

Efficacy of C1 esterase inhibitor concentrate in treatment of cutaneous attacks of hereditary angioedema

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ABSTRACT

Background: Although treatment with C1 esterase inhibitor (C1-INH) concentrate is well established for hereditary angioedema (HAE) attacks in general, data that assess its efficacy for cutaneous attack treatment are sparse.

Objective: To assess efficacy of plasma-derived, nanofiltered C1-INH concentrate for cutaneous attack treatment by comparing treated attacks from the uncontrolled I.M.P.A.C.T.2 study with historical data for untreated attacks.

Methods: Cutaneous attack data from patients with HAE who were treated for cutaneous edema with 20 IU/kg body weight C1-INH concentrate in the uncontrolled I.M.P.A.C.T.2 study (38 patients) were compared with data from untreated patients from an historical data base (46 patients) and included subset analyses for facial edema (treated group, 21 patients; untreated group, 33 patients) and peripheral edema (30 patients in each group). Average attack duration (AAD) per patient was the efficacy end point used to compare treated and untreated patients. Differences were assessed with a Wilcoxon test (primary analysis) and a log-rank test; AAD per patient was analyzed descriptively and graphically with Kaplan-Meier curves.

Results: The AAD per patient of all cutaneous attacks or facial and peripheral cutaneous attack subsets was significantly faster with C1-INH treatment than without treatment (Wilcoxon and log-rank tests, both $p < .0001$ for all comparisons). Mean AADs per patient for all, facial, and peripheral attacks were 2.04, 1.45, and 2.16 days, respectively, in the C1-INH-treated group, and were 3.74, 4.45, and 2.98 days, respectively, in the untreated group. Kaplan-Meier curves corroborated the observed group differences.

Conclusion: Treatment of cutaneous HAE attacks (all attacks or facial and peripheral attack subsets) with 20 IU/kg C1-INH concentrate provided faster attack resolution compared with no treatment.

(Allergy Asthma Proc 36:1–7, 2015; doi: 10.2500/aap.2015.36.3844)

Hereditary angioedema due to C1 esterase-inhibitor (C1-INH) deficiency (hereditary angioedema C1-INH, referred to hereafter as HAE) is a rare genetic disease that involves either impaired production of functional C1-INH (HAE type I) or production of dysfunctional C1-INH (HAE type II). The clinical presentation is characterized by unpredictable episodic attacks of edema. Almost all patients with HAE experience swelling of the skin,¹ which can affect virtually any body location, including the face and genitals^{2,3}; however, mucosal edema in the abdomen and

upper airways is also common.^{4–6} At best, cutaneous attacks are uncomfortable and can be temporarily disfiguring; however, cutaneous attacks can be very painful and debilitating, and, in the case of facial cutaneous attacks, may be followed by edema in the upper airways, which can be fatal due to the potential for asphyxiation.^{6–8}

C1-INH concentrate is a reliable and effective first-line treatment option for HAE attacks.^{9–11} A plasma-derived, nanofiltered, and virus-inactivated C1-INH concentrate (Berinert; CSL Behring, Marburg, Germany) has been approved to treat acute HAE attacks in numerous countries, including the United States, and can also be used for short-term prophylaxis (preprocedure prevention of HAE attacks) in Europe.

Since 1973, the efficacy and safety of C1-INH concentrate in the treatment of HAE has been demonstrated through extensive clinical experience (>500,000 administrations)^{4,12–14} and several clinical studies.^{2,10,11,15–19} In the randomized, placebo-controlled, parallel-group International Multicenter Prospective Angioedema C1-INH Trial (I.M.P.A.C.T.1) study in which single abdominal attacks or facial cutaneous attacks were treated, 20 IU/kg was established as an effective dose of C1-INH concentrate.¹¹ In I.M.P.A.C.T.1, the average time to symptom relief for

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Presented at European Academy of Allergy and Clinical Immunology Conference in June 22–26, 2013, Milan, Italy.

