

ORIGINAL ARTICLE

IMMUNODEFICIENCIES

Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study

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To cite this article: Reshef A, Moldovan D, Obtulowicz K, Leibovich I, Mihaly E, Visscher S, Relan A. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study. *Allergy* 2013; **68**: 118–124.

Keywords

hereditary angioedema; prophylaxis; recombinant human C1 inhibitor.

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Accepted for publication 25 September 2012

DOI:10.1111/all.12060

Edited by: Hans-Uwe Simon

Abstract

Background: Hereditary angioedema (HAE) is a disease characterized by recurrent tissue swelling affecting various body locations. Recent literature shows that patients with frequent attacks may benefit from long-term prophylaxis. This study evaluated the safety and prophylactic effect of weekly administrations of recombinant C1INH (rhC1INH).

Methods: Patients with a history of HAE attacks occurring $\geq$ every 2 weeks received a once weekly administration of 50 U/kg rhC1INH. Hereditary angioedema attack history was collected at screening. Breakthrough attacks during the study were recorded at each visit. Following a 2-week run-in period, HAE patients received 8 weekly rhC1INH administrations and were followed-up for an additional 6 weeks. Efficacy was evaluated by comparing the HAE attack incidence during the treatment period to the historical attacks over the previous 2 years. Safety evaluation was based on clinical laboratory and adverse events (AEs) reports.

Results: The 25 participants reported a mean of 0.9 attacks/week over the past 2 years. The mean breakthrough attack rate during the treatment period was 0.4 attacks/week (95% CI 0.28–0.56). A total of 30 treatment-emergent-AEs were reported in 13 patients, all mild to moderate. One patient died from a laryngeal attack 25 days after last study drug administration. The only possible drug related AEs reported were dry mouth, dizziness and anxiety in one patient and hypotension in another. There were no allergic AEs and no neutralizing antibodies observed.

Conclusions: Weekly administrations of 50 U/kg rhC1INH appeared to reduce the frequency of HAE attacks and were generally safe and well tolerated.

Hereditary angioedema (HAE) is a rare disease characterized by recurrent attacks of tissue swelling affecting various body locations. In patients with relentless and frequent attacks, long-term prophylaxis (LTP) has been proposed [1, 2]. Prophylaxis is aimed at reducing the burden of the disease by preventing the occurrence and attenuating the attacks. Based

on clinical experience LTP is provided to patients who suffer from frequent attacks despite optimal on-demand treatments [3]. This was previously achieved by attenuated androgens, anti-fibrinolytic agents and plasma-derived C1INH concentrates. However, oral drugs have been associated with adverse reactions, require regular monitoring and are unsuitable for children and women [1, 4–6]. An observational study of 14 patients followed for up to 19 years showed that weekly administration of pd C1INH reduced the frequency of attacks in some but not all patients [7]. Recently, a double-blind, placebo-controlled, crossover study in 22 patients,

Abbreviations

C1INH, C1 inhibitor protein; HAE, hereditary angioedema; rhC1INH, recombinant human C1INH.

twice weekly administration of 1000 U pd C1INH concentrate (Cinryze[®], Viropharma) was shown to reduce the frequency of HAE attacks by 50% [8].

Recombinant C1 esterase inhibitor, (rhC1INH; Ruconest[®]; Pharming Technologies B.V., Leiden, the Netherlands) is a highly purified, recombinant human C1 esterase inhibitor produced and purified from the milk of pathogen-free transgenic rabbits, expressing the gene encoding for human C1INH to >99% purity [9]. The efficacy and safety of rhC1INH has been evaluated and established in two randomized, placebo-controlled, double-blind clinical studies, undertaken in HAE patients during acute angioedema attacks [10, 11].

We took a further step forward in pharmacotherapy of HAE by studying a prophylactic regimen with rhC1INH in HAE patients experiencing frequent attacks.

Methods

Overall study design and plan

This was an open-label observational study of once weekly administration of rhC1INH at 50 U/kg given over an 8-week period.

