C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis

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BACKGROUND: Hereditary angioedema (HAE) caused by functional deficiency of C1-inhibitor (C1-INH) is a rare disease that manifests with recurrent spontaneous nonallergic edema of the subcutaneous tissues and mucous membranes. In cases of laryngeal edema that are not treated immediately, HAE is associated with high mortality rates. Attenuated androgens (e.g., danazol) are usually administered for prophylaxis, but associated side effects may limit their use. This study investigated the efficacy, safety, and quality of life (QoL) associated with a pasteurized plasma-derived C1-inhibitor (pC1-INH) concentrate for individual replacement therapy (IRT) in patients with severe HAE suffering from frequent attacks who were intolerant or not responding to danazol.

STUDY DESIGN AND METHODS: Twenty-two patients with severe HAE and danazol incompatibility or insufficient efficacy of danazol were recruited. Intraindividual comparisons of efficacy, safety, and QoL with pC1-INH concentrate IRT versus danazol treatment were made using retrospective and prospective patient data. Pharmacokinetic data were collected for 15 of the 22 patients.

RESULTS: In patients receiving pC1-INH regularly, the median number of attacks per year decreased significantly compared to danazol prophylaxis ($p < 0.001$), and the 24 laryngeal edema episodes per year ceased. Superior efficacy of pC1-INH was found for all QoL variables (e.g., general condition, social activities). No transmission of human immunodeficiency virus or hepatitis A, B, or C was observed.

CONCLUSION: In patients with severe HAE who experience severe side effects and/or lack of efficacy of danazol prophylaxis, very early substitution with pC1-INH can completely abolish the incidence of potentially fatal laryngeal edema and can reduce the incidence of acute attacks.

Hereditary angioedema (HAE) is caused by functional deficiency of C1-inhibitor (C1-INH).[1] C1-INH deficiency manifests as spontaneous, often acute, recurrent nonallergic swelling of the subcutaneous tissues, usually involving the face, throat, abdomen, and extremities.[2,3] However, any part of the body can be affected by swellings including the central nervous system. It is a rare disease, with an estimated prevalence of 1 in 50,000.[3] Because the disease is not well known among physicians, rapid and precise diagnosis is usually delayed.[4] In cases of misdiagnosed or mistreated acute HAE-related laryngeal edema, the disease may become life-threatening, because acute edema due to HAE is unresponsive to standard therapy such as antihistamines, steroids, and epinephrine.[5] Without emergency replacement of C1-INH concentrate, mortality rates of up to 56% have been reported from

ABBREVIATIONS: C1-INH = C1-inhibitor; CL = confidence limit; HAE = hereditary angioedema; IRT = individual replacement therapy; IVR = in vivo recovery; pC1-INH = pasteurized C1-INH; QoL = quality of life.

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laryngeal edema, but even where pasteurized C1-INH (pC1-INH) concentrate is available, mortality from laryngeal edema can reach 40% due to inappropriate or late administration.[6,7]

Avoiding acute attacks in HAE patients is the primary goal of treatment. For many years, and before the introduction of pC1-INH, acute attacks of HAE were treated by infusing fresh-frozen plasma.[8] More specifically, C1-INH concentrate has been reported as beneficial in the management of acute attacks in HAE patients.[3,4,9-13] For long-term prophylaxis, attenuated androgens (e.g., danazol) are used.[14] However, the use of danazol raises general concern; since it is associated with a multitude of side effects, it is not recommended for children and is also contraindicated in pregnant women.[15] In adults, danazol can cause weight gain, microscopic hematuria, hepatic side effects, liver tumors, anxiety, altered libido, alopecia, and hypertension.[16-19] Despite its worldwide use, in Germany, danazol was never registered for long-term prophylaxis in HAE. As an alternative, antifibrinolytics such as tranexamic acid or ε-aminocaproic acid are used for long-term prophylaxis. These agents have fewer side effects, but lower efficacy compared with attenuated androgens.[5,12,20]

In line with hemophilia treatment or treatment of primary immunodeficiencies, where the optimal therapeutic approach is the replacement of the missing protein to prevent disease-related complications, we decided to investigate the use of a pC1-INH in individual replacement therapy (IRT; pC1-INH-IRT) for patients with HAE affected by a high frequency of severe attacks and who were unresponsive to established long-term treatment with attenuated androgens.[21]

MATERIALS AND METHODS

Study design

This study received ethical approval from the institutional review board of the Johann-Wolfgang Goethe University (Frankfurt am Main, Germany). The efficacy and safety of IRT with a pC1-INH were investigated in 22 patients who suffered from severe HAE and who fulfilled the inclusion and exclusion criteria (detailed below). Severe HAE was defined as presence of either severe gastroabdominal, urogenital, and/or laryngeal attacks, at least once a week (i.e., at least 52 attacks/year in any location).

