Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE SKIN AND EYE DISEASES

C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks – final results of the I.M.P.A.C.T.2 study

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To cite this article: Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, Moy JN, Offenberger J, Jacobson KW, Yang WH, Eidelman F, Janss G, Packer FR, Rojavin MA, Machnig T, Keinecke H-O, Wasserman RL. C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks – final results of the I.M.P.A.C.T.2 study. *Allergy* 2011; **66**: 1604–1611.

Keywords
Berinert; C1 esterase inhibitor concentrate; C1-inhibitor replacement therapy; Hereditary Angioedema.

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Accepted for publication 5 August 2011

DOI:10.1111/j.1398-9995.2011.02702.x

Edited by: Werner Aberer

Abstract

Background: The placebo-controlled study International Multicentre Prospective Angioedema C1-INH Trial 1 (I.M.P.A.C.T.1) demonstrated that 20 U/kg C1 esterase inhibitor (C1-INH) concentrate (Berinert®; CSL Behring, Marburg, Germany) is effective in treating acute abdominal and facial Hereditary Angioedema (HAE) attacks.

Methods: I.M.P.A.C.T.2 was an open-label extension study of I.M.P.A.C.T.1 to evaluate the safety and efficacy of long-term treatment with 20 U/kg C1-INH for successive HAE attacks at any body location. Efficacy outcomes included patient-reported time to onset of symptom relief (primary) and time to complete resolution of all symptoms (secondary), analysed on a per-patient and per-attack basis. Safety assessments included adverse events, vital signs, viral safety and anti-C1-INH antibodies.

Results: During a median study duration of 24 months, 1085 attacks were treated in 57 patients (10–53 years of age). In the per-patient analysis, the median time to onset of symptom relief was 0.46 h and was similar for all types of attacks (0.39–0.48 h); the median time to complete resolution of symptoms was 15.5 h (shortest for laryngeal attacks: 5.8 h; 12.8–26.6 h for abdominal, peripheral and facial attacks). Demographic factors, type of HAE, intensity of attacks, time to treatment, use of androgens and presence of anti-C1-INH antibodies had no clinically relevant effect on the efficacy outcomes. There were no treatment-related safety concerns. No inhibitory anti-C1-INH antibodies were detected in any patient.

Conclusions: A single dose of 20 U/kg C1-INH concentrate is safe and provides reliable efficacy in the long-term treatment of successive HAE attacks at any body location.

Abbreviations
bw, body weight; C1-INH, C1 esterase inhibitor; HAE, Hereditary Angioedema; I.M.P.A.C.T., International Multicentre Prospective Angioedema C1-INH Trial.

Hereditary Angioedema (HAE) (type I and II) is a rare autosomal dominant disorder, characterized by C1 esterase inhibitor (C1-INH) deficiency (1); the estimated prevalence is between 1 : 10 000 and 1 : 50 000 individuals (2). Patients

with HAE have intermittent attacks of oedema involving the extremities, submucosa of the gastrointestinal tract, external genitalia, face, or upper airway (3). The first-line therapy for HAE attacks in most countries includes replacement therapy with C1-INH concentrate (4).

Berinert® (CSL Behring, Marburg, Germany) is a highly purified, pasteurized and lyophilized plasma-derived C1-INH concentrate that has been approved in more than 30 countries for the treatment of HAE attacks, most recently in the United States (2009) and Canada (2010).

While extensive clinical experience supports the efficacy of C1-INH concentrate (5–7), and the efficacy of treating single attacks with C1-INH concentrate has been demonstrated in randomized, placebo-controlled studies (8–11), only limited data from prospective studies are available on long-term treatment of successive HAE attacks with C1-INH concentrate (10). The International Multicenter Prospective Angioedema C1-INH Trial 2 (I.M.P.A.C.T.2) is an extension of the randomized, placebo-controlled I.M.P.A.C.T.1 that previously established 20 U/kg body weight (bw) as an effective dose of C1-INH concentrate in the treatment of abdominal and facial HAE attacks (9). Whereas only single abdominal or facial attacks were treated in I.M.P.A.C.T.1, the objective of I.M.P.A.C.T.2 was to assess the efficacy and safety of long-term treatment of successive HAE attacks at any body location, including the larynx. Interim results from I.M.P.A.C.T.2 for a subset of abdominal and facial attacks and laryngeal attacks have been published previously (12, 13). Here, we report the final results from 1085 attacks at any body location that were treated during a median study duration of 24 months, including >200 peripheral attacks. To date, this is the largest number of HAE attacks treated in a prospective study. For the first time, development of anti-C1-INH antibodies was assessed as a safety variable in a prospective study of C1-INH.