The study was conducted according to the ethical principles of the declaration of Helsinki (2004) and informed consent was provided by all patients prior to enrolment. The protocol, patient information sheet and informed consent form were approved by appropriate Independent Ethics Committees.

Selection of study population

Twenty-five adult HAE patients from three countries (Romania 10, Israel 8, and Poland 7) with a confirmed diagnosis of C1 inhibitor deficiency (Type I or II) were included in the study (Fig. 1).

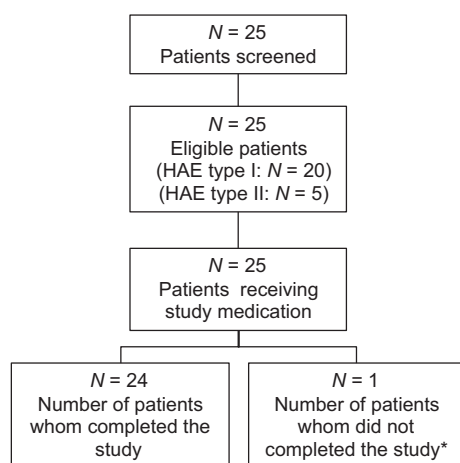


Figure 1 Disposition of study patients. *The patient died 25 days after the last study drug administration due to a hereditary angioedema attack.

All patients had a history of frequent HAE attacks occurring at least every 2 weeks. Patients were excluded if they had a history of allergic reactions to C1INH products or to rabbit protein or elevated IgE against rabbit epithelium (dander).

Treatments administered

A dose of 50 U/kg body weight rhC1INH was administered by slow IV injection over 4–5 min, once a week during an 8-week period. Breakthrough acute attacks could be treated with rhC1INH.

Study outcomes

The primary objective of the study was to evaluate the occurrence of HAE attacks under prophylactic administration of rhC1INH (50 U/kg/week).

The secondary objective was to evaluate pharmacokinetic/pharmacodynamic (PK/PD) parameters, immunogenicity and safety of repeated administration of rhC1INH.

Efficacy measurements

Past 2 years attack history and HAE attacks experienced during the study were recorded.

Pharmacokinetic/pharmacodynamic measurements

Pharmacokinetic parameters, including $C_{\max}$ and AUC_{last} , for functional and antigenic C1INH and C4 were based on concentration time curves after the 1st and 8th administration. Functional C1INH was determined as inhibitory activity against C1 esterase with a chromogenic assay, and levels of C4 antigen were determined by nephelometry. All complement assays were performed in a central laboratory.

Immunology assessments

Blood sampling for immunological analyses took place at screening, pre-administration (eight times), and at day 7 and 42 after the last administration of rhC1INH. These included: anti-Host Related Impurities [Anti-HRI (total Ig)], anti-rhC1INH IgM and IgG. Blood levels of specific IgE to rabbit dander and cow's milk was determined at screening. All analyzed anti-HRI antibody and anti-rhC1INH antibody samples above the cut-off value for the assays were re-tested in a displacement assay for confirmation. In addition, if anti-rhC1INH antibodies were confirmed in the displacement assay, the sample was tested with a neutralizing antibody assay. All immunology analyses were performed in a central laboratory.

Safety measurements

Physical examination, vital signs, ECG and laboratory data including routine hematology, biochemistry, c-reactive protein (CRP), activated partial thromboplastin time (aPTT)

Table 1 Baseline characteristics for the overall study population

	N	Mean (SD)	Min–Max	N (%)
Age (years)	25	37.9 (13.4)	18–65	
Weight (kg)	25	73.1 (15.6)	46–99	
Height (cm)	25	166.5 (7.4)	155–184	
BMI (kg/m ²)	25	26.37 (5.53)	18.3–38.2	
Gender				
Female				20 (80)
Male				5 (20)
Race				
Caucasian				25 (100)

and prothrombin time (PT), were recorded at each visit. Number and severity of adverse events (AEs) experienced during the study period was monitored.

