Safety and Efficacy of Physician-Supervised Self-Managed C1 Inhibitor Replacement Therapy

Louanne M. Tourangeau^a Anthony J. Castaldo^b Donna K. Davis^b
James Koziol^c Sandra C. Christiansen^{a, d} Bruce L. Zuraw^{a, e}

^aUniversity of California, San Diego, ^bUnited States Hereditary Angioedema Association, ^cThe Scripps Research Institute, ^dSouthern California Kaiser Permanente, and ^eSan Diego VA Medical Center, La Jolla, Calif., USA

Key Words

C1 inhibitor • Hereditary angioedema • Home infusion •
C1 inhibitor deficiency

Abstract

Background: C1 inhibitor (C1INH) has recently been approved in the USA for the treatment of acute attacks in hereditary angioedema (HAE) patients. The literature suggests that treatment with C1INH is most effective when administered early in an attack. Home infusion of C1INH allows for the earliest possible intervention since patients can initiate therapy at the first sign of symptoms. **Methods:** We performed an observational, prospective study on 39 subjects with HAE utilizing two groups of patients: one receiving on-demand C1INH replacement therapy in a medical facility and the other self-managing on-demand C1INH replacement therapy in the home setting under the supervision of a treating physician. All subjects completed online questionnaires weekly for 8 weeks. **Results:** There were statistically significant decreases in attack duration ($p < 0.0001$), pain medication use ($p < 0.0001$) and graded attack severity ($p < 0.005$) in the subjects who received C1INH in the home setting versus the clinic-based group. Attack frequency was similar between the groups. The home group experienced more

frequent injection-related side effects; however, the clinic group noted more severe adverse events from C1INH. **Conclusion:** Physician-supervised self-managed C1INH replacement therapy is a safe and effective treatment for patients with HAE with potential benefits in diminishing attack duration and attack severity.

Copyright © 2011 S. Karger AG, Basel

Introduction

Hereditary angioedema (HAE) is a rare, autosomal dominant disease that is clinically characterized by recurrent episodes of subcutaneous or submucosal edema. Common sites for swelling include the extremities, bowels, genitalia, face, tongue, or larynx. Angioedema attacks typically begin in the first decade, worsen with puberty and persist throughout life. Disease severity is variable and untreated HAE patients experience attacks every 1–2 weeks on average, with the frequency ranging from almost never to as often as every 3 days [1, 2]. Angioedema attacks often follow a predictable course with swelling that increases slowly but continuously over the first 24 h and then gradually abates over the following 48–72 h. HAE attacks involving the oropharynx or the abdomen

are associated with significant risk of morbidity and mortality [3, 4].

Genetically, HAE is characterized by mutations in the SERPING1 gene [5] and can be divided into 2 major types. Type I HAE is defined by decreased antigenic and functional C1 inhibitor (C1INH) levels, whereas type II HAE has normal C1INH antigenic levels but decreased C1INH functional levels. Clinically, type I and II HAE present in a similar fashion. More recently, a third type of familial angioedema has been described which is associated with normal C1INH antigenic and functional levels and sometimes associated with a defect in factor XII (Hageman factor) [6, 7] and/or estrogen dependency.

Due to the morbidity and mortality caused by recurrent swelling attacks in HAE, medical intervention is both necessary and life saving for many patients. Treatment includes management of acute attacks, short-term prophylactic therapy to prevent future attacks, and long-term prophylaxis. Recently, C1 inhibitor replacement therapy has become available in the US and has been shown to be highly effective for both acute and prophylactic management of HAE attacks [8–11]. Administration of C1INH rapidly halts attack progression [12–15], with improvement typically noted within 30–60 min.

Theoretical considerations as well as clinical observations suggest that C1INH replacement is most effective when administered early in an attack [16–23]. While patients typically receive acute attack treatment at a clinic or hospital, several studies suggest that home infusion of C1INH is safe and provides a superior outcome compared to treatment at a medical facility [17–20, 24]. As a result, a recent HAE international home therapy consensus recommends that every patient with physician-diagnosed HAE be considered for physician-supervised, self-managed home C1INH replacement therapy and that therapy should be started as soon as the patient notices symptoms of an HAE attack [25]. We hypothesized that physician-supervised self-managed C1INH home replacement therapy would result in better control of HAE attacks compared to clinic treatment with C1INH. The aim of this study was to investigate the safety and efficacy of self-managed home C1INH replacement compared to C1INH given in the clinical setting.