Methods

Study design

This prospective, open-label, uncontrolled, multicentre extension study (I.M.P.A.C.T.2, clinicaltrials.gov identifier: NCT00292981) was conducted between August 2005 and February 2010 at 15 centres in North America that had participated in I.M.P.A.C.T.1; it was designed to provide additional safety and efficacy data on the long-term use of C1-INH concentrate for the treatment of subsequent HAE attacks at any body location.

The study protocol was approved by the institutional review board at each participating centre or a central institutional review board; written informed consent was obtained from each patient or, in the case of a minor, by a legally acceptable representative.

Patients were eligible for I.M.P.A.C.T.2 if they had any type of HAE attack and had previously participated in I.M.P.A.C.T.1, for which they had to be ≥6 years of age with HAE type I or II. Treatment with C1-INH concentrate in I.M.P.A.C.T.1 had to be >24 h before enrolment into I.M.P.A.C.T.2. Patients eligible for I.M.P.A.C.T.1 who had a laryngeal attack could be directly enrolled in I.M.P.A.C.T.2. The main exclusion criteria were a history of hypersensitivity to C1-INH concentrate, use of any C1-INH concentrate within 24 h before start of treatment, use of fresh frozen or native plasma within 7 days before treatment start, HAE type III and acquired angio-oedema.

Reflecting clinical practice, generally no restrictions were specified for the time between the onset of an attack and the start of C1-INH replacement therapy, for the intensity of an attack, or for prior or concomitant medications.

After enrolment, patients received a single intravenous dose of 20 U/kg bw of C1-INH concentrate for each attack evaluated at the study centre. Additional doses of C1-INH concentrate were given for some attacks. After treatment, patients were observed at the study centre until the onset of symptom relief.

Study outcomes

The primary endpoint was the time from start of treatment to onset of symptom relief, as determined by the patient's responses to a standard question posed at predetermined intervals. The secondary endpoint was the patient-reported time to complete resolution of HAE symptoms. Vital signs were measured at appropriate intervals until discharge from the clinic or until 24 h after treatment, whichever occurred first. Adverse events were recorded for 7–9 days after treatment of each attack. Anti-C1-INH antibodies were evaluated at a baseline visit, every 3 months thereafter and at the end of the study, using a direct binding enzyme-linked immunosorbent assay, as described previously (14). Assays included a screening assay, a confirmatory assay for determination of isotypes of antibodies, and, for positive samples (titre ≥1 : 50), an anti-C1-INH antibody inhibition assay [based on the principle of the VIII-Bethesda assay (15)] for assessing the neutralizing capacity of the respective antibodies. All analyses were conducted at the CSL Behring central laboratory for clinical testing (Marburg, Germany); the assays were fully validated. Assays for markers of viral infection were performed before treatment of the first attack and 7–9 days (parvovirus B19) or 12 weeks (human immunodeficiency virus type 1 and 2 and hepatitis A, B and C virus) after treatment of this attack and at the end of the study.

Statistical analysis

Efficacy and safety data were analysed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). There was no sample size calculation, as all patients in North America who had participated in I.M.P.A.C.T.1 or had been eligible for I.M.P.A.C.T.1 and developed laryngeal oedema were eligible for I.M.P.A.C.T.2.

Efficacy

Efficacy analyses were based on the intention-to-treat principle and included all patients and attacks treated with C1-INH concentrate. Descriptive statistics were calculated for all

Table 1 Demographic and baseline characteristics

Characteristic	Intention-to-treat population (n = 57)
Sex and number (%) of patients	
Female	38 (66.7)
Male	19 (33.3)
Age (years) at study start	
Mean (SD)	31.9 (11.98)
Range	10–53
Race or ethnic group and number (%) of patients	
Caucasian	50 (87.7)
Black	3 (5.3)
Oriental	2 (3.5)
Hispanic	1 (1.8)
Other	1 (1.8)
BMI (kg/m^2) at study start	
Mean (SD)	26.9 (4.90)
Range	18–38
Primary disease characteristic and number (%) of patients	
HAE type I	49 (86.0)
HAE type II	7 (12.3)
Unknown*	1 (1.8)