All patients kept regular diaries to record information such as the timing, localization, severity and possible triggers of the attack, and treatment (including dose and batch number). All patients were also advised by medical professionals on how to recognize the early signs of an attack (e.g., pain, swelling, nausea, typical skin irritation, croakiness) and to strictly administer pC1-INH at this time.

Retrospective data were obtained from patient diaries, patient histories, and other medical documentation, including the safety of treatment and use of concomitant medication. All data were transferred into a case report form by a medical professional, with the exception of attack frequency, which was documented in patient diaries. The case report form also documented the patient's quality of life (QoL). The prospective phase of the study began after informed patient consent was obtained; patient data were documented in case report forms, as described for the retrospective phase.

Patient data collected during the retrospective and prospective phases were compared intraindividually. Long-term treatment during the retrospective phase was oral danazol (e.g., Danazol-Ratiopharm, Ratiopharm, Ulm, Germany), while IRT with intravenous (IV) pC1-INH (Berinert P; CSL Behring GmbH, Marburg, Germany) was administered during the prospective part of the study. Laryngeal attacks during the danazol long-term therapy phase were treated with pC1-INH.

Danazol was evaluated retrospectively for treatment-associated adverse drug reactions. Adverse drug reactions were defined as severe if they required repeated medical treatment. Moderate adverse drug reactions required treatment, but not repeatedly. Mild adverse drug reactions did not require treatment.

In the prospective evaluation phase, adverse drug reactions were evaluated for pC1-INH therapy. Continuous screening for viral safety included assessment of serological markers for hepatitis A, B, or C viruses (HAV, HBV, and HCV, respectively) and human immunodeficiency virus (HIV) Types 1 and 2. Pharmacokinetic analyses were performed during an attack-free and substitution-free interval of a minimum of 3 days.

Inclusion and exclusion criteria for the prospective study

Inclusion criteria were as follows: patients aged 18 years or older with HAE, presenting with primarily severe and frequent attacks (i.e., gastrointestinal, urogenital, or laryngeal attacks occurring at least once a week, with possible involvement of more than one side), who discontinued long-term prophylaxis with danazol due to lack of efficacy (danazol doses up to 1000 mg/day), intolerability, and/or severe side effects. Exclusion criteria included patients aged less than 18 years, patients with known or reported hypersensitivity to pC1-INH, pregnancy, or lack of informed consent.

Study medication

Based on documented attack intervals and pC1-INH consumption per attack, an individual regimen for pC1-INH-IRT was prepared for each patient, including a customized dose of pC1-INH. Patients then adapted the frequency of

pC1-INH administration according to the early signs of an acute attack (i.e., before edema and/or colicklike abdominal pain emerged).

Patients usually administered a dose of 500 to 1000 U of pC1-INH up to twice a week. All patients were trained on self-infusion of pC1-INH. Training was carried out by health care professionals (i.e., hemophilia nurses) and included instructions on optimum storage conditions (between +2 and +25°C), reconstitution (using Mix2Vial, Medimop Medical Projects Ltd, Ra'anana, Israel), administration (via venipuncture with a butterfly needle, under sterile conditions), appropriate care of peripheral veins, and documentation of the dose (including the batch number) in the patient diary. Patients were eligible for self-infusion if they successfully self-administered pC1-INH four times under the supervision of a medical professional.

The predefined working definition for "preventing the progression of an attack" was as follows: the progression of an attack has been prevented if the intensity of symptoms did not worsen after administration of pC1-INH and is followed by a complete resolution of all symptoms. If progression of an attack could be prevented, administration of pC1-INH was considered efficacious and the attack was not recorded.