Results

Study population- baseline

A total of 25 patients were included in the study (Table 1). All patients included in the study had a history of frequent HAE attacks over the past 2 years with a mean attack rate of 0.9 attacks per week (range 0.4–4.5). Twenty three patients reported the impact of attacks on their quality of life to be major or resulting in disability.

The participating centers were similar with respect to demographics and baseline characteristics. However, Romanian patients tended to be older (mean age 44.1 years), while mean ages of patients from Israel and Poland were 34.1 and 33.4 years, respectively.

Efficacy outcomes

Over the 8 week treatment period the mean breakthrough attack rate was 0.4 attacks per week (95% CI 0.28–0.56) and the median 0.25 attacks per week; see Table 2 and Fig. 2.

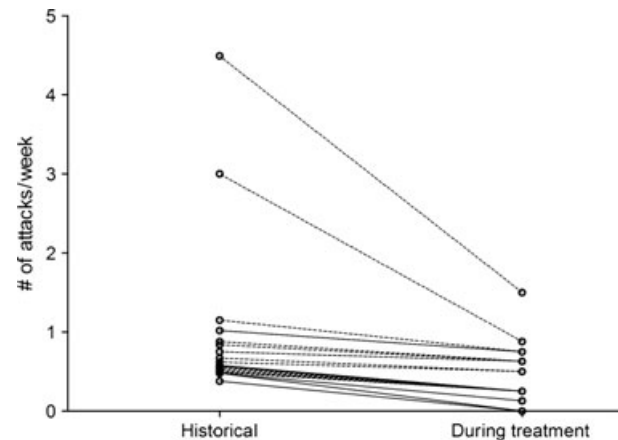
A total of 21 patients (84%) experienced an attack during the treatment period, six of whom were treated with rhC1INH (Table 3).

Concomitant medication

Most patients (24) were taking one or more concomitant medication during the study period. Twelve (48%) patients received in total 20 pdC1INH treatments: 12 for acute

Table 2 Hereditary angioedema breakthrough attacks

Over past 2 years attacks per week		During the 8 weeks study period attacks per week	
Mean	0.9	Mean	0.4
95% CI of mean	0.51–1.30	95% CI of mean	0.27–0.56
Median	0.6	Median	0.3
Range	0.4–4.5	Range	0.0–1.5

**Figure 2** Attack frequency before and during the treatment period.**Table 3** rhC1INH administrations during study

	Number of patients (N)	Number of administrations (N)
Scheduled rhC1INH administrations*	21	8
rhC1INH administered for breakthrough attacks†	4	7
	3	1
	2	2
	1	4
Total rhC1INH administrations	25	207
Range of rhC1INH administrations/patient		(7–11)

*Four patients received unscheduled administrations.

†Total amount of treated breakthrough attacks $N = 21$, 7 of these attacks were treated with rhC1INH, and 12 were treated with pdC1INH.

HAE attacks and 8 prior to dental treatment or surgery. Another frequently reported drug was paracetamol (five patients).

Laboratory measurements

Hereditary angioedema parameters at screening and during the study

Median levels of functional C1INH, antigenic C1INH, C1q, and C4 at screening are summarized in Table 4.

Upon administration of 50 U/kg of rhC1INH, maximal functional C1INH concentrations ranged from 119% to 255% at visit 1 and from 124% to 305% at visit 8.

Pharmacodynamics and pharmacokinetics of C4 and functional C1INH during rhC1INH treatments are shown in Fig. 3a,b.

Overall, there was a consistency in levels of antigenic C1INH, functional C1INH and C4 levels between the 1st and 8th treatments (Table 5).

Table 4 Functional C1INH, antigenic C1INH, C1q and C4 at baseline

	Normal range	N	Median	Min–Max
Functional C1INH (%)	70–130	25	<28	<24–41
Antigenic C1INH (g/l)*	0.21–0.39	20	0.053	<0.030–0.195
C1q (IU/ml)	33.6–96.0	25	79.5	12.7–146
C4 (g/l)	0.1–0.4	24	0.0561	<0.0145–0.272

Below the level of quantification (BLQ) values are included as half BLQ.