BMI, body mass index; HAE, Hereditary Angioedema; *N*, number of patients; SD, standard deviation.
*For this patient, the type of HAE was reported as 'unknown'; the patient was retrospectively found not to have HAE.

efficacy outcomes on a per-patient and per-attack basis and two-sided 95% confidence intervals were calculated for the median times to onset of symptom relief and to complete resolution of HAE symptoms. Per-patient analyses were based on the mean times of all attacks in a given patient. Missing times to onset of symptom relief or to complete resolution of HAE symptoms were imputed with conservative values. Efficacy analyses were conducted based on all attacks and by body location of HAE attacks. Subgroup analyses were conducted by gender, age class, race/ethnic group, type of HAE, intensity of HAE attack, time from start of attack to start of treatment, use of androgens and presence of anti-C1-INH antibodies (i.e. antibody detection at least once during the study).

Safety and tolerability

All patients treated with C1-INH concentrate were included in the safety analysis. Adverse events were coded according to the Medical Dictionary for Regulatory Affairs (version 13.0). Incidence rates were calculated for adverse event preferred terms. Data for anti-C1-INH antibodies, vital signs and viral safety were analysed descriptively.

Results

Study population

A total of 1085 HAE attacks in 57 patients were treated with C1-INH concentrate. Thirty-eight patients were women and 19 were men (Table 1). Patients were between 10 and 53 years of age, including 1 child <12 years of age and six adolescents <17 years of age. Majority of patients had HAE type I (49 patients); seven patients had HAE type II. In one patient with unknown HAE, retrospective genetic testing did not confirm the diagnosis of HAE.

Patients were in the study for a median duration of 24 months (range: 0–51 months), during which time they received C1-INH concentrate for a median of 7 attacks (range: 1–184 attacks). The predominant type of HAE attack was abdominal, followed by peripheral, facial and laryngeal attacks (Table 2).

Efficacy outcomes

Only the results from the per-patient analysis are discussed in the text; results of the per-attack analysis are available in Table 3.

Table 2 Hereditary Angioedema attack characteristics

Attack characteristic	Abdominal	Peripheral	Facial	Laryngeal
Number (%) of patients (N = 57)	51 (89.5)	30 (52.6)	21 (36.8)	16 (28.1)
Number (%) of attacks (N = 1085)*	747 (68.8)	235 (21.7)	51 (4.7)	48 (4.4)
Number (%)† of attacks by intensity according to the patients' assessment at baseline for each attack				
Mild	127 (17.0)	82 (34.9)	13 (25.5)	7 (14.6)
Moderate	453 (60.6)	135 (57.4)	28 (54.9)	21 (43.8)
Severe	162 (21.7)	18 (7.7)	10 (19.6)	20 (41.7)
Median time between estimated start of attack and treatment in hours (range)‡	5.88 (0.98–149.82)	5.87 (1.00–60.00)	4.28 (0.55–24.67)	3.15 (0.85–94.50)

HAE, Hereditary Angioedema; *N*, number of patients/attacks.
*Three patients experienced four HAE attacks that were classified as 'other' ['right inner cheek' (not reported as facial attack according to the investigator because there were no external facial signs); 'scrotal swelling'; 'moderate nonpitting oedema to midline buttocks superior to anus' and 'other'].
†Percentages based on the number of attacks per attack type.
‡The time between the estimated start of the attack and treatment was missing for three abdominal attacks, one peripheral attack and one facial attack.

Table 3 Per-attack analysis of efficacy endpoints, administration of additional doses of C1-INH and rebound attacks – I.M.P.A.C.T.2 results