Methods

Study Design

The United States HAE Association conducted an investigator-designed survey of subjects with physician-diagnosed HAE who were receiving on-demand C1INH either at home or in a

medical facility from December 2007 to March 2008. C1INH was provided in the form of a human plasma-derived concentrate from Sanguin (Cetor) or Lev Pharmaceuticals (Cinryze). C1INH was administered by intravenous injection by either trained medical personnel at a medical facility (clinic group) or by the patient or family member away from a medical facility (home group). The C1INH dose was 1,000 units, irrespective of subject weight. Most subjects in both groups used 1 dose per attack; however, subjects could use a second 1,000-unit dose if the first dose was not effective. The median dose per attack was 1,000 units for all patients included in the study; however, the clinic group used a small but significantly higher mean dose of C1INH ($1,014 \pm 120$ units) than the home group (916 ± 187 units; $p < 0.0001$). The Western Institutional Review Board approved this study.

After subjects signed informed consent, they were given a password for online access to a computerized questionnaire consisting of three parts: (1) a health survey to determine past medical history, (2) an interval history to obtain information regarding attack frequency, attack severity, amount of medication used for the previous week, and (3) a Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) at the beginning and end of the study. Thirty-nine subjects receiving on-demand C1INH in the home or clinic were enrolled and divided into two groups. The first group consisted of 18 subjects receiving on-demand intravenous C1INH infusions at a clinic or a medical facility, and the second group consisted of 21 subjects who self-administered on-demand intravenous C1INH as replacement therapy under the supervision of their physician. Both groups were treated with C1INH concentrate on demand for acute attacks of angioedema. Subjects filled out the online form weekly for 8 weeks.

Subjects in the self-administration group received training in the home or in a medical facility. A registered nurse provided training in the majority of cases; however, 3 of the patients felt comfortable with intravenous infusion based on prior knowledge/training, a career in health care, or a family member in health care. Two subjects received training directly from a physician. Although the subjects in the home group self-infused C1INH away from a medical facility, all subjects reported that their physician supervised the process, including initiating the infusion training, periodic monitoring of the dose and use of C1INH, as well as routine follow-up.

Each study subject underwent patient-specific training based on his or her level of comfort and knowledge. The time for each patient to practice intravenous initiation ranged from 0 min to 3 h. Each patient remained in training until they felt comfortable initiating their own intravenous infusion. Depending on each patient's level of comfort, patients were given the opportunity to practice on oranges, family members, health care professionals and/or themselves. Following successful initiation of an intravenous infusion, subjects were allowed to practice until they felt completely comfortable with the procedure. The entire training period from beginning to proficiency ranged from 10 min to 10 h. After training, all patients reported that they felt comfortable with self-infusion in their home.

The primary endpoint was the duration of attacks treated during the study. Secondary endpoints included the number of attacks over the 8-week period, the severity of attacks, use of narcotic pain medications, and the safety and tolerability of the therapy.