Assays and blood sampling for pharmacokinetic evaluation and analysis

Functional C1-INH plasma levels were determined by chromogenic assay with C1-INH (Berichrom, Dade Behring, Marburg, Germany). Blood samples were collected before and after administration of a bolus injection of 1000 U of IV pC1-INH at predetermined time intervals over a 3-day period.

C1-INH plasma levels were fitted to a single-compartment model with nonlinear regression, including an intercept term for the endogenous level. Pharmacokinetic variables calculated included time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), classical in vivo recovery (classical IVR), and incremental IVR. Recoveries (%) were calculated as follows:

$$\text{Classical IVR} = \frac{\text{Actual increase in C1-INH (U/mL)} \times 100}{\text{Expected increase in C1-INH (dose [U]/plasma volume [mL])}}$$

$$\text{Incremental IVR} = \frac{\text{Actual increase in C1-INH (\%)}}{\text{Dose (U/kg body weight)}}.$$

Plasma volume was estimated based on the formula by Nadler and colleagues.[22] A 100% increase in C1-INH was assumed to be 1 U/mL.

QoL

QoL assessment was based on an adapted scoring system introduced and validated by Tait and colleagues.[23] Patients documented their QoL by scoring family and home responsibility, social activities, occupation, life support activity, general condition and condition during attacks, absence from work/school, and stays in the hospital. The patients' general condition and their condition during attacks were presented using an 11-point scale for each item (0 = very bad and 10 = very good). For the remaining four QoL variables, a five-point scale was applied.

Statistical analysis

Data management and statistical analyses were carried out by an independent statistical institute (BBS, Neuberg, Germany). Statistical software (SAS, Version 8.2 for MS Windows, SAS Institute, Cary, NC) was used for data management and performance of statistical analyses. Target variables for efficacy were the number of patients with attacks, localization, and the mean annual number of attacks. The total score of six items describing QoL was determined: four items on a five-point scale and two items on an 11-point scale were totaled using a common 11-point scale to achieve an equal weighting for each item. Safety target variables were the number of adverse drug reactions during danazol and pC1-INH treatment, type and frequency of concomitant medication, and results of viral marker testing. Descriptive statistics were calculated for all variables using means, standard deviations (SDs), medians, minimum, maximum (quantitative variables) or absolute and relative frequencies (qualitative variables), and the number of evaluable observations in both cases. In case of nonsymmetrical distributions (differences between mean and median values), median values were preferred for interpretation of the results. Box plots were used to describe the underlying distributions of the endpoints. As a whole, the analysis was performed as an explorative data evaluation using the results of significance tests (Type I error, $\alpha = 0.05$) and 95% confidence limit (CL) on a descriptive basis only. Wilcoxon's signed rank test was used for intraindividual comparisons. Tests on predefined hypotheses were not performed; this analysis was explorative and descriptive with respect to the interpretation of any test results.

RESULTS

Baseline data

Twenty-two patients were recruited, of whom 13 were women and 9 were men. The mean age was 41.8 ± 10.1 and 35.8 ± 7.3 years for female and male patients, respectively. The median age at first manifestation was 6 years (range, 0-27 years) and the median age at first diagnosis

was 26 years (range, 5-44 years), resulting in a delay in diagnosis of 15.5 years (median). The median time to first visit at our hospital was 32 years (range, 9-54 years) after the first manifestation of disease, whereas the diagnosis preceded the first visit to our hospital by a median of 16 years (range, 1-28 years). While receiving danazol for long-term treatment (median, 11.25 years; range, 0.5-23.5 years), the most common localizations of attacks were the gastrointestinal tract (all patients) and the extremities (all patients); less common were acute edema of the face (15 of 22 patients), laryngeal edema (14 of 22 patients), and the urogenital system (13 of 22 patients). The annual attack rates per localization for the respective treatment phases are listed in Table 1.

