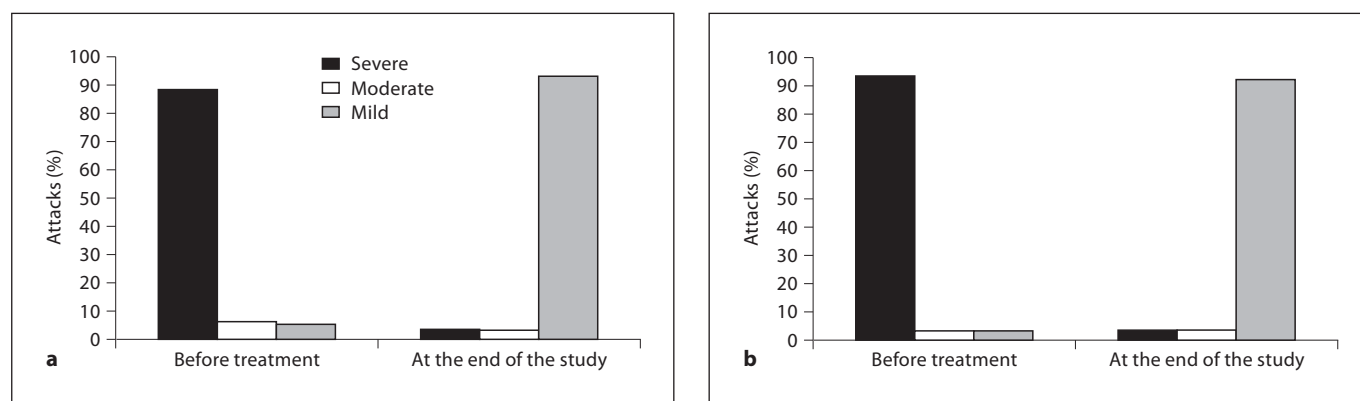
Six patients in the LRT group reported 2–4 extremely severe abdominal attacks occurring during the last 2–6 years of the study: abdominal pain developed rapidly, within 5 min to 1 h after the onset of the attack. No such attacks were reported before LRT. Five patients on LRT and 1 patient on WTD reported skin edema that occurred rapidly at 3–6 body sites simultaneously. These multilocal skin edemas had never occurred before LRT or WTD. All 5 patients received high doses of C1-INH concentrate (1,750–7,000 U per week).

Frequency of the Attacks

In 8 of the 14 patients in the LRT group, the number of attacks per month was lower during the last 12 months of the study compared with the time before LRT; it was

Table 2. LRT in HAE-C1-INH

Pat. No.	Duration of LRT years	At the beginning of LRT			At the end of the study					Number of attacks per month before LRT	Number of attacks per month at the end of LRT	Comments
		interval between injections days	days and dosage of C1-INH concentrate injections per week, U	total weekly dose, U	interval between injections days	days and dosage of C1-INH concentrate injections per week, U	total weekly dose, U	duration of the last dose years	mean time interval between a missed injection and the next attack, h			
1	19	2.3	3 × 500	1,500	2	3.5 × 500	1,750	4	3	5	3.5	
2	8	2.8	2.5 × 500	1,250	2	3.5 × 500	1,750	7	48	4	4	
3	11	7	1 × 500	500	3.5	2 × 500	1,000	10	12–24	2	2.5	
4	11	2.3	3 × 500	1,500	1.8	3.9 × 1,000	3,900	4	3–4	4	1.5	
5	5	3.5	2 × 500	1,000	3.5	2 × 1,000	2,000	1	6–12	3	6	
6	5	7	1 × 1,000	1,000	1	7 × 1,000	7,000	1.5	5–6	2.5	30	discontinued
7	7	3.5	2 × 1,000	2,000	3.5	2 × 2,000	2,000	7	24	1.1	4	discontinued
8	15	7	1 × 500	500	1	7 × 500	3,500	6	20–24	1.3	0	
9	6	7	1 × 500	500	7	1 × 500	500	6	>3 weeks	2.5	0	
10	12	3.5	2 × 1,000	2,000	1.9	3.7 × 1,000	3,700	3	18	7	1	
11	10	3	2.3 × 1,000	2,300	2	3.5 × 500	1,750	1.5	1–5	6	1.5	
12	5	3.5	2 × 500	1,000	3.5	2 × 500	1,000	5	48–72	1	6	
13	11	2.3	2 × 500, 1 × 1,000	2,000	2.8	2.5 × 500	1,250	5	24–48	8.4	2.7	
14	12	7	1 × 500	500	7	1 × 500	500	12	2–3 weeks	1.5	0.2	