*Antigenic C1INH presented only for the Type I hereditary angioedema patients.

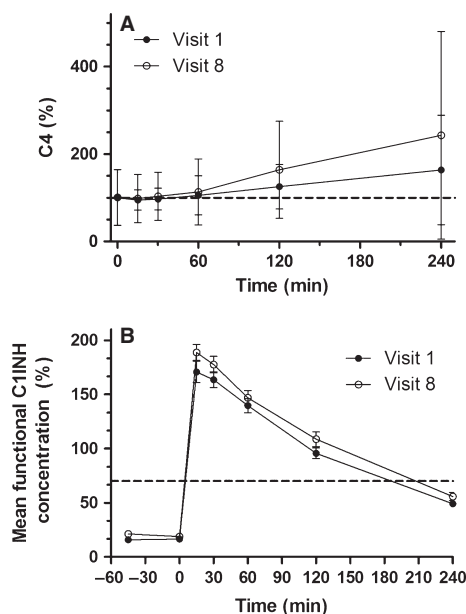


Figure 3 (A) Normalized C4 concentrations following rhC1INH administration on Visit 1 and Visit 8. C4 values following rhC1INH administration were normalized by using each patient's baseline value as 100% (dotted line represents 100%). (B) Pharmacokinetics of rhC1INH treatments on visit 1 and visit 8. The dotted line represents the lower limit of the normal range of functional C1INH concentrations in a healthy population.

Tolerability and safety issues

Immunology assessments

Anti-rhC1INH. Prior to rhC1INH treatment, two of 25 patients had presence of anti-rhC1INH antibodies confirmed by the displacement assay. Two patients developed IgG antibodies anti-rhC1INH after the 3rd weekly exposure to rhC1INH, which persisted until the last follow-up visit in one and decreased after the 4th–5th administration in the

second. None of these antibody responses were accompanied by clinical symptoms of hypersensitivity, or other clinically significant abnormalities in routine hematology and biochemistry evaluations. Neutralizing antibodies were not detected in any patient.

Anti-HRI. Three patients had anti-HRI antibodies prior to first exposure. Eleven out of all 25 patients had above cut-off anti-HRI values in the screening enzyme-linked immunosorbent assay (ELISA) assay confirmed by the displacement assay. These antibody responses were not accompanied by clinical symptoms of hypersensitivity, or abnormalities in routine hematology and biochemistry and urinalyses results.

IgE antibodies. All screening anti-rabbit IgE samples were negative (<0.35 kU/l). A single baseline borderline value for cow's milk IgE (0.48 kU/l) was reported in one patient without any clinical signs of allergy or abnormal routine laboratory values following rhC1INH exposure.

Adverse events

A total of 30 treatment-emergent AEs were observed during the study in 13 patients (52%). Two were serious AEs: acute appendicitis and laryngeal edema. The former was resolved 3 days after onset with an appendectomy. The latter was a 50 year old female patient who experienced laryngeal edema and fatally suffocated 25 days after the last administration of the study drug.

Two events were of severe intensity, eight events were of moderate intensity and 20 events were of mild intensity. Four events were considered possibly drug-related by the investigator. All these events were of mild intensity. These events were dry mouth, dizziness, hypotension (5 days after dosing), and anxiety. There were no events that led to study drug discontinuation or study interruption.

Discussion

Hereditary angioedema is a chronic disease manifested by recurrent episodes of tissue swelling that are painful, disfiguring and potentially life-threatening. Recent statistics from the US (2004–2007) revealed 10 125 hospitalizations of patients with HAE, of which 3216 (31.8%) had HAE as the principal diagnosis [12]. Prophylactic treatment of HAE is aimed to reduce the burden of the disease, both on the patient and on health-care systems, by preventing and attenuating angioedema recurrences [2].

Recombinant C1INH is a novel biotech alternative to human plasma-derived C1INH concentrate, with minimized risk for infection and virtually unlimited supplies. It has a proven efficacy and safety for the treatment of acute attacks of HAE in randomized, placebo-controlled clinical studies [10, 11]. Therefore, it is a desirable solution for many patients with attacks and a debilitating disease course.