Table 1. Subject demographics and retrospective disease severity

Parameter	Clinic group (n = 18)		Home group (n = 21)		p value ¹
	mean $\pm$ SD	median (IQR)	mean $\pm$ SD	median (IQR)	
Age at start of study, years	39.78 $\pm$ 10.96	40 (34.25–43.75)	38.30 $\pm$ 14.61	34 (27–49)	0.573
Gender (female:male)	16:2		15:6		0.191
Age at HAE symptom onset, years	9.15 $\pm$ 6.29	8 (4–16)	6.60 $\pm$ 4.97	5 (3–11)	0.310
Age at HAE diagnosis, years	16.92 $\pm$ 8.85	19 (12–24)	16.75 $\pm$ 10.71	15 (10–21)	0.480
Known family history of HAE (yes:no)	17:1		13:8		0.019
Lifetime ED visits	133.7 $\pm$ 313.0	45 (4–115)	101.7 $\pm$ 166.1	50 (10–100)	0.81
Missed work/school days per year	39.0 $\pm$ 44.0	15 (10–43.7)	128.5 $\pm$ 31.2	50 (20–144)	0.04
Lifetime hospitalizations	90.9 $\pm$ 237.8	14 (2–37.5)	57.7 $\pm$ 136.2	10 (3–50)	0.97
Lifetime surgeries	0.67 $\pm$ 1.28	0 (0–1)	0.20 $\pm$ 0.52	0 (0–0)	0.15
Lifetime intubations	0.5 $\pm$ 1.34	0 (0–0)	0.8 $\pm$ 2.69	0 (0–0)	0.90
Average attacks per year	78.7 $\pm$ 47.9	81 (38.5–111.25)	94.0 $\pm$ 54.6	99 (60–122)	0.28
Average annual extremity attacks	28.1 $\pm$ 17.9	24 (12–46)	32.1 $\pm$ 20.0	39 (12–51)	0.45
Average annual facial attacks	6.5 $\pm$ 11.8	2 (1–6)	7.15 $\pm$ 11.5	4 (2–6)	0.71
Average annual throat attacks	6.0 $\pm$ 12.5	1.5 (1–5)	6.0 $\pm$ 11.9	2.5 (1–4)	1.00
Average annual genitourinary attacks	11.1 $\pm$ 13.2	7 (2–15)	12.2 $\pm$ 12.0	7 (4–20)	0.37
Average annual abdominal attacks	27.1 $\pm$ 17.1	22 (12–40)	36.7 $\pm$ 17.0	47.5 (24–51)	0.06

ED = Emergency department.

¹ Mann-Whitney rank-sum test for continuous variables; Fisher's exact test for discrete variables.

Statistical Analysis

Results are reported both as the mean $\pm$ SD as well as the median with interquartile range (IQR). Because most of the endpoints had non-Gaussian distributions, we utilized non-parametric procedures, primarily the Wilcoxon-Mann-Whitney test, for comparing the clinic and home groups. Attacks were taken as individual events. A p value $\leq$ 0.05 was considered statistically significant.

Results

Study Population

The clinic group consisted of 18 subjects and the home group included 21 subjects. All study participants had physician-diagnosed HAE. Baseline characteristics and historical measures of disease severity for the two groups were compared based on their initial health survey questionnaire (table 1). No differences were seen in age at entry, gender, age at symptom onset, age at diagnosis, number of lifetime emergency department visits, lifetime hospitalizations, total intubations, total number of attacks/year, or number of attacks/year involving the extremities, face, throat, genitourinary tract, or abdomen between the two groups. Both groups had relatively severe HAE, based on the average number of attacks per year: a median of 81 total attacks/year (IQR 38.5–111.25) in the clinic group

and 99 attacks/year (IQR 60–122) in the home group. The home group did report significantly more missed days of work or school per year (50, IQR 20–144) than did the clinic group (15, IQR 10–43.7; p = 0.04). The home group used C1INH a total of 167 times (0–17 injections per patient over 8 weeks, median 7, IQR 2–13), whereas the clinic group used C1INH a total of 69 times (0–18 injections per patient over 8 weeks, median 2, IQR 0–6.5).

Impact of Home C1INH Replacement Therapy on Number and Severity of Acute Attacks

As expected, the weekly attack frequency was not significantly different between the two groups (clinic group, median 1, IQR 0–2; home group, median 1, IQR 0–2; p = 0.82) (table 2). Subjects also graded the overall severity of their attacks on a scale of 1–10. The home treatment group reported a statistically significant lower attack severity (median 4, IQR 3–7) than the clinic treatment group (median 5, IQR 4–8; p < 0.005) (fig. 1; table 2).

Efficacy of Home versus Clinic C1INH Replacement Therapy for Acute Attacks

Subject-reported efficacy of C1INH for acute attacks was similar in the two cohorts. 87.2% of clinic subjects who received clinic C1INH replacement therapy and 86.8% of home subjects who received C1INH as home re-