Statistic	All attacks (*n* = 1085)*	Abdominal (*n* = 747)	Peripheral (*n* = 235)	Facial (*n* = 51)	Laryngeal (*n* = 48)
Time to onset of symptom relief (h)					
Median (range)	0.37 (0.05–497.0)†	0.32 (0.05–497.0)†	0.50 (0.07–31.37)	0.40 (0.08–15.33)	0.25 (0.10–1.25)
Number (%) of attacks with time to onset of symptom relief of					
<1 h	1011 (93.2)	716 (95.9)	204 (86.8)	42 (82.4)	45 (93.8)
<4 h	1076 (99.2)	746 (99.9)	228 (97.0)	50 (98.0)	48 (100)
Time to complete resolution of HAE symptoms (h)					
Median (range)	14.28 (0.17–497.0)†	10.45 (0.18–497.0)†	23.48 (0.17–497.0)†	28.33 (0.87–107.9)	8.38 (0.63–61.83)
Number (%) of attacks with additional doses of 20 U/kg bw C1-INH or rebound attacks					
Additional doses	12 (1.1)	12 (1.6)	0	0	0
Rebound attacks‡	1 (<0.1)	1 (0.1)	0	0	0

bw, body weight; C1-INH, C1 esterase inhibitor; HAE, Hereditary Angioedema; *N*, number of attacks.

*Three patients experienced four HAE attacks that were classified as 'other' ('right inner cheek' [not reported as facial attack according to the investigator because there were no external facial signs); 'scrotal swelling'; 'moderate nonpitting oedema to midline buttocks superior to anus' and 'other'].

†As retrospective genetic testing did not confirm the diagnosis of HAE, one patient was discontinued from the study after having been treated for one abdominal event. The time to complete resolution of all HAE symptoms of 497 h for this event was included in the analysis and was used for conservative imputations of missing values.

‡Defined as new attacks starting before complete resolution of HAE symptoms of the previous attack.

Time to onset of symptom relief

The median time to onset of symptom relief was 0.46 h (Table 4). The individual average time to onset of symptom relief was < 1 h in 89.5% of patients. The median times to onset of symptom relief were comparable for all types of attacks (between 0.39 and 0.48 h).

Time to complete resolution of HAE symptoms

The median time to complete resolution of HAE symptoms was 15.5 h (Table 4). The individual average time to complete resolution of HAE symptoms was < 24 h in 71.9% of patients. The median time to complete resolution of HAE symptoms was shortest for laryngeal attacks.

Multiple doses of C1-INH concentrate

A single dose of 20 U/kg bw of C1-INH concentrate was sufficient to effectively treat 1073 of 1085 HAE attacks (99%). Additional doses of C1-INH concentrate (up to a total dose of 60 U/kg bw per attack) were administered for 12 abdominal attacks in six patients for worsening of the HAE attacks (four cases; identified by worsening symptoms after initial symptomatic improvement that were reported as adverse events) or because the patients felt that the attack did not resolve quickly enough (eight cases) (Table 3). The time to complete resolution of HAE symptoms for these attacks was > 24 h, while the time to onset of symptom relief ranged between 0.18 and 0.75 h (except for one attack with a time to onset of symptom relief of 3.25 h). None of the attacks treated with additional doses of C1-INH concentrate were associated with adverse drug reactions.

Subgroup analyses

Both the median times to onset of symptom relief and complete resolution of HAE symptoms were comparable when analysed by gender, intensity of HAE attack, time from estimated start of attack to start of treatment, use of androgens and presence of noninhibitory anti-C1-INH antibodies; the confidence intervals overlapped for all subgroups (Fig. 1). Although the numbers of patients in some subgroups by age group, race/ethnic group (data not shown) and type of HAE were too small for meaningful conclusions, there were no trends to suggest any differences in the median times to onset of symptom relief or complete resolution of HAE symptoms (Fig. 1A,B).

Safety and tolerability

Twenty-five patients (43.9%) experienced at least one adverse event (Table 5). Most adverse events were mild or moderate in intensity. One patient discontinued from the study owing to an infusion-related reaction (see Table 5 for details). The most frequently reported adverse events were headache (five patients) and nasopharyngitis (three patients). The only adverse events that indicated worsening of an HAE attack occurred in a patient who had adverse events that mostly represented worsening of symptoms of four abdominal attacks (see above). No emergency procedures were needed for patients with laryngeal attacks.

Nineteen patients (33.3%) tested positive for anti-C1-INH antibodies at least once; eight of these patients already had antibody-positive results at screening for I.M.P.A.C.T.1. None of the anti-C1-INH antibodies detected were inhibitory. There was no clinically relevant association of the presence of noninhibitory anti-C1-INH antibodies with the efficacy of C1-INH (Fig. 1E,F) and there were no clinically relevant differences in the proportions of patients experiencing adverse events (data not shown).