The present study aimed at exploring the efficacy of rhC1INH for the prophylaxis of HAE attacks. Participants had a recent history of multiple attacks, significantly

Table 5 Results of repeated hereditary angioedema (HAE) laboratory values

Analyte	Parameter	Ratio V8/V1*	95% CI		P-value
			Lower limit	Upper limit	
Functional C1INH	AUC ₀₋₄ [†] (%/h)	1.06	0.98	1.14	0.1384
	C _{max} [†] (%)	1.04	0.98	1.11	0.1768
Antigenic C1INH [‡]	AUC ₀₋₄ [†] (g/l/h)	1.02	0.91	1.15	0.6738
	C _{max} [†] (g/l)	1.07	0.93	1.24	0.3387
C4	AUC ₀₋₄ [†] (g/l/h)	1.00	0.74	1.33	0.9750
	C _{max} [†] (g/l)	1.19	0.89	1.59	0.2188

*V8/V1 = Visit 8 compared to Visit 1 data

†Data is analyzed using repeated measures ANOVA.

‡Antigenic C1INH includes data for Type II HAE patients (N = 5).

affecting their quality of life, with 88% reporting at least 50 or more attacks in the last 2 years. The study compared rate of historical attacks to 'breakthrough' attacks occurring during 8 weekly administrations of prophylactic HAE treatments. Using this protocol we have shown that attack rate can be reduced, which conforms with the aims of prophylaxis in HAE management. This is the first study to investigate the application of rhC1INH for prophylactic purposes.

Hereditary angioedema patients most difficult to treat require numerous on-demand interventions, suffer from severe psychosocial and family problems and adopt dependence on health-care resources [12, 13]. The concept of long-term prophylactic treatment (LTP) for HAE was developed to meet the needs of patients in whom on-demand acute treatment is inadequate to minimize the suffering related to the disease. LTP is aimed at reducing the burden of the disease by preventing the occurrence and attenuating the attacks. Conceptually, the treatment is provided between attacks, and recommended to patients who suffer from frequent attacks (i.e. >12 moderate-to-severe attacks per year) despite optimized on-demand treatment [1, 14]. The circumstances under which on-demand treatment could be considered to have been inadequate are still debated between experts, without unanimous consensus [2]. Some maintain that the decision should be based on a subjective, patient-to-patient evaluation, and others hold the view that the definition of insufficient benefit from on-demand therapy must be based on objective evidence, i.e. such as 24 days per year with even mild angioedema symptoms, or more than one severe attack per year [14]. Controversy also exists as to the relative advantages of LTP compared with on-demand treatment of early symptoms. Long-term prophylaxis reduces attack frequency and severity, and improves quality of life [15]. However, breakthrough attacks still occur and the total usage of pdC1INH is often increased [15, 16]. The current study also found that nearly all patients (84%) had at least one breakthrough attack despite prophylaxis with rhC1INH.

Intravenous, human plasma-derived C1INH concentrates has been used for LTP since 1989. The first double-blind, placebo-controlled cross-over study (six patients in two 17-day period), with pdC1INH at 25 U/kg every 3 days, has shown to reduce HAE disease activity by 60% [17]. Recently

another pdC1INH product (Cinryze®, Viropharma) was administered to 22 patients in two 12-week period, at 1000 U every 3–4 days, showing a reduction of HAE attacks by 50% [from 12.73 to 6.26, ($P < 0.001$)]. Additionally, it also reduced the severity and duration of attacks, the need for open label C1INH rescue administrations, and the number of days with HAE-related swelling [8]. There was, however, a significantly variable response, with some patients experiencing no change in attack frequency while others having almost no attacks. Similar findings were observed in other uncontrolled clinical studies [7, 16, 18].