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HAE attacks was significantly reduced with C1-INH concentrate compared with placebo (0.5 versus 1.5 hours [$p = .0025$, with a one-sided, two-sample Wilcoxon test], 43 versus 42 patients).¹¹ I.M.P.A.C.T.1 was followed by I.M.P.A.C.T.2, an open-label, uncontrolled, single-arm study in which the safety and efficacy of 20 IU/kg of C1-INH concentrate for successive HAE attacks at any body location was assessed in 57 patients for a total of 1085 HAE attacks.¹⁰ While I.M.P.A.C.T.1 included only facial and abdominal attacks, I.M.P.A.C.T.2 provided valuable data about the treatment of HAE attacks at all body locations.

The objective of the current analysis was to assess the efficacy of 20 IU/kg of C1-INH concentrate for treatment of acute cutaneous attacks (including facial and peripheral attacks) by comparing data from I.M.P.A.C.T.2 patients with historical data on untreated cutaneous attacks. This was of interest because the placebo-controlled I.M.P.A.C.T.1 study did not assess treatment of peripheral cutaneous attacks with 20 IU/kg of C1-INH concentrate and only assessed a low number of facial cutaneous attacks (9 facial attacks), and the I.M.P.A.C.T.2 study, which assessed a large number of cutaneous attacks, did not have a control group. Because it would be unethical to conduct another placebo-controlled study to formally prove the efficacy of 20 IU/kg of C1-INH concentrate versus placebo for cutaneous HAE attacks, use of an historical untreated control group was selected for the current analysis.

The historical untreated cutaneous attack data selected for the comparison with I.M.P.A.C.T.2 data were derived from an earlier observational study by Bork *et al.*,² conducted between 1976 and 2007, which assessed the efficacy of fixed doses of 500 and 1000 IU of C1-INH concentrate for treatment of cutaneous attacks by comparing cases in which the same patients were treated or not treated with C1-INH concentrate for cutaneous attacks. Fixed doses were used throughout this study because a body-weight-adjusted C1-INH concentrate regimen had not yet been approved when this study was conducted. Analysis of results of this study indicated that fixed doses of C1-INH concentrate are effective for the treatment of cutaneous HAE attacks by performing intrasubject comparisons of 2104 cutaneous HAE attacks treated in the clinic with 9046 untreated attacks. The current analysis compared cutaneous attack data (average attack duration [AAD] per patient) from patients treated with 20 IU/kg of C1-INH concentrate in I.M.P.A.C.T.2 with the untreated cutaneous attack data from the study by Bork *et al.*²

PATIENTS AND METHODS

Patients

Two patient groups were compared in this study: an active treatment group of patients who were

treated for successive cutaneous attacks with 20 IU/kg of C1-INH concentrate (Berinert; CSL Behring, Marburg, Germany) in the open-label, uncontrolled I.M.P.A.C.T.2 study¹⁰ and a group of historical control patients who had cutaneous attacks that were not treated and were part of an earlier study (Bork *et al.*²). Patients in the active treatment group were treated with a single intravenous dose of 20 IU/kg of C1-INH concentrate for each successive cutaneous attack. All data for the active treatment group were collected at study centers in North America between August 2005 and February 2010. All data for the historical controls were collected between 1976 and 2007 at the Angioedema Outpatient Service, University Hospital, Mainz, Germany, and were stored in a hospital data base. Further details of the methods and results from patients in each group are described by Craig *et al.*¹⁰ and Bork *et al.*²

In I.M.P.A.C.T.2, all attack severities were treated. Patients in I.M.P.A.C.T.2 assessed attack severity as mild ("did not interfere with routine activities"), moderate ("interfered with routine activities"), or severe ("impossible to perform routine activities"); whereas, in the study by Bork *et al.*,² "patients were counseled that mild skin swellings should not be treated," although "treatment was recommended for all facial and genital attacks." Mild skin swellings were defined as "swellings limited to the back of one hand or foot or swellings at one extremity or at the trunk, with a diameter of <20 cm." Although the recommendation not to treat mild peripheral swellings could have created a bias in the data when comparing these patients with the patients from I.M.P.A.C.T.2 (in which mild attacks were treated), most of the cutaneous attacks that were not treated in the study by Bork *et al.*² occurred either before the patients had been diagnosed with HAE and were reported by patients retrospectively (*i.e.*, after HAE diagnosis) or occurred when C1-INH concentrate was unavailable.