No clinically relevant changes in vital signs were observed after administration of C1-INH concentrate and there were no

Table 4 Per-patient analysis of efficacy endpoints – I.M.P.A.C.T.2 and I.M.P.A.C.T.1 results

	I.M.P.A.C.T.2 results					
	20 U/kg bw C1-INH*					Placebo
Statistic	All attacks (n = 57)	Abdominal (n = 51)	Peripheral (n = 30)	Facial (n = 21)	Laryngeal (n = 16)	(n = 0)
Time to onset of symptom relief (h)						
Median (range)	0.46 (0.17–497.0)†	0.39 (0.17–497.0)†	0.43 (0.17–27.16)	0.48 (0.10–5.61)	0.44 (0.20–1.25)	n.a.
95% CI	0.39; 0.53	0.33; 0.48	0.29; 0.55	0.25; 0.79	0.31; 0.69	n.a.
Number (%) of patients with individual average time to onset of symptom relief of:						
<1 h	51 (89.5)	49 (96.1)	27 (90.0)	18 (85.7)	14 (87.5)	n.a.
<4 h	55 (96.5)	50 (98.0)	29 (96.7)	20 (95.2)	16 (100)	n.a.
Time to complete resolution of HAE symptoms (h)						
Median (range)	15.48 (0.64–497.0)†	12.75 (0.64–497.0)†	22.73 (5.07–497.0)†	26.63 (0.95–61.83)	5.79 (0.63–48.25)	n.a.
95% CI	11.64; 21.59	8.19, 15.19	18.73, 27.16	7.38, 43.01	2.05, 25.90	n.a.
	I.M.P.A.C.T.1 results‡					
	20 U/kg bw C1-INH					Placebo
Statistic	All attacks (n = 43)§	Abdominal (n = 34)	Peripheral (n = 0)	Facial (n = 9)	Laryngeal (n = 0)	(n = 42)§
Time to onset of symptom relief (h)						
Median (range)	0.50 (0.17–5.77)	0.50 (0.17–5.22)	n.a.	0.92 (0.25–5.77)	n.a.	1.42 (0.20–5.90)
Number (%) of patients with individual average time to onset of symptom relief of:						
<1 h	30 (69.8)	25 (73.5)	n.a.	5 (55.6)	n.a.	16 (38.1)
<4 h	37 (86.0)	30 (88.2)	n.a.	7 (77.8)	n.a.	26 (61.9)
Time to complete resolution of HAE symptoms (h)						
Median (range)	4.92 (0.47–1486)	3.56 (0.47–1486)	n.a.	35.17 (7.93–81.53)	n.a.	7.79 (0.33–1486)

bw, body weight; C1-INH, C1 esterase inhibitor; CI, confidence interval; HAE, Hereditary Angioedema; *N*, number of patients; n.a., not applicable.

*Of the total of 1085 attacks, the dose of C1-INH concentrate was 40–60 U/kg bw for 12 attacks (in six patients).

†The maximum time to complete resolution of 497 h occurred in a patient for whom retrospective genetic testing did not confirm the diagnosis of HAE; the patient was treated for one event. This value was also used for conservative imputations of some missing values.

‡Based on actual values recorded; see Craig et al. (9). No imputation was used for the time to onset of symptom relief. Missing values of time to complete resolution were imputed with the maximum value of 1486 h.

§Data for time to onset of symptom relief are missing for one patient.

proven cases of any infections with human immunodeficiency virus, hepatitis viruses, or human B19 virus during the study.

Discussion

The efficacy and safety of C1-INH concentrate in the treatment of HAE has been mainly based on retrospective and uncontrolled studies [reviewed by Bork (5), Cicardi et al. (6), and Farkas et al. (7)]. The first randomized, placebo-controlled study with C1-INH concentrate was conducted by Waytes et al. (8), followed by I.M.P.A.C.T.1, which demonstrated the efficacy of 20 U/kg bw C1-INH concentrate (9).

While I.M.P.A.C.T.1 included only single abdominal and facial attacks, the open-label study I.M.P.A.C.T.2 evaluated the efficacy and safety of 20 U/kg bw C1-INH concentrate for long-term treatment of successive attacks at any body location; it included the largest number of attacks treated in a prospective study to date.