**Fig. 1.** Severity of attacks in patients on LRT (a) and WTD (b).

higher in 5 patients and unchanged in 1 patient (table 2). Among the 8 patients with fewer attacks, 2 patients were completely symptom-free; the others had 0.2–3.5 attacks per month. The attacks that still occurred in 12 patients under LRT were triggered by either an infection or emotional stress or occurred without any recognizable triggering factor.

Five patients in the LRT group (patients 3, 5, 6, 7, and 12) experienced a continuous increase in the frequency of their attacks from the beginning (mean number of attacks per month 1.9, SD 0.8) to the end of the study (mean

number of attacks per month 9.7, SD 10.2). The frequency of the attacks increased by 125, 200, 364, 600 and 1,200% despite the fact that in 4 of these patients the weekly dose of C1-INH concentrate was increased (table 2). One woman (patient 6) had to discontinue LRT after 5 years because of numerous attacks; she had received 1,000 U C1-INH concentrate daily for the past 1.5 years.

In 12 out of 14 patients, a tendency to develop more attacks started between 6 months and 2 years after the beginning of LRT and persisted during the whole LRT period. The first symptoms of attacks appeared early, i.e.

Table 3. Attack frequency and injection intervals before, at the beginning, and at the end of WTD

Pat. No.	Time period between the first injection of C1-INH concentrate and the beginning of WTD, years	Duration of WTD until study end, years	Interval between injections at the beginning of treatment with C1-INH concentrate, days	Interval between injections at the beginning of WTD, days	Interval between injections at the end of WTD, days	Duration of the last dose, years	Attack frequency per month before the first injection of C1-INH concentrate	Attack frequency per month at the beginning of WTD	Attack frequency per month at the end of WTD
15	29	5	7	7	2.8	1	5	4.3	12
16 ¹	15	12	12	7	3.5	3	2.3	4.3	9
17 ¹	15	7	15	7	3.5	3	2	4.3	10
18 ¹	10	8	40	7	3.5	3	0.75	4.3	8.6
19	15	4	30	7	7	4	1	4.3	4.3
8	15	2 ²	24	7	7	1	1.25	4.3	4.3

¹ These patients have been described earlier [26].

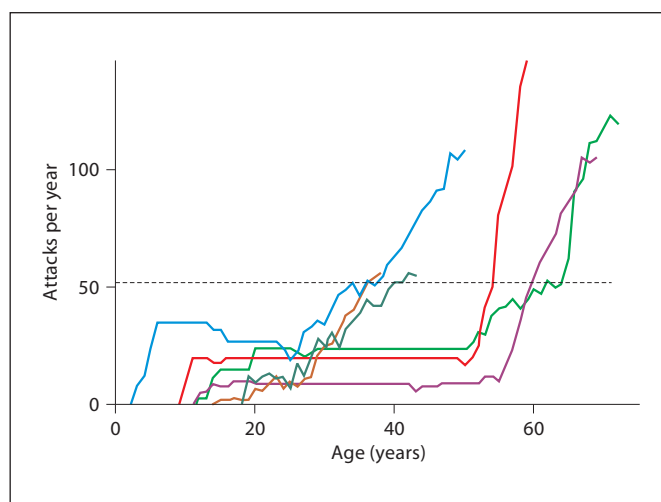
² Afterwards, the patient shifted to LRT.

within several days after the injection of C1-INH concentrate – earlier than before LRT. If a planned injection was not given to those patients, the next attack occurred after a very short time; the time interval after a missed but planned injection of C1-INH concentrate and the onset of the next attack as reported by the patients ranged from 1 h to 3 days at the end of the study (table 2). By shortening the interval between injections, those patients were able to prevent the next attack by a timely injection of C1-INH concentrate. Patients 9 and 14 (the patients with the lowest weekly doses) did not observe any new attacks when the injections were missed.