Efficacy End Points

Efficacy data in this analysis relate to acute attacks of cutaneous edema of any severity that occurred in the face or peripheral locations. In addition to a combined analysis of all the patients with facial or peripheral attacks, facial and peripheral attacks were analyzed as separate subsets. Facial attacks were of interest due to the potential for subsequent development of potentially life-threatening laryngeal edema, and peripheral attacks were of interest due to their tendency to spread to other locations when left untreated.^{2,7,8,21}

In I.M.P.A.C.T.2, the efficacy of C1-INH concentrate was assessed as the time from the start of treatment to "onset of symptom relief" (primary efficacy end point) and to "complete resolution of HAE symptoms" (sec-

ondary efficacy end point). Because no study medications or placebo were administered to patients in the historical control group, the time from the start of treatment was not applicable to these patients, and the duration of the entire attack was measured instead. Therefore, in the current analysis, a modified efficacy end point, AAD per patient, defined as the per-patient average of the durations between attack onset and complete resolution of all attack symptoms, was used to allow meaningful comparison of the two groups.

For the I.M.P.A.C.T.2 data set, AAD (in hours) of all the treated cutaneous attacks was calculated per patient as the sum of all attack durations per patient divided by the number of attacks per patient. Missing values for the time between the start of an attack and complete resolution of all symptoms were imputed by the sum of the maximum time to treatment resolution over all attacks documented for the patient in the I.M.P.A.C.T.2 data set (if the patient had more than one attack) and the individual time between the start of the attack and study drug administration. For the historical control group, AAD (in hours) was calculated for each patient by using a weighted average as follows: the AAD (in days) at each cutaneous location was multiplied by the number of attacks at that location. The sum of all these values was then multiplied by 24 and divided by the total number of cutaneous attacks for the patient. Attack locations were categorized as trunk, genital, facial, foot, or hand.

Data Analysis

For the primary test, the AADs per patient of each patient group were compared by using a two-sample Wilcoxon test on AADs per patient between the C1-INH-treated and C1-INH-untreated groups, and, for the secondary test, the AADs per patient were compared by using a two-sided log-rank test on AADs per patient between treated and untreated groups. For the Wilcoxon test, the null hypotheses ($H_0: p = .50$ [AADs per patient in untreated group $\geq$ AADs per patient in treated group]) was assessed versus the two-sided alternative hypothesis ($H_1: p \neq .50$ [AADs per patient untreated group $\geq$ AADs per patient treated group]) when accepting a maximum type-I error rate of 5% ($\alpha = .05$).

In addition, a Hodges-Lehmann estimator, including confidence intervals (CIs), for the median difference of AADs per patient between C1-INH-treated and C1-INH-untreated groups was calculated to estimate the treatment effect.²⁰ AAD per patient was also analyzed descriptively (including mean, 90% CI, standard deviation, median, range, quantiles) and graphically (Kaplan-Meier curves). All statistical analyses were performed with SAS software (SAS Institute Inc., Cary, NC).

RESULTS

Demographic Characteristics

For all cutaneous attacks, data from 38 patients treated with 20 IU/kg of C1-INH concentrate were compared with data from 46 untreated control patients; for the subset of facial cutaneous attacks, data from 21 patients treated with C1-INH concentrate were compared with data from 33 untreated control patients; and for the subset of cutaneous peripheral attacks, data from 30 patients treated with C1-INH concentrate were compared with data from 30 untreated control patients (Table 1). The proportions of patients with HAE type I and type II were comparable between the treated and untreated groups for all cutaneous attacks and for the peripheral attack subset, whereas the proportion of patients with type II HAE was higher in the treated compared with untreated group for the facial attack subset (23.8% compared with 12.1%).