The primary efficacy endpoint in I.M.P.A.C.T.2 was, as in I.M.P.A.C.T.1 (9), the time to onset of symptom relief. This endpoint was also used in other HAE studies (8, 16) and has been validated recently by the association with single symptom intensity (17). In I.M.P.A.C.T.2, the median time to onset of symptom relief for attacks at any body location was 0.46 h, consistent with I.M.P.A.C.T.1, where the median time to onset of symptom relief for single abdominal or facial attacks treated with the same 20 U/kg bw dose of C1-INH concentrate was 0.50 h (see Table 4). Comparisons of the times to complete resolution of HAE symptoms between I.M.P.A.C.T.1 and I.M.P.A.C.T.2 are biased because in I.M.P.A.C.T.1, in contrast to I.M.P.A.C.T.2, blinded rescue study medication (C1-INH or placebo) was given in case of insufficient relief of symptoms 4 h after the start of the initial therapy.

C1 esterase inhibitor concentrate was effective in treating attacks at any body location, as indicated by the median time to onset of symptom relief of ≤0.50 h for all types of attacks in I.M.P.A.C.T.2. Untreated peripheral attacks can last many days (18); therefore, there is a need for a therapy with a short time to onset of symptom relief. In our study, the median time to onset of symptom relief for peripheral