TABLE 1. Attack rates per year by localization (n = 22)

Phase	Localization	Mean ± SD	Median	95% CL (median)	Q25%, q75%*	Minimum, maximum	Localization of attacks†
Retrospective phase	Extremities	50.0 ± 37.6	48	24, 104	24, 104	2, 104	22 (100)
	Facial	36.6 ± 37.9	24	0, 52	0, 52	0, 104	15 (68)
	Gastrointestinal	50.0 ± 37.6	48	24, 104	24, 104	2, 104	22 (100)
	Urogenital	28.4 ± 32.6	24	0, 52	0, 52	0, 104	13 (59)
	Laryngeal	32.3 ± 36.1	24	0, 52	0, 52	0, 104	14 (64)
Prospective phase	Extremities	7.1 ± 22.4	0	0, 2	0, 2	0, 104	6 (27)
	Facial	0.6 ± 2.6	0	0, 0	0, 0	0, 12	2 (9)
	Gastrointestinal	1.2 ± 5.1	0	0, 0	0, 0	0, 24	3 (14)
	Urogenital	7.0 ± 22.8	0	0, 0	0, 0	0, 104	4 (18)
	Laryngeal	0	0	0, 0	0, 0	0, 0	0
Changes (frequency of attacks per site)	Extremities	–42.8 ± 49.2	–44	–52, –12	–101, –12	–104, 98	
	Facial	–36.0 ± 38.2	–24	–52, 0	–52, 0	–104, 0	
	Gastrointestinal	–48.7 ± 38.7	–46.5	–52, –24	–104, –24	–104, 0	
	Urogenital	–21.4 ± 41.2	–14.5	–48, 0	–50, 0	–104, 104	
	Laryngeal	–32.3 ± 36.1	–24	–52, 0	–52, 0	–104, 0	

* q25% and q75% = first and third quartile, respectively.
† Data are reported as number (%).

Efficacy

According to the study design, all patients (n = 22) suffered from recurrent attacks under danazol for long-term treatment. The median frequency of attacks was 48 per year (range, 2-104 per year; 95% CL, 24, 104; data not shown). Patients receiving pC1-INH-IRT reported a median of zero attacks (as defined by nonprogression, i.e., progression of angioedema which was prevented by pC1-INH administration) per year (range, 0-104/year; 95% CL, 0, 3; data not shown). The number of patients suffering from severe attacks was reduced from 22 patients under danazol for long-term treatment to 10 patients during pC1-INH-IRT. In 1 patient who previously suffered from a maximum of 104 attacks per year under treatment with danazol, all attacks were successfully resolved after administration of pC1-INH. However, due to a misunderstanding, the patient did not follow the predefined working definition and therefore documented any aborted attacks as fully developed attacks (thus confusing this with lack of efficacy).

The change from danazol treatment to IRT with pC1-INH resulted in a decrease of 43 attacks per year (median; 95% CL, –52, –12; $p < 0.001$). The distributional characteristics (minimum, maximum, quartiles, median) are depicted as box plots in Fig. 1. The analysis of attacks by localization confirmed these results: the change from danazol treatment to pC1-INH-IRT showed a median decrease in annual attacks of 44 for extremities (95% CL, –52, –12), 24 for facial (95% CL, –52, 0), 47 for gastrointestinal (95% CL, –52, –24), 15 for urogenital (95% CL, –48, 0), and 24 for laryngeal attacks (95% CL, –52, 0). No laryngeal edema was observed under pC1-INH-IRT (Fig. 2).

QoL

All QoL variables significantly improved when patients changed from danazol for long-term treatment to IRT with pC1-INH: the median score for patients under danazol prophylaxis for family and home responsibility was 2.5

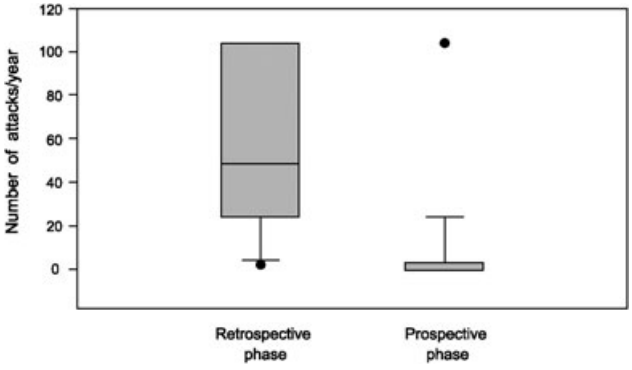

Fig. 1. Number of attacks per year over all affected sites: distributional characteristics (minimum, maximum, quartiles, median) presented as box plots. The middle line stands for the median value while the top and bottom end of the box represent the 25th and 75th percentiles, respectively. The lower and upper bars extending from box plot represent 10th and 90th percentile values, respectively. Values outside the 10th or 90th percentile are plotted as dots.