In addition, for the facial attack subset only, there was a slightly higher proportion of females in the treated group relative to the untreated group (81.0% versus 69.7%). On average, the treated patients were younger than the untreated patients (all attacks, 30.7 versus 41.9 years; facial, 27.8 versus 42.1 years; cutaneous, 31.9 versus 42.7 years). However, age was recorded at baseline for the treated patients from I.M.P.A.C.T.2, whereas it was recorded at the end of the study for the untreated historical control patients, which might account for this difference. Fewer cutaneous attacks were assessed among the treated patients than the untreated patients due to the different time periods over which data were collected (for treated versus untreated, all attacks: 288 versus 9046 attacks; facial, 51 versus 628; peripheral, 237 versus 8418). Data were collected for fewer than 5 years from treated patients in the I.M.P.A.C.T.2 study, whereas data were collected for up to 31 years from untreated historical control patients in the study by Bork *et al.*²

Efficacy

The mean AAD per patient for all cutaneous attacks was shorter in the treated patients (2.04 days) compared with the untreated patients (3.74 days), and the difference in AAD per patient for all cutaneous attacks between treated and untreated patients was significant (Wilcoxon test $p < .0001$ and log-rank test $p < .0001$) (Table 2). Mean AAD per patient was also shorter for treated patients compared with untreated patients for the facial (1.45 versus 4.45 days) and peripheral (2.16 versus 2.98 days) attack subsets, and the difference in AAD per patient between the treated and untreated patients for both attack subsets was significant (facial, Wilcoxon test $p < .0001$ and log-rank test $p < .0001$; peripheral, Wilcoxon test $p < .00001$ and log-rank test $p < .0001$). The median difference between the treated

Table 1. Demographic characteristics of patients with cutaneous HAE attacks

Parameter	Patients treated with C1-INH	Untreated historical controls
Total attacks		
N	38	46
Age, $\pm$ SD (range), y	30.7 $\pm$ 11.83 (10–53)	41.9 $\pm$ 16.11 (7–70)
Sex		
Male, no. (%)	11 (28.9)	15 (32.6)
Female, no. (%)	27 (71.1)	31 (67.4)
HAE type		
Type I, no. (%)	33 (86.8)	40 (87.0)
Type II, no. (%)	5 (13.2)	6 (13.0)
Cutaneous HAE attacks		
Total no.	288	9046
Mean no. per patient	7.58	196.65
Facial attack subset		
N	21	33
Age, mean $\pm$ SD (range), y	27.8 $\pm$ 12.35 (10–53)	42.1 $\pm$ 16.26 (7–70)
Sex		
Male, no. (%)	4 (19.0)	10 (30.3)
Female, no. (%)	17 (81.0)	23 (69.7)
HAE type		
Type I, no. (%)	16 (76.2)	29 (87.9)
Type II, no. (%)	5 (23.8)	4 (12.1)
Facial HAE attacks		
Total no.	51	628
Mean no. per patient	2.43	19.03
Peripheral attack subset		
N	30	30
Age, mean $\pm$ SD (range), y	31.9 $\pm$ 11.94 (10–53)	42.7 $\pm$ 15.60 (17–70)
Sex		
Male, no. (%)	10 (33.3)	9 (30.0)
Female, no. (%)	20 (66.7)	21 (70.0)
HAE type		
Type I, no. (%)	26 (86.7)	28 (93.3)
Type II, no. (%)	4 (13.3)	2 (6.7)
Peripheral HAE attacks		
Total no.	237	8418
Mean no. per patient	7.90	280.6

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; N = total number of patients; SD = standard deviation. Note that patients who experienced both facial and peripheral attacks could be included in both subsets.

and untreated groups, as estimated by the Hodges-Lehmann estimator (C1-INH treated group values minus untreated group values), was -1.64 days (95% CI, -2.24 to -1.24 days) for all cutaneous attacks, -2.61 days (95% CI, -4.02 to -1.84 days) for facial attacks, and -1.25 days (95% CI, -1.52 to 0.92 days) for peripheral attacks, which indicates that attack durations were shorter for the treated patients compared with the untreated patients. In line with this, Kaplan-Meier curves for all cutaneous attacks indicated that the AAD per patient was ≤ 2 days in $\sim 76\%$ of treated patients, whereas it was ≤ 2 days in only $\sim 11\%$ of the untreated

patients (Fig. 1). For facial and peripheral attacks, Kaplan-Meier curves indicated that the AAD per patient was ≤ 2 days in $\sim 71\%$ of treated patients with facial attacks and $\sim 83\%$ of treated patients with peripheral attacks compared with $\sim 4\%$ of untreated patients with facial attacks and $\sim 7\%$ of untreated patients with peripheral attacks (data not shown).