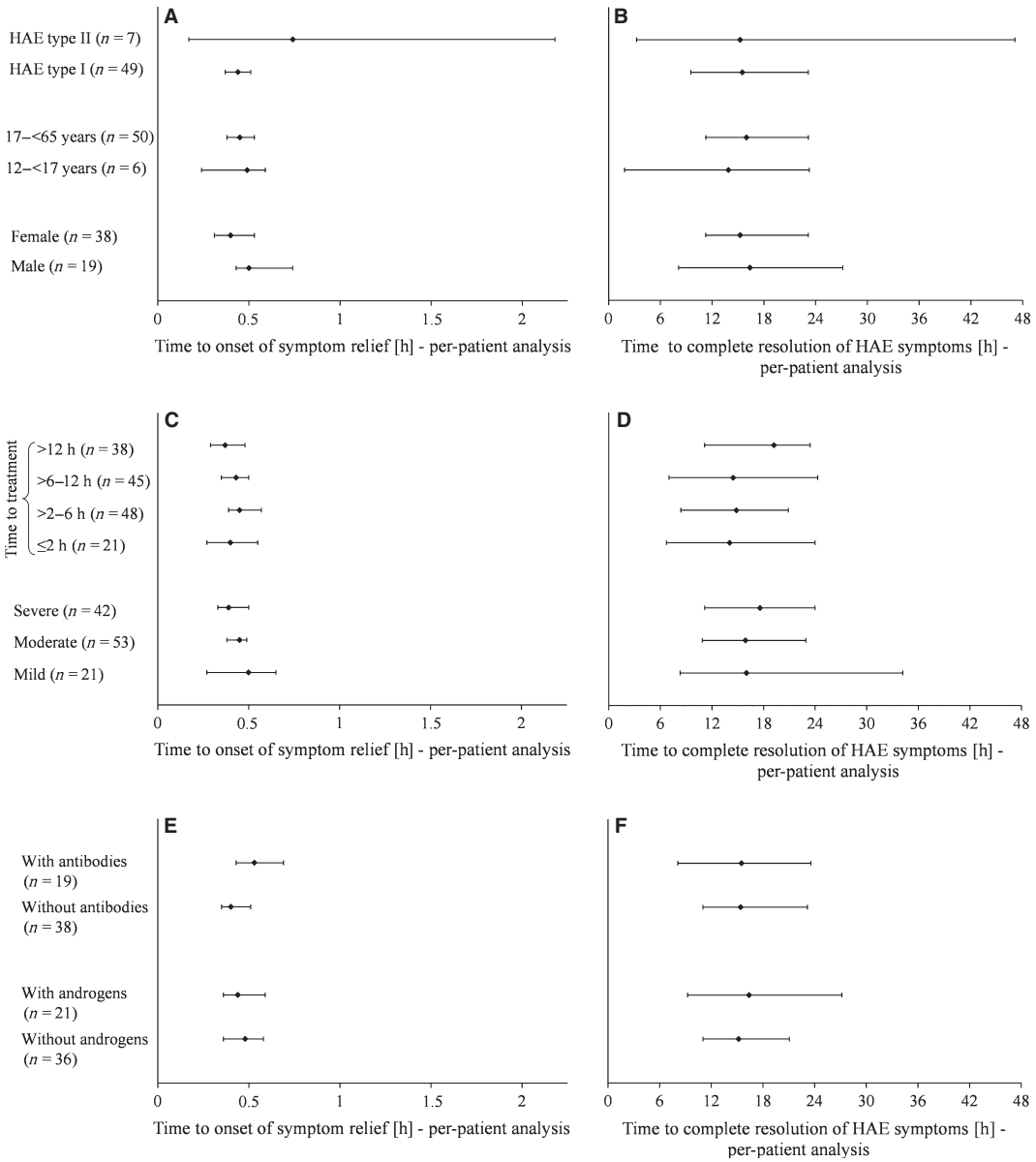

Figure 1 Subgroup analyses. Median times to onset of symptom relief and complete resolution of Hereditary Angioedema symptoms and 95% confidence intervals (per-patient analysis) by demographic characteristics (A, B), attack characteristics (C, D) and use of androgens and presence of anti-C1-INH antibodies (E, F). Data are not shown for one patient with unknown type of HAE and one patient in the age group of 3 to <12 years.

attacks was 0.43 h and the median time to complete resolution of HAE symptoms was 22.7 h, suggesting that C1-INH replacement therapy is effective in the treatment of peripheral attacks and provides rapid relief from often distressing symptoms, which, if left untreated, may progress to other body locations and disrupt daily activities for several days.

No inhibitory antibodies were detected in any patient in I.M.P.A.C.T.2, which is in agreement with previously published studies (19–21). As also reported by Varga et al. (14), the presence of noninhibitory anti-C1-INH antibodies had no effect on the efficacy of C1-INH concentrate. Furthermore, when adverse events were analysed by the presence of anti-C1-INH antibodies, there were no relevant differences between patients with and without anti-C1-INH antibodies. Thus, there is no indication that the presence of anti-C1-INH antibodies in some patients could be of clinical relevance. Overall, treatment with C1-INH concentrate was well tolerated with a low risk of adverse drug reactions, confirming previous experience with the C1-INH concentrate, which has been in clinical use over the last 30 years, with more than 500 000 treatments (22).

Table 5 Summary of adverse events and adverse events experienced by at least two patients or for at least five attacks

Type of adverse event Preferred term	Number (%) of patients (n = 57)	Number (%) of attacks (n = 1085)
Patients/attacks with adverse events	25 (43.9)	59 (5.4)
Patients/attacks with at least possibly related adverse events	8 (14.0)	9 (0.8)
Patients/attacks with serious adverse events	1 (1.8)*	1 (<0.1)*
Discontinuations of study medication owing to adverse events	1 (1.8)†	1 (<0.1)†
Headache	5 (8.8)	8 (0.7)
Nasopharyngitis	3 (5.3)	3 (0.3)
Abdominal pain	2 (3.5)	8 (0.7)
Upper respiratory tract infection	2 (3.5)	5 (0.5)
Abdominal discomfort	2 (3.5)	2 (0.2)
Hereditary Angioedema‡	2 (3.5)	2 (0.2)
Influenza-like illness	2 (3.5)	2 (0.2)
Rash	2 (3.5)	2 (0.2)
Vulvovaginal mycotic infection	2 (3.5)	2 (0.2)
Nausea	1 (1.8)	7 (0.6)

n, number of patients/attacks.

*One patient (retrospectively found not to have HAE) had two serious adverse events (exacerbation of abdominal symptoms treated with C1-INH concentrate; staphylococcal infection) that were unrelated to study medication.

†Infusion related reaction 2 min after the start of infusion for the second attack of the patient in this study; the event resolved after 4.6 h and could not be clearly defined as allergic or anaphylactoid.

‡Only to be reported as adverse event in case of worsening symptoms during a treated attack. One new attack (started after resolution of the previous attack) was nevertheless reported as adverse event (attack treated outside study centre; not with study medication). See asterisk for details on the other adverse event of Hereditary Angioedema.