Table 2. Interval efficacy and safety/tolerability results

Parameter	Clinic group (n = 18)		Home group (n = 21)		p value ¹
	mean ± SD	median (IQR)	mean ± SD	median (IQR)	
Attack frequency/severity					
Average attacks/week	0.83 ± 0.98	1 (0–2)	1.02 ± 0.96	1 (0–2)	0.82
Attack severity (scale of 1–10)	5.67 ± 2.69	5 (4–8)	4.75 ± 2.46	4 (3–7)	<0.005
Efficacy					
Attack duration, h	34.2 ± 27.5	30.5 (12–48)	8.0 ± 13.5	3.0 (1.5–6.0)	<0.0001
Pain medications per week	1.75 ± 3.13	0 (0–3)	0.38 ± 0.98	0 (0–0)	<0.0001
Safety/tolerability results					
Bleeding from injection site, %	0.58 ± 7.6	0 (0–0)	7.81 ± 26.9	0 (0–0)	<0.001
Pain/inflammation at injection site, %	1.73 ± 13.1	0 (0–0)	7.21 ± 25.9	0 (0–0)	0.009
Infection at injection site, %	0 ± 0	0 (0–0)	0.30 ± 5.5	0 (0–0)	0.47
Difficulty with injection (scale of 0–3)	0.03 ± 0.17	0 (0–0)	0.31 ± 0.60	0 (0–0)	<0.0001
Severity of C1INH side effects (scale of 0–3)	0.22 ± 0.71	0 (0–0)	0.01 ± 0.16	0 (0–0)	<0.0001

¹ Mann-Whitney rank-sum test.

Fig. 1. Severity of angioedema attacks in the clinic and home treatment groups ($p < 0.005$). Each attack is shown as a single black filled circle. Subjects graded each attack from 1 to 10 (1 being very mild and 10 being very severe). The mean severity for each group is shown as a straight line.

Fig. 2. Duration of angioedema attacks in the clinic and home treatment groups ($p < 0.0001$). Each attack is shown as a single black filled circle. The mean duration for each group is shown as a straight line.

Table 3. Impact on life activities and SF-36 data

HAE impact or SF-36 score	Clinic group (n = 18)		Home group (n = 21)		p value ¹
	mean ± SD	median (IQR)	mean ± SD	median (IQR)	
Negative impact on school/job ²	0.48 ± 0.92	0 (0–1)	0.42 ± 0.79	0 (0–1)	0.886
Negative impact on family life ²	1.09 ± 1.09	1 (0–2)	0.53 ± 0.83	0 (0–1)	<0.0001
Negative impact on social life ²	1.02 ± 1.12	1 (0–2)	0.51 ± 0.91	0 (0–1)	<0.0001
Days missed school/job per week	0.56 ± 3.46	0 (0–0)	0.18 ± 0.53	0 (0–0)	0.687
Days family/friends missed school/job per week due to subject's HAE	0.25 ± 0.73	0 (0–0)	0.10 ± 0.40	0 (0–0)	0.045
Nights of disrupted sleep per week	1.61 ± 4.39	1 (0–2)	0.50 ± 1.07	0 (0–1)	<0.0001
SF-36 initial physical aggregate score	36.52 ± 3.38	37.10 (34.12–38.75)	35.91 ± 3.33	36.29 (33.83–38.17)	0.749
SF-36 final physical aggregate score	37.00 ± 2.38	36.69 (35.14–38.01)	38.77 ± 2.69	38.37 (37.34–41.11)	0.040
Change in physical aggregate score	0.49 ± 2.81	0.49 (–1.14 to 2.50)	2.86 ± 3.87	2.23 (0.78–5.56)	0.043
SF-36 initial mental aggregate score	30.92 ± 6.85	31.06 (25.59–37.38)	30.52 ± 6.39	30.13 (24.90–36.33)	0.813
SF-36 final mental aggregate score	32.30 ± 7.97	35.96 (25.59–38.09)	34.66 ± 6.31	36.41 (30.53–39.45)	0.321
Change in mental aggregate score	1.38 ± 5.74	1.01 (–0.72 to 2.82)	4.14 ± 7.69	3.08 (–0.53 to 10.49)	0.257

¹ Mann-Whitney rank-sum test. ² Graded on a scale of 0–3.

placement therapy reported that therapy was effective for controlling attacks. Attack duration, the primary end-point, was dramatically shorter in the home group (3.0 h, IQR 1.5–6.0) compared to the clinic group (30.5 h, IQR 12–48; $p < 0.0001$) (fig. 2; table 2). Of note, despite the similar frequency of attacks, the home treatment group used CIINH replacement significantly more often than the clinic infusion group ($p < 0.0001$). Repeating the analysis of duration only for attacks that were treated with CIINH did not alter the outcome, with a significantly shorter median duration of attack still observed in the home group (home group, median 2.0 h, IQR 1.25–6; clinic group, median 13.0 h, IQR 6–48; $p < 0.0001$). Pain medication use was assessed as a surrogate marker for efficacy. Consistent with the primary efficacy results, the home group reported a significant decrease in prescription pain medication use compared to the clinic group ($p < 0.0001$) (fig. 3; table 2).