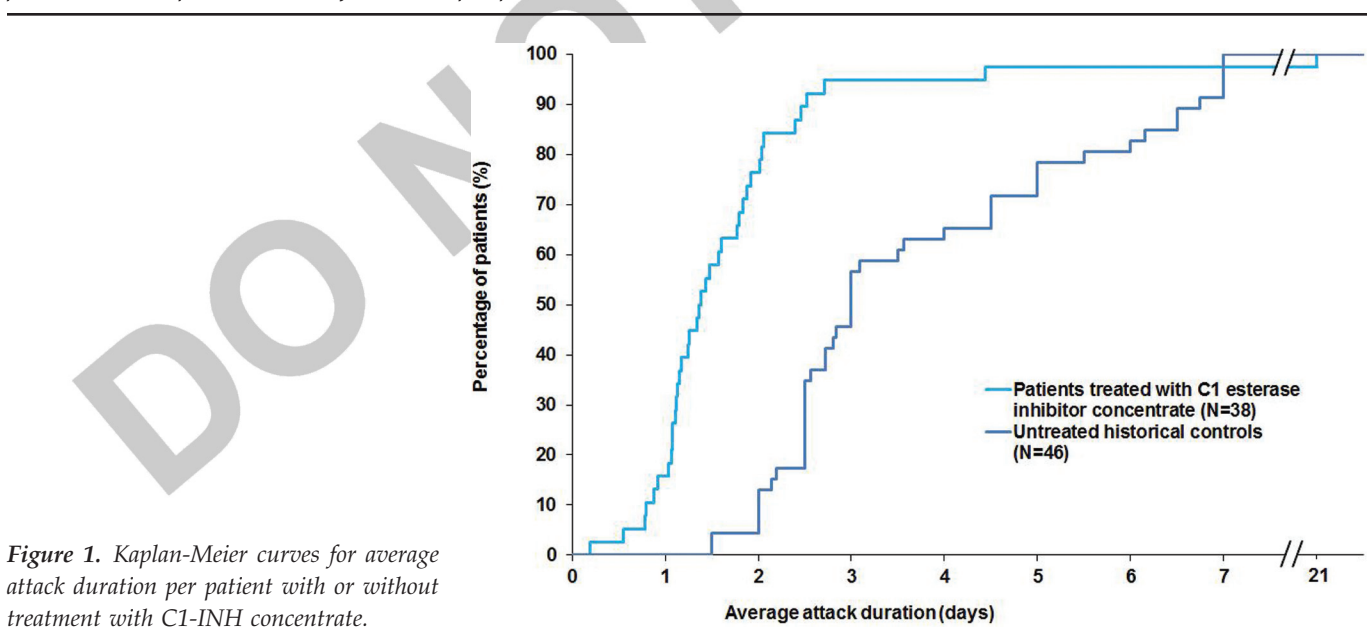
DISCUSSION

Data on the efficacy of C1-INH concentrate for treatment of cutaneous HAE attacks are sparse. At the

Table 2. Average attack duration per patient in patients treated with C1-INH concentrate and untreated historical controls

	Average Attack Duration, days		Primary Analysis, Wilcoxon Test	Secondary Analysis, Log-Rank Test
	Patients Treated With C1-INH	Untreated Historical Controls		
Total attacks				
N	38	46	$p < .0001$	$p < .0001$
Mean $\pm$ SD	2.04 $\pm$ 3.25	3.74 $\pm$ 1.50		
90% CI	1.16–2.93	3.31–4.17		
Median (range)	1.37 (0.19–21.02)	3.00 (1.50–7.00)		
Quantiles (25%, 75%)	(1.08, 1.92)	(2.50, 5.00)		
Facial attacks				
n	21	33	$p < .0001$	$p < .0001$
Mean $\pm$ SD	1.45 $\pm$ 1.03	4.45 $\pm$ 1.99		
90% CI	1.07–1.84	3.86–5.04		
Median (range)	1.26 (0.19–4.39)	4.00 (2.00–9.50)		
Quantiles (25%, 75%)	(0.61, 2.02)	(2.50, 6.50)		
Peripheral attacks				
n	30	30	$p < .00001$	$p < .0001$
Mean $\pm$ SD	2.16 $\pm$ 3.63	2.98 $\pm$ 1.28		
90% CI	1.03–3.29	2.58–3.37		
Median (range)	1.29 (0.70–21.02)	2.50 (1.50–7.00)		
Quantiles (25%, 75%)	(1.08, 1.78)	(2.19, 3.09)		