Under WTD, the number of attacks increased in 4 patients and remained constant in 2 (table 3). The mean number of attacks per week in the 6 patients was 4.3 (SD 1.9) at the beginning of the study and 8.0 (SD 3.1) at the end. When a treatment frequency of less than once per week was included, the treatment period extended to 22.8 years (SD 6.6 years, range 17–34 years); during that period, the number of attacks increased greatly in all 6 patients (fig. 2), from 2.1 (SD 1.6, range 0.75–5) to 8.0 (SD 3.1, range 4.3–12) per month on average. Three patients reported that the interval between injections had to be shortened by 1 day every 3 years on average. In 4 patients, the frequency of the attacks reached a plateau and remained constant at the end of the study for several years (table 3).

Adverse Drug Reactions, Increase in the Frequency of the Attacks, and Other Risks

A few drug-related adverse reactions were observed: headache in 1 patient, lightheadedness following 9 injections for 9 attacks altogether in 2 patients, and 1 anaphy-

**Fig. 2.** Number of attacks per year treated by WTD in 6 patients with HAE-C1-INH.

lactic reaction in 1 patient. Damage to the veins because of the numerous injections was a major problem in 4 patients who subsequently received a portacath and was a minor problem in 4 other patients who were able to continue self-administration of the medication. Plasma samples of 11 patients were assayed for antibodies to C1-INH of the IgG, IgA, and IgM type; no antibodies could be detected.

Patients' Opinions

Seventeen of the 19 patients were satisfied or very satisfied with their treatment. Fifteen patients seriously worried about having to discontinue the treatment be-

cause of its high cost – about EUR 600 per 500-unit vial in Germany. Two patients even threatened to commit suicide if this kind of treatment were no longer available to them.

The regularity of new attacks after several hours or days when attacks were not treated with C1-INH concentrate and the need for an increase in the weekly drug dose over the years led 12 patients in the LRT group to believe that they had a kind of medication dependency. In all patients of the WTD group, the slowly but continually increasing number of attacks over many years, and the fear of a worse attack if not treated early enough led to the same feeling of medication dependency. All patients on WTD worried about the continually increasing number of attacks.

Discussion

We reported on 19 patients with HAE-C1-INH who frequently received C1-INH concentrate intravenously over a long period of time. The most important benefit of the treatment was a reduction in symptom severity: the vast majority of attacks became mild or very mild. The fact that 4 patients even accepted a portacath in order to receive the C1-INH concentrate demonstrates how important this kind of treatment was to them. In the opinion of most patients, the improvement of their quality of life by WLTC, compared with their disease burden before treatment, obviously greatly outweighed the disadvantages.

Eight patients in the LRT group benefited also in that they had fewer attacks than before LRT; 2 of those patients became completely symptom free. In other LRT patients, however, the number of attacks increased during LRT or was unchanged. In contrast, Levi et al. [22] reported on 10 patients with HAE-C1-INH and 2 patients with acquired angioedema due to C1-INH deficiency, all of whom experienced not only reductions in symptom severity but also less frequent attacks during LRT; at least some of those individuals, however, simultaneously received additional long-term treatments. In a recent study, 20 HAE-C1-INH patients received a prophylactic treatment for 3 months [27]; 2 of the 20 experienced an increase in the number of attacks over time of 85 and 8%, respectively.

In most patients in our study, a kind of medication dependency was suspected. These patients felt that they needed another injection within a time interval of several days; otherwise, a new attack would inevitably occur.

Such a regular pattern of attacks was not present before LRT; the pattern usually appeared between 6 and 24 months after the start of LRT. In addition, in more than half of our patients who received LRT, the weekly doses of C1-INH concentrate had to be increased to maintain the attack-mitigating or preventive effect. In 2 patients, the weekly doses could be kept constant, but this was at the cost of an increase in the frequency of the attacks. In the 6 patients of the WTD group, we observed a slow but continuous increase in the number of HAE attacks.

All these observations suggest that there is an increasing disease activity in most patients that is hidden by the effectiveness of the C1-INH concentrate. Two additional signs can be regarded as indicators of increasing disease activity: (1) the occurrence of some extremely severe and rapidly developing abdominal attacks, and (2) the rapid occurrence of simultaneous skin edema at several body sites in some of the patients.