Impact of CIINH Replacement Therapy on Life Activities

The effect of home versus clinic CIINH administration on the negative impact of HAE on life activities was assessed as a secondary efficacy outcome. On a weekly basis, subjects answered questions regarding the impact of their HAE on various life activities using a scale from 0 (no interference) to 3 (significant negative impact) (table 3). The home group reported statistically less interference with family life ($p < 0.0001$), social life ($p < 0.0001$),

nights of disrupted sleep ($p < 0.0001$), and days that family or friends had to miss school or work due to the subject's HAE ($p = 0.045$) compared to the clinic group (table 3).

Tolerability and Adverse Effects of CIINH Replacement Therapy

A greater number of adverse effects were reported with the injections in the home CIINH replacement group (table 2). There was a statistically significant increase in the percentage of injections leading to bleeding events ($p < 0.001$), pain ($p = 0.009$) and difficulty with the injection ($p < 0.0001$) in the home group. No difference was observed in the rate of injection site infections. Almost all of these side effects were minor, and no serious adverse events were reported in either group. Interestingly, the clinic group reported a significantly greater overall severity of side effects (graded on a scale of 0–3, from none to severe) than what was reported by the home group ($p < 0.0001$).

Quality of Life Comparison between Study Groups Based on SF-36 Data

The impact of CIINH replacement therapy on quality of life is shown in table 3. At study entry, the aggregated physical score was similar in both groups (clinic group, median 37.10, IQR 34.12–38.75; home group, median 36.29, IQR 33.83–38.17; $p = 0.749$); however, the home group showed a significantly greater improvement in the

Fig. 3. Number of prescription pain medications used per week in the clinic and home treatment groups ($p < 0.0001$). Each week is shown as a single black filled circle. Open circles represent 5 separate weeks, each requiring no pain medications. The mean weekly pain medication use for each group is shown as a straight line.

aggregated physical score over the course of the study (change in the clinic group, median 0.49, IQR -1.14 to 2.50; change in the home group, median 2.23, IQR 0.78–5.56; $p = 0.043$). The aggregated mental score was also similar in both groups at entry (clinic group, median 31.06, IQR 25.59–37.38; home group, median 30.13, IQR 24.90–36.33; $p = 0.813$), and improved more in the home group over the course of the study but failed to reach significance (change in the clinic group, median 1.01, IQR -0.72 to 2.82; change in the home group, median 3.08, IQR -0.53 to 10.49).

Discussion

This study compared the efficacy, safety and tolerability of self-administered, physician-supervised on-demand C1INH replacement therapy in the home setting to on-demand C1INH replacement therapy in a medical facility. No difference was found in the ability of C1INH

replacement therapy to reduce angioedema symptoms between the two groups; however, the home treatment group demonstrated highly significant reductions in total duration of angioedema attacks, maximal attack severity and requirement for pain medication use. There were no serious adverse effects in either group, and no subject stopped C1INH replacement therapy because of tolerability issues. The home group experienced more injection-related side effects than the clinic group, but had less severe overall side effects from the C1INH administration. Overall, home injection with C1INH proved to be more efficacious and just as safe and tolerable as clinic administration for the treatment of acute attacks of angioedema in severely affected HAE patients.

The improved efficacy of physician-supervised self-managed C1INH home replacement therapy is likely a consequence of a decreased lag time between the first sign of an attack and the prompt initiation of therapy. By correcting the enhanced vascular permeability earlier in an attack, home treatment likely diminishes the amount of fluid moving from the vasculature into the interstitial space, decreases maximal severity of swelling, and consequently decreases the time to resolution. The significant reduction in median duration of attacks in the home group ($p < 0.0001$) was clinically meaningful as shown by significant improvement in the need for prescription pain medications, decreased interference with life activities, and increased improvement in quality of life measures.

Drawing from the experience of hemophilia patients who have been administering clotting factors for prophylactic or emergent therapy since the 1980s, there has been a gathering consensus that home infusion is a superior means of treatment. Hemophilia patients and their physicians recognized some time ago that it was not practical for patients to visit an infusion center multiple times each week [26]. As a consequence, home therapy programs were established and shown to be feasible, beneficial to the patient and cost-effective [20]. Accordingly, home infusion is currently regarded as standard of care for hemophilia patients, extending even to the pediatric population where children can be started on home therapy before the age of two.