An important aspect of acute HAE treatment is to achieve reliable symptom relief that avoids the need for additional treatments or re-dosing. In I.M.P.A.C.T.2, a single dose of 20 U/kg bw of C1-INH concentrate was sufficient to effectively treat 99% of HAE attacks. Additional doses of 20 U/kg bw of C1-INH concentrate were given for 12 abdominal attacks, only 4 of which were associated with worsening symptoms. Re-dosing or the use of rescue medication to achieve symptom relief from HAE attacks was also reported in recent studies of other HAE treatments. In an open-label study with a recombinant C1-INH concentrate, additional doses were needed for 9% of attacks treated with 50 U/kg and for 34% of attacks treated with 18–40 U/kg (23). With a nanofiltered C1-INH concentrate (fixed-dose regimen of 1000 U per attack) for the treatment of attacks, re-dosing was required in 65.7% of patients because the treated attacks had not started to improve after 1 h (10). With ecallantide, five of 36 patients (13.9%) required medical interventions within 24 h after treatment because of incomplete response (24). With icatibant, re-dosing was needed in 10% of attacks in two studies that consisted of a controlled phase and an open-label phase (25). Three of 11 patients treated with icatibant for laryngeal attacks received rescue medication within the first 24 h and one patient required intubation (26). In contrast, no emergency procedures or additional medication were needed for any of the 48 laryngeal attacks treated in our study.

Conclusions

I.M.P.A.C.T.2 showed that C1-INH concentrate at a single dose of 20 U/kg bw is safe and provides reliable efficacy for the long-term treatment of successive HAE attacks at any body location.

Source of funding

Funding was from CSL Behring, Marburg, Germany.

Author contributions

All authors were involved in the conception and design of the study as well as in its conduct and the generation of data. The statistical analyses of the data were conducted by Heinz-Otto Keinecke. The results of these analyses were interpreted and discussed by all authors at scientific meetings held during the development of this manuscript. Timothy J. Craig and Thomas Machnig coordinated writing of the manuscript with the named authors; the sponsor also engaged a consultant medical writer (Christina Wendel) to assist with preparation of the manuscript in cooperation with the authors. The sponsor placed no restrictions on any of the authors regarding statements made in the manuscript.

Acknowledgments

We thank all sub-investigators and other members of the I.M.P.A.C.T.2 study group, whose valuable contributions were essential to the success of this study. We also thank Sylvia Herget, Kerstin Jung, Margaret Mitchell and Xiang Ma (CSL Behring, Germany and USA) for their assistance in the conduct of the study, Silke Jasky-Gamb, Silke Kuhl and Dirk Spruck (Accovion GmbH, Germany) for data management and statistical programming on behalf of CSL Behring GmbH and Christina Wendel (Trilogy Writing & Consulting GmbH) for medical writing services on behalf of CSL Behring GmbH.

Conflict of interest

Drs Craig, Bewtra, Bahna, Hurewitz, Schneider, Levy, Moy, Offenberger, Jacobson, Yang, Eidelman, Janss, Packer and Wasserman all received research support as investigators in this study sponsored by CSL Behring. Dr Craig reports having served as a consultant for Dyax, ViroPharma and CSL Behring and having received research support as an investigator from Pharming, Dyax, Shire (formerly Jerini), CSL Behring and ViroPharma. Dr Craig has leadership positions in the American College of Allergy, Asthma and Immunology,

the American Academy of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology. Dr Bewtra reports having received research support from the National Institutes of Health. Dr Bahna reports having received research support from CSL Behring, Shire and Pharming. Dr Bahna was president of the American College of Allergy, Asthma and Immunology during 2009/2010. Dr Hurewitz reports having received research support from Shire, Dyax and CSL Behring. Dr Levy reports having served as a consultant for CSL Behring and Shire, and having received research support from CSL Behring, Dyax, ViroPharma, Pharming and Shire. Dr Yang reports having served as a consultant for CSL Behring and having received research support from CSL Behring, Pharming, Shire and Dyax. Dr Janss reports having received research support from CSL Behring. Drs Schneider, Moy, Offenberger, Jacobson, Eidelman and Packer report no additional sources of funding. Drs Rojavin and Machnig are employees of CSL Behring. Mr. Keinecke is an employee of Accovion GmbH, which provides statistical consultancy services to CSL Behring. Dr Wasserman reports having served as a consultant for CSL Behring, Baxter Bioscience and Talecris and having received research support from CSL Behring, Baxter Bioscience and Biotest.

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