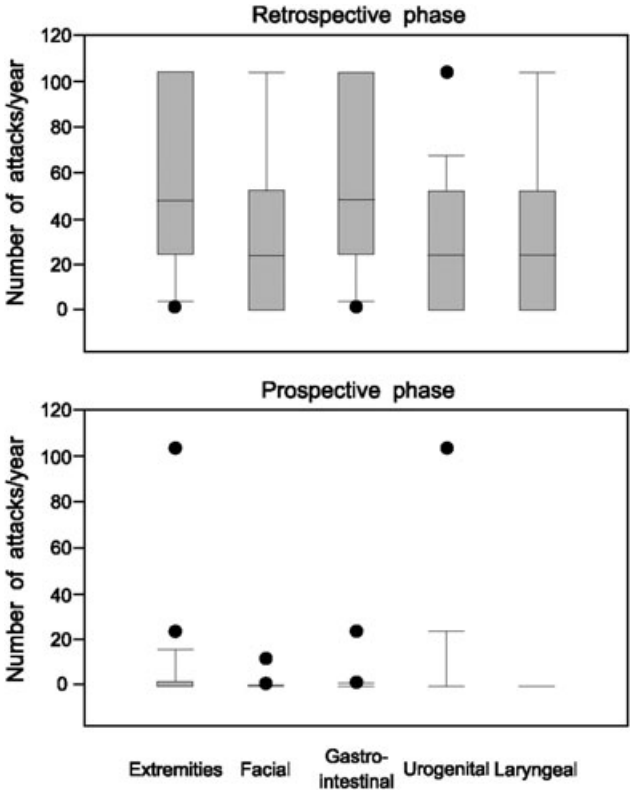

Fig. 2. Annual attack rates by localization presented in a box and whisker plot analysis. Definitions of plots are similar to those described for Fig. 1. The differences for each system involved are significant (Wilcoxon signed rank test; $p < 0.001$) for the retrospective and prospective phases, respectively. No attacks involving laryngeal edema were observed for patients during pC1-INH-IRT.

compared with 7.5 for patients on pC1-INH-IRT and the corresponding improvements for the remaining variables were also in the same range (social activities, 2.5 vs. 7.5; occupation, 2.5 vs. 8.8; life support activity, 2.5 vs. 8.8; general condition, 2.5 vs. 8.8; condition during attacks, 0.0 vs. 8.0). This was also reflected in the median values for all variables summarized by the total score: 12.5 (95% CL, 10, 18) versus 48.5 (95% CL, 45, 57; $p < 0.001$; Fig. 3).

Furthermore, the subjective improvement in QoL could be confirmed by objective variables such as absence from work/school due to HAE (danazol, median 24 days/year; pC1-INH-IRT, median 0 days/year; $p < 0.001$; data not shown) and days in hospital due to HAE per year (Table 2).

Adverse drug reactions

All patients under danazol treatment experienced adverse drug reactions. The most disabling adverse drug reactions are listed in Table 3. Common adverse events were depression, headache, increased body weight, amenorrhea, virilization, and hypertension. Liver adenoma was identified in two patients (9%).

During IRT with pC1-INH, most symptoms, such as weight gain or amenorrhea, regressed, but virilization and liver adenoma normalized only slowly. Supposedly danazol-related adverse drug reactions like hypertension, liver adenoma, or myocardial infarction ($n = 1$; data not shown) required appropriate treatment. One patient did not respond to treatment for hypertension. Other adverse drug reactions caused by long-term, high-dose danazol treatment, such as voice alteration or alopecia, did not disappear over time, in spite of IRT with pC1-INH for more than 2 years (data not shown).

The severity and number of adverse drug reactions in the patients with severe HAE receiving danazol treatment generally increased with the dose administered. However, a relationship between dose administered and number of adverse drug reactions was not always evident, as we observed adverse drug reactions even with doses below 200 mg (Table 4). Three patients receiving pC1-INH experienced mild adverse drug reactions (two cases of redness at the injection site; one case of vertigo), which did not require medical treatment.