An emerging international consensus recommends that all HAE attacks be treated as soon as possible in order to limit the morbidity and mortality that may be associated with attacks. This study confirms that physician-supervised, self-administered home C1INH therapy is a safe and effective means to implement this strategy. Importantly, subjects receiving on-demand C1INH in

the clinic were also significantly less likely to seek treatment of acute attacks, an outcome that further highlights the advantage of self-administration.

Based on the improved outcomes we observed from self-administration of C1INH, we suggest that other effective treatments of acute HAE attacks may similarly benefit from early self-administration. Additional options for physician-supervised, self-administered HAE therapies may eventually include icatibant, ecallantide and recombinant human C1INH. Icatibant, a bradykinin B2 receptor antagonist administered by subcutaneous injection, was approved for treatment of acute attacks in Europe in 2008 and in the US in 2011. Ecallantide, a potent inhibitor of plasma kallikrein administered by subcutaneous injection, was approved for use in the USA for acute attacks in 2009; however, a black box warning for possible anaphylactic reactions has precluded its self-administration [27]. Rhucin, a recombinant human C1INH, recently completed two successful phase 3 studies and is under review by the Food and Drug Administration. Rhucin (Ruconest) was recently approved by the European Medicines Agency for Europe.

Self-administered C1INH replacement therapy also provides HAE patients with an improved sense of control over an extremely burdensome disease. A literature review performed by Longhurst et al. [20] revealed that patients who received self-administered C1INH either for prophylaxis or on demand experienced improved quality of life and decreased frequency, duration and severity of attacks.

In addition, our findings are consistent with a previous retrospective report by Levi et al. [19] that examined outcomes in 31 patients using on-demand C1INH treatment and 12 patients using C1INH prophylactic therapy compared to historical controls. In this study, self-treated subjects receiving on-demand C1INH experienced significant improvement in both time to beginning of relief and time to resolution. Interestingly, the mean attack duration was 5.9 ± 2.2 h in self-treated subjects compared to 13.8 ± 2.9 h in conventionally treated subjects, which is similar to the effect we observed. Kreuz et al. [17] conducted a study of 22 patients with severe HAE that investigated the safety, efficacy and quality of life associated with self-administration of C1INH concentrate over danazol prophylaxis. They found a reduced incidence of attacks and superior efficacy for all quality of life variables investigated.

Several limitations of our study need to be addressed. We studied 39 severely affected HAE subjects. Although this is a relatively small sample size, it should be noted

that HAE is a rare disease, and to our knowledge, this is the largest prospective study with statistically significant results. Nonetheless, the combination of a small sample size and high disease severity may limit the ability to generalize our study findings to the HAE population as a whole. Furthermore, our study was performed using an observational prospective design. It was not feasible to randomize subjects because certain subjects were not comfortable with self-injection, and other subjects did not live in close enough proximity to a medical facility to ensure safe travel to the facility for treatment of acute attacks. Additionally, the use of patient-reported outcomes as a clinical endpoint has been widely debated; however, the World Health Organization has taken the stance that patient involvement in their health care is not only desirable but a social, economic and technical necessity [28, 29]. Lastly, any voluntary patient survey may involve reporting and recall bias that could affect the results. To limit this problem, we asked patients to fill out their survey weekly in order to decrease recall errors.

In conclusion, our findings provide additional impetus to alter the standard of care for HAE by making physician-supervised self-administered C1INH replacement therapy a mainstay of on-demand treatment. Our data, together with results from previous studies [19, 20], reveal that self-administration of C1INH for on-demand treatment of acute attacks of angioedema in HAE is safe and results in decreased attack duration, improved quality of life and better patient control over their disease state. We propose that physician-supervised self-managed on-demand C1INH replacement therapy is more effective and equally safe as clinic-based care. Consequently, we recommend that all HAE patients be provided with the option of C1INH self-replacement.

Acknowledgements

We would like to thank the HAE patients who participated in this study. Louanne M. Tourangeau, MD, is supported in her fellowship training by a NIH T32 AI 07469 grant.