We could not identify other risk factors that might explain this hidden increase in disease activity. Therefore, we assume that the increase might be due to the large number of intravenous injections of C1-INH concentrate. Hence, there is some concern that frequent and long-term administration of C1-INH concentrate may lead to an increase in disease activity. This apparently is not the case in all patients but predominantly in those receiving a high weekly dose. On the other hand, most of the attacks can still be prevented or their severity strongly reduced by the administration of the same C1-INH concentrate. At present, we do not know whether the necessary injection intervals will become even shorter over time or whether the weekly doses will need to be continually increased. Because the weekly dose and injection interval did not change within recent years in some of the patients, it is also possible that in some individuals a certain plateau might be reached and that a dose increase will not become necessary in the future. Obviously, the presently assumed increase in disease activity following LRT and WTD could be shown only because the observation period was very long. In the patient series reported by Levi et al. [22], the observation period only ranged from 1.6 to 4.3 years; in the CINRYZE study [27], the observation period was only 3 months. Both observation periods were probably too short to detect long-term side effects.

The pathophysiological background of the observed increases in the frequency of the attacks and disease activity that accompanied frequent injections of C1-INH can only be speculated about: activation of the contact system might be facilitated as a direct or indirect consequence of the frequent injections of C1-INH concentrate.

It is possible that the change from a high C1-INH level immediately after an injection to a low level several days later, i.e., the drop in the C1-INH level, especially when it occurs frequently, might lower the threshold for contact system activation.

Treatment of severe HAE-C1-INH with weekly injections of C1-INH concentrate is very expensive. Besides the medication costs for the treatment of acute attacks and chronic disease management, additional expenses have to be considered. Such expenses include direct costs – for emergency room and hospital visits for acute attacks, doctor’s office visits, and concomitant procedures and tests – as well as indirect costs including travel, childcare, missed work days, reduced income, and reduced productivity associated with HAE [28]. These additional expenses have to be taken into account when evaluating the overall costs of treatment with weekly injections of C1-INH concentrate and when comparing these costs with other HAE treatments.

Concerning therapeutic alternatives for severe HAE-C1-INH, attenuated androgens can be ruled out because the patients had severe side effects or declined this kind of treatment. Treatment with tranexamic acid would probably not be effective enough in these patients. As a further possible therapeutic alternative, icatibant might be considered. Icatibant (30 mg as a subcutaneous injection) has been approved by the European Commission for the symptomatic treatment of HAE. Its half-life is about 1.2 h and thus probably too short to prevent acute attacks of HAE-C1-INH in a long-term treatment regimen. It can be used for acute attacks, however. As icatibant did not become available until September 2008 in Germany, practical experience with this drug outside of clinical studies is scant. An increase in the frequency of attacks after frequent injections of icatibant has not been reported up to now.

The present study has the following limitations. First, and most importantly, the results of this observational study cannot be interpreted as the demonstration of a causal link between frequent injections of C1-INH concentrate and increased disease activity. As is typical of observational studies, the finding that patients who received high doses of the medication experienced an increase in disease activity could be explained alternatively by background variables, i.e., disease severity. Second, even though our sample size was relatively large, given that HAE is a rare disease, the absolute sample size was small. However, the number of years of treatment was high (175 years). Third, the observation period was relatively long, but not long enough to enable the investiga-

Table 4. Benefits and risks of WLTC

Comments	
<i>How can patients benefit from WLTC?</i>	
(1) Considerably less severe attacks; nearly always only mild attacks	in all patients
(2) Complete avoidance of attacks	only on LRT; only in a few patients
(3) Less frequent attacks	in most patients on LRT; not in those on WTD
(4) Occurrences of attacks lose their unpredictability	in some patients
(5) Treatment with attenuated androgens can be avoided	
<i>What do patients on WLTC have to accept?</i>	
(1) A high number of intravenous injections	all patients
(2) An increasing number of attacks and injections of C1-INH concentrate	some patients on LRT; most patients on WTD
(3) No complete symptom freedom despite the treatment	most patients on LRT; all patients on WTD
(4) Despite the treatment, occurrence of sudden attacks, some of which occur more rapidly and are more severe than usual	some patients on LRT or WTD
(5) Shortening of the interval between injections of C1-INH concentrate	some patients
(6) Short time interval before the next attack if an injection of C1-INH concentrate is missed	some patients

tors to determine whether the assumed increase in disease activity will continue or plateau.

In conclusion, we observed that WLTC considerably improved HAE-C1-INH. However, patients who receive WLTC might have to accept several accompanying disadvantages of the treatment (table 4). We believe that clinicians who apply this kind of treatment should be aware of the risks and benefits.

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