C1-INH = C1 esterase inhibitor; CI = confidence interval; N = number of patients; SD = standard deviation. Note that patients who experienced both facial and peripheral attacks could be included in both subsets.



recommended dosage of 20 IU/kg of C1-INH concentrate for treatment of acute HAE attacks, I.M.P.A.C.T.1 and I.M.P.A.C.T.2 provided data for cutaneous attack treatment; however, in the placebo-controlled I.M.P.A.C.T.1, few cutaneous attacks (9 facial attacks in 9 patients) were treated with 20 IU/kg of C1-INH concentrate and in I.M.P.A.C.T.2, although a higher number of attacks were treated with 20 IU/kg of C1-INH

concentrate, including attacks at any cutaneous location, there was no control group with which a comparison could be performed. Due to the risk to patients for treating cutaneous HAE attacks with placebo, it is considered unethical to conduct another placebo-controlled study to formally prove the efficacy of C1-INH concentrate versus placebo for cutaneous HAE attacks. Thus, in the present analysis, we compared the I.M.P.A.C.T.2 data for

cutaneous attacks treated with 20 IU/kg of C1-INH concentrate with historical data for untreated cutaneous attacks to assess whether the recommended dose of C1-INH concentrate provides a clinical benefit to patients with cutaneous HAE attacks.

In the current analysis, the average duration of cutaneous HAE attacks per patient (all attacks and facial and peripheral attack subsets) was statistically significantly shorter in patients treated with 20 IU/kg of C1-INH concentrate relative to untreated patients. In line with this, the median difference between the treated and untreated groups, as estimated by the Hodges-Lehmann estimator, was -1.64 days for all cutaneous attacks, -2.61 days for facial attacks, and -1.25 days for peripheral attacks, which was a clinically relevant treatment effect and which indicates that patients recovered considerably faster from cutaneous HAE attacks after treatment with 20 IU/kg of C1-INH concentrate compared with no treatment.

These results are consistent with findings from our 2008 study,² in which intraindividual comparisons between untreated attacks and attacks treated with fixed doses of C1-INH concentrate (500 or 1000 IU) revealed that the average cutaneous HAE attack duration was significantly lower after C1-INH concentrate compared with no treatment (1.7 compared with 3.2 days, respectively; $p < .0001$, Wilcoxon test). However, unlike in the current analysis, this was demonstrated with fixed doses of C1-INH concentrate (500 to 1000 IU), not doses adjusted for patient body weight, the latter of which was in line with the current dosing recommendations.

Results of the current analysis are in agreement with the rapid onset of symptom relief observed for facial attacks in the placebo-controlled I.M.P.A.C.T.1 study. However, differences between C1-INH concentrate and placebo in I.M.P.A.C.T.1 did not reach statistical significance due to the small number of patients that experienced facial attacks: 9 in the 20 IU/kg C1-INH concentrate group and 8 in the placebo group.¹¹

Although the efficacy of C1-INH concentrate for the treatment of acute HAE attacks in general is well established through more than 30 years of clinical experience and several controlled trials, the current analysis adds to the limited efficacy data that directly compare C1-INH concentrate with placebo or no treatment for cutaneous HAE attacks specifically.^{2,4,11-18} Controlled studies have mainly investigated the treatment of abdominal HAE attacks, with relatively low numbers of patients experiencing cutaneous HAE attacks.^{11,17}