It has been postulated that functional C1INH levels exceeding 0.4 U/ml provide protection [19, 20] and more recently it was reported that very few attacks occurred in patients treated prophylactically with pdC1INH with plasma levels (C_{max}) above 0.68 U/ml [8, 21]. Nevertheless, no correlation between attack frequency and C1INH levels in plasma was observed in the only published controlled prophylaxis study [8], and a threshold C1INH activity plasma level that provided protection against HAE attacks could not be identified [22].

It has been argued that rhC1INH's shorter half-life may not be adequate for prophylaxis. However, despite the different half-lives of rhC1INH and pdC1INH (ranging from 1.6 h for rhC1INH to >30 h for pdC1INH products), clinical relapses were not seen in any of the recent RCT studies using intravenous C1INH, including rhC1INH [10, 23].

Choi et al. have suggested that even short and transient restoration of C1INH plasma levels was sufficient to block the activated pathways and vasoactive mediators leading to tissue edema for a prolonged time, or alternatively, that rhC1INH exerted a sustained effect on the vascular endothelium involved in extravasations and tissue fluid accumulation [24]. This is supported by recent observations in clinical trials where peak levels rather than half-life of C1INH products were shown to reflect clinical efficacy and prevention of relapses [23].

In terms of pharmacokinetics, no significant differences in PK between visit 1 and visit 8 and no loss of efficacy was observed in the functional C1INH plasma levels. Additionally, C4 levels increased following treatment with rhC1INH with no significant difference between the first and last visit.

This is in-line with the observation of a lag time of 6–24 h between rhC1INH administration and maximal increase of plasma, which may reflect decreased breakdown or increased de-novo C4 synthesis [9].

Possible immunogenicity of a new therapeutic protein is an important consideration. Previous studies with rhC1INH in total of 424 treatments, including repeated dose administrations, have shown that the rhC1INH has a low potential to induce untoward immune response (i.e. anti-HRI or anti-C1INH antibodies) [25]. In the present study an occasional presence of confirmed antibodies to rhC1INH was found, without evidence for neutralizing or sensitizing activity. Antibodies to HRI were found during the study, but without any clinical relevance.

Adverse events observed during 13 weeks of study were assessed as not related to rhC1INH. There were no events that led to study medication discontinuation or interruption. No trends in laboratory values were observed.

The key limitation of this study was the open-label design which may have influenced patients' perception of the efficacy of rhC1INH. More importantly, attack rate prior to study entry was obtained from the patients' recollection, which is subject to various potential biases, while patients' recent attacks were routinely recorded during the treatment period. In addition, there can be significant intra-patient variation in their disease course over time. Therefore, future studies of patients with highly frequent attacks should include meticulous recording of each HAE attack, including severity.

Given the safety and efficacy of human pdC1INH and our observations in this pilot study, the prophylactic use with rhC1INH should be further investigated. Furthermore, rhC1INH may be considered for self-administration, which was found effective in some studies and has shown to improve quality of life in patients with frequent attacks [14, 16, 26–29].

In summary, weekly administration of 50 U/kg rhC1INH appeared to reduce the frequency of HAE attacks and was generally safe and well tolerated. These encouraging findings warrant further investigation of the clinical value of prophylaxis with rhC1INH.

Glossary

C1INH: C1 inhibitor protein; ELISA: Enzyme-Linked Immuno-Sorbent Assay, HAE: hereditary angioedema; rhC1INH recombinant human C1INH; prophylaxis, Open-label study; TEAE: treatment-emergent adverse event. HRI: Host Related Impurities. PK/PD: Pharmacokinetic/Pharmacodynamic AUC_{0–4}: area under the curve between 0 and 4 h after infusion, C_{max}: Maximal concentration,

Acknowledgments

This study design, implementation and data analysis was sponsored by Pharming Technologies, B.V., the Netherlands.

Conflict of interest

AR and SV are employees of Pharming Technologies BV. ARE has received funding for research of angioedema from Pharming Technologies BV, Shire Human Genetic Therapies Inc., CSL Behring and Dyax Corp. He also is a member on the global advisory board of Shire Human Genetic Therapies Inc. DM has provided expert consultation services and received speaker honoraria and research funding from Pharming Technologies BV and Shire Human Genetic Therapies Inc. He has also received research funding from CSL Behring. IL has received travel grants and funding for research of angioedema from Pharming Technologies BV, Shire Human Genetic Therapies Inc and CSL Behring. KO and EM have no conflict of interest to declare.