During long-term treatment with danazol, 4 of the 22 patients enrolled took concomitant medication (beta blockers and antidepressant drugs, $n = 2$; beta blockers only, $n = 2$), while none of the patients did so under pC1-INH-IRT. Assessment of virus markers demonstrated no evidence for transmission of HIV-1/2, HAV, HBV, or HCV.

Pharmacokinetics

The 15 patients for whom pharmacokinetic data were collected included 2 male and 13 female patients. The mean

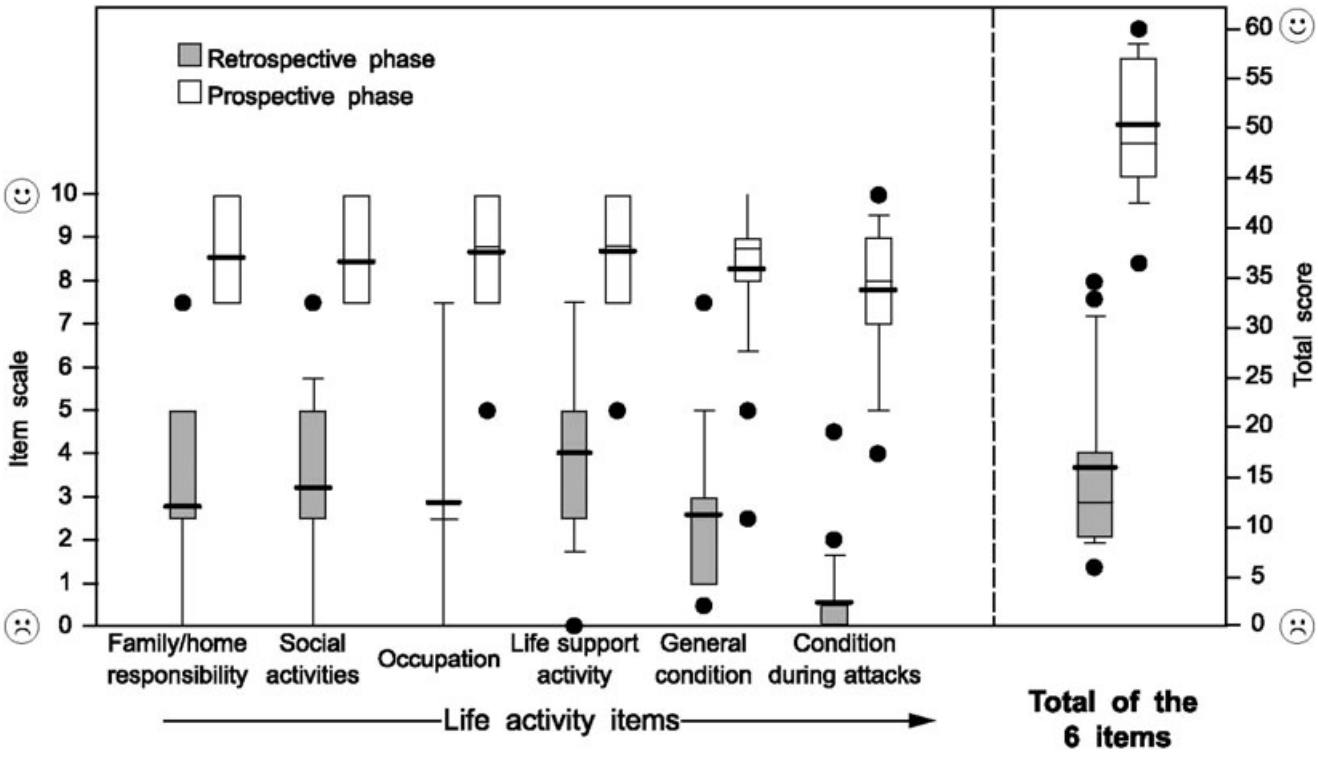

Fig. 3. QoL improvements: life activity items and total score (standardized items on an 11-point scale). All item values achieved during pC1-INH-IRT improved significantly compared with danazol prophylaxis (Wilcoxon signed rank test; $p < 0.001$) resulting in a significant improved total score for patients receiving pC1-INH-IRT. Bold bars in the middle of the box represent mean values while normal bars stand for median values.