The observed differences in cutaneous HAE attack duration (all cutaneous attacks and facial and peripheral attack subsets) between C1-INH-treated and untreated patients in the current analysis are clinically meaningful. The clinical importance of treating facial cutaneous HAE attacks is highlighted by observations

that up to 28.5% of facial swelling episodes may be either accompanied by or quickly followed by laryngeal edema, which can be life threatening.^{2,7,8} In addition, although edema of the extremities may be considered as having little clinical importance, untreated HAE attacks affect the extremities, can spread, are often located at multiple body locations, may be painful and distressing, and may disrupt daily activities for several days.^{2,21,22} Extremities are also one of the most common body sites affected by edema after the abdomen.^{22,23} Thus, use of a C1-INH concentrate to reduce the duration of cutaneous attacks, which are experienced by almost all patients with HAE, would be clinically beneficial.¹ Indeed, in Bork *et al.*,² we demonstrated that C1-INH concentrate can reduce the spread of cutaneous HAE attacks to other body locations. In this study, after treatment with C1-INH concentrate, none of the 483 facial attacks occurred simultaneously with a laryngeal attack, whereas without treatment, 51 of 628 facial attacks (8.1%) were accompanied by laryngeal edema.² Likewise, no treated peripheral attacks in Bork *et al.*² were complicated by further swelling at another limb or by spreading of swelling to larger skin areas, whereas spreading was reported in 29% of untreated peripheral attacks.

There were several advantages and limitations associated with the design and conduct of the current analyses. One important advantage was that, by using historical data for untreated attacks, we were able to avoid the ethical dilemma of conducting a study in which patients' HAE attacks were not treated with C1-INH concentrate. The risk to patients for treating cutaneous attacks with placebo was considered greater than the potential limitations of making comparisons to historical data sets.

However, the use of historical data to make comparisons has some unavoidable shortcomings, including differences in methodology between I.M.P.A.C.T.2¹⁰ and Bork *et al.*² and the inability to randomize patients into study groups, which would minimize or eliminate potential bias. Some demographic characteristics (age [all attack types], HAE type [facial attack subset only], and sex [facial attack subset only]) did differ between treated and untreated groups; however, a subgroup analysis of I.M.P.A.C.T.2 data revealed no clinically relevant or consistent indications that suggested that sex, age, or HAE type would have an effect on efficacy.¹⁰ Thus, a comparison of the untreated and treated groups in the current study can be made regardless of demographic differences.

Another potential limitation was the possibility for cutaneous attacks in the untreated control group (Bork *et al.*²) to differ in terms of attack severity compared with I.M.P.A.C.T.2. In Bork *et al.*,² "patients were counseled that mild skin swellings should not be treated" (with the exception of facial and genital attacks), which

could have resulted in a greater number of mild peripheral cutaneous attacks being included in the untreated group than in the treated group. However, untreated attack data were mainly derived from either retrospective reports of attacks that had occurred before patients were diagnosed with HAE, or instances in which C1-INH concentrate was not available to the patients for other reasons. Thus, untreated cutaneous attacks from the historical data set and treated cutaneous attacks from I.M.P.A.C.T.2 did not necessarily differ in severity, but a difference cannot be ruled out.

In summary, 20 IU/kg of C1-INH concentrate provided clinically relevant faster cutaneous HAE attack resolution (across all attacks and facial and peripheral cutaneous attack subsets) relative to no treatment. This analysis is consistent with the reduced duration of cutaneous HAE attacks that was observed after treatment with fixed doses of C1-INH concentrate (500 or 1000 IU) compared with no treatment that was observed in the study by Bork *et al.*² The current analysis provides relevant information regarding the potential clinical benefit of treating cutaneous attacks at the recommended dose of 20 IU/kg of C1-INH concentrate through comparison of treated patients with an untreated control group. This analysis had the advantage of assessing a much larger number of patients with cutaneous attacks than was assessed in the previous controlled trial, I.M.P.A.C.T.1, and assessing a greater variety of attack locations (facial plus peripheral locations) than I.M.P.A.C.T.1 (facial attacks only).

ACKNOWLEDGMENTS

We thank Michael Riley, Eva Kestner, and Jasmine Smith of Trilogy Writing and Consulting GmbH, Frankfurt am Main, Germany, for providing medical writing services on behalf of CSL Behring.

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