References

- Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B et al. International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;**6**:24.
- Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012;**67**:147–157.
- Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;**66**:192–196.
- Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanazolol. *J Allergy Clin Immunol* 1987;**80**:855–860.
- Cicardi M, Bergamaschini L, Cugno M, Hack E, Agostoni G, Agostoni A. Long-term treatment of hereditary angioedema with attenuated androgens: a survey of a 13-year experience. *J Allergy Clin Immunol* 1991;**87**:768–773.
- Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol* 2008;**100**:153–161.
- Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int Arch Allergy Immunol* 2011;**154**:81–88.
- Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;**363**:513–522 e14.
- van Doorn MB, Burggraaf J, van Dam T, Eerenberg A, Levi M, Hack CE et al. A phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. *J Allergy Clin Immunol* 2005;**116**:876–883.
- Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S et al. Recombinant human C1 inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010;**126**:821–827.
- Moldovan D, Reshef A, Fabiani J, Kivity S, Toubi E, Shlesinger M et al. Efficacy and safety of recombinant human C1 inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. *Clin Exp Allergy* 2012;**000**:929–935.
- Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema hospitalizations in

- the United States, 2004–2007. *Allergy Asthma Proc* 2011;**32**:248–254.
13. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 2010;**31**:407–414.
 14. Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 2004;**114**(3 Suppl):S51–S131.
 15. Longhurst HJ, Farkas H, Craig T, Aygoren-Pursun E, Bethune C, Bjorkander J et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 2010;**6**:22.
 16. Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1 inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol* 2006;**117**:904–908.
 17. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 1996;**334**:1630–1634.
 18. Bork K, Witzke G. Long-term prophylaxis with C1 inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1 inhibitor deficiency. *J Allergy Clin Immunol* 1989;**83**:677–682.
 19. Spath PJ, Wuthrich B, Butler R. Quantification of C1 inhibitor functional activities by immunodiffusion assay in plasma of patients with hereditary angioedema—evidence of a functionally critical level of C1 inhibitor concentration. *Complement* 1984;**1**:147–159.
 20. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;**295**:1444–1448.
 21. Cocchio C, Marzella N. Cinryze a human plasma-derived C1 esterase inhibitor for prophylaxis of hereditary angioedema. *P T* 2009;**34**:293–328.
 22. Maplethorpe C. CINRYZE (C1 Inhibitor) for routine prophylaxis against HAE attacks. [FDA Briefing document] 2008; Available from: <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm094092.pdf>.
 23. Hack CE, Relan A, van Amersfoort ES, Ciccardi M. Target levels of functional C1 inhibitor in hereditary angioedema. *Allergy* 2012;**67**:123–130.
 24. Choi G, Soeters MR, Farkas H, Varga L, Obtulowicz K, Bilo B et al. Recombinant human C1 inhibitor in the treatment of acute angioedema attacks. *Transfusion* 2007;**47**:1028–1032.
 25. Hack CE, Manne M, Baboeram A, Oortwijn B, Relan A. Immunogenicity assessment of recombinant human C1 inhibitor: an integrated analysis of clinical studies. *Bio-Drugs* 2012;**26**:303–313.
 26. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1 inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol* 2009;**19**:147–151.
 27. Aygören-Pürsün E, Martinez-Saguer I, Rusicke E, Klingebiel T, Kreuz W. On demand treatment and home therapy of hereditary angioedema in Germany – the Frankfurt experience. *Allergy Asthma Clin Immunol* 2010;**6**:21.
 28. Kreuz W, Rusicke E, Martinez-Saguer I, Aygören-Pürsün E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. *Transfusion* 2012;**52**:100–107.
 29. Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. *Clin Exp Immunol* 2007;**147**:11–17.