TABLE 2. Number of days hospitalized/year (22 patients)

Phase	Mean ± SD	Median	95% CL (median)	Q25%, q75%*	Minimum, maximum	Number (%) of patients affected
Retrospective phase	15.9 ± 23.2	3	2, 20	2, 20	0, 78	18 (82)
Prospective phase	0.0 ± 0.0	0	0, 0	0, 0	0, 0	
Changes (frequency of attacks per site)	–15.9 ± 23.2	–3	–18, –2	–20, –2	–78, 0	
Significance (signed rank test)				$p < 0.001$		

* q25% and q75% = first and third quartiles, respectively.

TABLE 3. Danazol adverse events, retrospective phase, grouped by symptom and severity

	Number of patients with adverse events			
Symptom	Mild	Moderate	Severe	Total*
Depression		9	8	17 (77)
Increase of transaminases	7	9	1	17 (77)
Headache	3	4	8	15 (68)
Increase in body weight	4	6	2	12 (55)
Amenorrhea	1	11		12 (55)
Indisposition	2	8	1	11 (50)
Hot flushes		6	2	8 (36)
Virilization	1	3	3	7 (32)
Hypertension		4	1	5 (23)
Liver adenoma			2	2 (9)

* n = 22 patients (100%); multiple symptoms possible in each patient. Data are reported as number (%).

dose of C1-INH concentrate administered was 1115.7 ± 160.3 U. Pharmacokinetic variables are shown in Table 5.

DISCUSSION

Attenuated androgens, in particular danazol, are a well-established long-term treatment option for the prophylaxis of HAE attacks. The patients in this study had previously used danazol for long-term therapy; however, they presented with increasing danazol incompatibility and/or insufficient efficacy despite high doses of up to 1000 mg/day.

Our approach was derived from currently established regimens in patients suffering from hemophilia A or B, where the missing protein, Factor (F)VIII or F IX, respectively, is substituted to prevent bleeding.[21] Our results confirm a similar benefit for pC1-INH-IRT for long-term treatment in HAE patients.[6,10,11] The most intriguing finding of our study is the complete disappearance of laryngeal edema in the prospective study phase (i.e., patients receiving pC1-INH-IRT). As the occurrence of laryngeal edema in HAE patients is generally associated with high mortality, this finding is, to our knowledge, unparalleled.[6,7] Furthermore, our data also indicate that administration of pC1-INH after recognition of early signs of an attack is able to prevent the progression of an attack. Besides the direct effect on the occurrence of life-threatening laryngeal edema and on the progression of attacks, pC1-INH-IRT has a more favorable safety profile than danazol.[24] In an appraisal of 104 cases, Cicardi and colleagues[7] identified problems associated with long-term androgen use in HAE. Zurlo and Frank[25] reported common adverse drug reactions in 60 HAE patients using danazol, such as menstrual abnormalities (79%), weight gain (60%), muscle cramps/myalgia (40%), and elevations of liver enzymes (40%). Hosea and coworkers[18] reported data from 69 HAE patients using danazol, where headache (22%), elevated liver enzymes (14%), alopecia (17%), hirsutism (8%), change in libido (14%), and hypertension (10%) were the most frequent adverse drug reactions. Andriole and coworkers[26] described danazol-induced hematuria in 13 of 69 HAE patients, of whom 10 suffered from cystitis. In a controlled study investigating long-term danazol and stanozolol administration (n = 36) versus no long-term prophylactic therapy (n = 33) in HAE patients, significantly more patients in the danazol and stanozolol group (25%) suffered from hypertension compared to those in the control group (3%; p = 0.02).[17] In 15 of the 22 premenopausal women, menstrual irregularities occurred in the androgen-treated group. Further findings were weight gain (14 of 36 patients), acne (4 of 36 patients), hypothyroidism and myocardial infarction (1 patient of 36 each, respectively), and the occurrence of liver tumors associated with the use of androgens was described.[17] Severe side effects reported in the literature in association with the use of danazol include the occurrence of hepatocellular carcinoma, hepatocellular adenoma, and a connection between the occurrence of hepatic angiosarcoma and the use of androgenic-anabolic steroids.[27-29]

The present results provide evidence of a positive effect of IRT with pC1-INH on patient QoL. All QoL variables improved in patients receiving treatment with pC1-INH in contrast to treatment with danazol. It should be noted that the impact on QoL is underscored by the number of hospitalizations (Table 2). However, a general conclusion on the impact of danazol on QoL is not possible because the selected population comprised those patients with prior incompatibility or a lack of response to danazol therapy (selection bias). Therefore, our results should not be used to evaluate danazol treatment in general populations.