References

- Agostoni A, Cicardi M: Hereditary and acquired C1INH deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206–215.
- Bork K, Meng G, Staubach P, Hardt J: Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;119:267–274.
- Nzeako UC, Frigas E, Tremaine WJ: Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001;161:2417–2429.
- Frank MM, Gelfand JA, Atkinson JP: Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;84:580–593.
- Davis AE 3rd: C1INH and hereditary angio-neurotic edema. *Annu Rev Immunol* 1988;6:595–628.
- Binkley KE, Davis A 3rd: Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000;106:546–550.
- Bork K, Barnstedt SE, Koch P, Traupe H: Hereditary angioedema with normal C1INH activity in women. *Lancet* 2000;356:213–217.
- Craig TJ, Levy RJ, Wasserman RL, et al: Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009;124:801–808.
- Zuraw B, Cicardi M, Levy RJ, et al: Recombinant human C1INH for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010;126:821–827, e14.
- Waytes AT, Rosen FS, Frank MM: Treatment of hereditary angioedema with a vapor-heated C1INH concentrate. *N Engl J Med* 1996;334:1630–1634.
- Kunschak M, Engl W, Maritsch F, et al: A randomized, controlled trial to study the efficacy and safety of C1INH concentrate in treating hereditary angioedema. *Transfusion* 1998;38:540–549.
- Bork K, Barnstedt SE: Treatment of 193 episodes of laryngeal edema with C1INH concentrate in patients with hereditary angioedema. *Arch Intern Med* 2001;161:714–718.
- Cicardi M, Zingale L: How do we treat patients with hereditary angioedema. *Transfus Apher Sci* 2003;29:221–227.
- Farkas H, Jakab L, Temesszentandrási G, et al: Hereditary angioedema: a decade of human C1INH concentrate therapy. *J Allergy Clin Immunol* 2007;120:941–947.
- Bork K, Meng G, Staubach P, Hardt J: Treatment with C1INH concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 2005;45:1774–1784.
- Bright P, Gompels M, Dempster J, Longhurst H: Case series: UK experience of icatibant for acute attacks of hereditary angioedema. *Norwich, EAACI summer school*, 2009.
- Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Heller C, Klingebiel T: C1INH concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 2009;49:1987–1995.
- Bygum A, Andersen KE, Mikkelsen CS: Self-administration of intravenous C1INH therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol* 2009;19:147–151.
- Levi M, Choi G, Picavet C, Hack CE: Self-administration of C1INH concentrate in patients with hereditary or acquired angioedema caused by C1INH deficiency. *J Allergy Clin Immunol* 2006;117:904–908.
- Longhurst HJ, Carr S, Khair K: C1INH concentrate home therapy for hereditary angioedema: a viable, effective treatment option. *Clin Exp Immunol* 2007;147:11–17.
- Agostoni A, Aygoren-Pursun E, Binkley KE, 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:S51–S131.
- Kreuz W, Martinez-Saguer I, Rusicke E, Aygoren-Pursun E, Klingebiel T: Impact of the Frankfurt HAE therapy protocol on health-related quality of life (HRQoL) in 50 patients with hereditary angioedema. *Abstract 6th European C1INH Deficiency Workshop, Budapest*, 2009.
- Zuraw B, Davis D, Castaldo A: Safety and efficacy of physician supervised self-managed C1INH individual replacement therapy. *Abstract 6th European C1INH Deficiency Workshop, Budapest*, 2009.
- Bork K, Staubach P, Eckardt AJ, Hardt J: Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1INH deficiency. *Am J Gastroenterol* 2006;101:619–627.
- Longhurst HJ, Farkas H, Craig T, et al: HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 2010;6:22.
- Teitel JM, Barnard D, Israels S, Lillicrap D, Poon MC, Sek J: Home management of haemophilia. *Haemophilia* 2004;10:118–133.
- Caballero T, Lopez-Serrano C: Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J Allergy Clin Immunol* 2006;117:476–477, discussion 7.
- Ad Hoc Committee on Medical Ethics: American College of Physicians Ethics Manual. Part I: history of medical ethics, the physician and the patient, the physician's relationship to other physicians, the physician and society. *Ann Intern Med* 1984;101:129–137.
- Waterwork SLK: Reluctant collaborators: do patients want to be involved in decision concerning care? *J Adv Nurse* 1990;15:971–976.