Although pC1-INH-IRT is a highly effective and safe treatment for patients with severe HAE, IV administration of pC1-INH is not as convenient as oral danazol. The side effects that did occur following self-administration of pC1-INH were either caused by a too rapid IV administration or because the pC1-INH was administered at a suboptimum temperature (below 25°C). All of these adverse drug reactions were mild and did not require medical treatment. For plasma-derived proteins, a residual concern also remains about the virus safety. However, in this study and in our whole cohort of HAE patients receiving pC1-INH over the past 25 years, we have not observed any virus transmission. In addition, postmarketing data concerning the pC1-INH used in this study (Berinert P) revealed that from January 1985 through November 2008, there were no proven cases of virus transmission (data on file; CSL Behring).[19] Similar data on a different C1-INH concentrate product have been published by Levi and colleagues.[30]

TABLE 4. Danazol adverse events, retrospective phase, grouped by dose

Dose (mg/day)	Number of patients	Number of adverse events
≤200	5	21
201-400	9	54
401-600	6	39
601-1000	2	11

TABLE 5. Pharmacokinetic variables for plasma C1-INH activity assessed in 15 HAE patients on IRT

Variable	Median	Range	Mean	SD	CV (%)
T_{max} (hr)	0.5	0.3-8.0	1.3	2.1	156
$t_{1/2}$ (hr)	30.9	10.3-96.0	33.3	19.8	60
Classical IVR (% increase)/(U/mL)	101.4	54.0-254.1	108.2	48.3	45
Incremental IVR (response) (% increase)/(U/kg body weight)	2.9	1.4-6.9	3.2	1.3	40

CV = coefficient of variation.

The most recent pharmacokinetic data for a vapor-heated plasma C1-INH concentrate were reported by Kunschak and colleagues.[31] Some essential differences exist between our study and that of Kunschak and colleagues. The data in the study by Kunschak and colleagues were generated from patients having an acute attack over 24 hours, whereas in our study patients were studied over 72 hours during a symptom-free period. However, comparison of mean values is of some interest. In the study by Kunschak and colleagues, the mean half-life of plasma C1-INH activity in nine HAE patients was 37.87 ± 19.75 hours. In the 15 patients we report on here, the mean half-life of plasma C1-INH activity was 33.3 ± 19.8 hours. The mean time to maximal plasma C1-INH activity (T_{max}) was 1.3 hours. It also can be assumed that the mean half-life of plasma C1-INH activity is likely to be higher in patients during a symptom-free period than in patients having an acute attack with high turnover rates. In contrast, the data of our 15 study patients are similar to the data reported by Kunschak. The mean half-life of plasma C1-INH activity could hence be explained by a higher turnover rate of C1-INH in our patients even during the symptom-free period. The higher catabolic rates of C1-INH in these patients could also explain the high frequency of severe swelling symptoms. The half-life of any treatment for HAE is essential for efficacious therapy of acute attacks. The long half-life of pC1-INH (36 hr; prescribing information Berinert P, June 2008) is especially important in treating IRT patients who are suffering from severe and frequent attacks.

The median classical IVR in our study was 101.4%, and incremental IVR was a 2.9% increase/U/kg. It can be hypothesized that IRT patients show a higher tendency toward development of capillary permeability and subsequent reduced intravascular volume. Additional studies would be needed to investigate this question further.

We conclude that in patients with severe HAE who present with intolerable side effects to danazol and/or lack of response to danazol in spite of high dosages, IRT with pC1-INH is a suitable alternative assuming that the patient is willing to perform IV injections. Further studies are urgently needed to develop convenient therapies for HAE patients suffering from severe attacks and might require effective individual treatment.

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CONFLICT OF INTEREST

CSL Behring had no influence on the design of the study, the analysis or collection of the data, the content of the report, or the decision to submit the paper for publication.

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