

C1-inhibitor therapy for hereditary angioedema attacks: Prospective patient assessments of health-related quality of life

Againdra K. Bewtra, M.D.,¹ Robyn J. Levy, M.D.,² Kraig W. Jacobson, M.D.,³
Richard L. Wasserman, M.D.,⁴ Thomas Machnig, M.D.,⁵ and Timothy J. Craig, D.O.⁶

ABSTRACT

C1-inhibitor (INH) concentrate, which is recommended as first-line treatment for acute hereditary angioedema (HAE) attacks in many countries, was recently approved in the United States. We sought to solicit patients' feedback about their health-related quality of life (HRQoL) while being treated with C1-INH concentrate for acute HAE attacks under real-world conditions, as well as the personal impact of the availability of C1-INH on lifestyle and mental health domains. Subjects enrolled in an open-label study of C1-INH at 20 U/kg for acute HAE attacks were invited to participate in a prospectively designed survey to solicit "real-time" patient responses that were collected via an interactive voice response service or online with a personal computer. Eighteen subjects submitted 60 quarterly HRQoL and treatment impact survey responses over 29 months. Seventeen of 18 patients responding reported mean short form 12 HRQoL scores that were within a normal range. More than one-half indicated that C1-INH availability made them feel somewhat or much better, and >80% reported having a better outlook on the future and feeling more secure about the danger of life-threatening attacks. These data confirm a high level of HRQoL and a positive impact in lifestyle and emotional domains among patients who were treated for acute attacks of HAE with C1-INH concentrate.

(Allergy Asthma Proc 33:427–431, 2012; doi: 10.2500/aap.2012.33.3597)

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by sporadic, recurrent episodes of nonpruritic, nonpitting edema that typically involves the extremities, trunk, genitalia, face, tongue, or larynx.^{1,2} The physiological abnormality leading to HAE is a deficit in the quantity or functionality of C1-inhibitor (C1-INH).³ In the absence of sufficient C1-INH activity, activation of the classic complement pathway and other inflammatory mediators can go unregulated. A subsequent generation of exces-

sive levels of unregulated bradykinin has been implicated as a primary factor in the onset of angioedema.³

There is tremendous variability in duration and frequency of attacks, although edema usually escalates in severity for the initial 24–36 hours and then gradually resolves in another day or over several days.^{1,2} Abdominal or peripheral swelling frequently persists for several days or, in some cases, for >1 week.² Laryngeal edema can lead to death by asphyxiation.⁴ Bowel angioedema is particularly painful and similar in presentation to an acute abdomen, and failure to make the correct diagnosis has been associated with inappropriate abdominal surgery.⁵ The unpredictability, pain, and potentially life-threatening nature of HAE attacks have been shown to impact dramatically the health-related quality of life (HRQoL) in affected individuals.^{6,7} In a computer survey, 85% of HAE patients reported living with a constant fear of sudden airway closure.⁸

C1 esterase INH concentrate is the standard of care for serious HAE events in Europe and Canada, where it has been available for >20 years.^{9–11} Studies with C1-INH have shown it to be effective in acute HAE attacks.^{12,13} This treatment option for HAE attacks was not available in the United States until October 2009, when a pasteurized C1-INH replacement concentrate (Berinert; CSL Behring, Marburg, Germany) was approved by the U.S. Food and Drug Administration.

From the ¹Division of Allergy and Immunology, Creighton University School of Medicine, Omaha, Nebraska, ²Family Allergy and Asthma Center, P.C., Atlanta, Georgia, ³Allergy and Asthma Research Group, Eugene, Oregon, ⁴Dallas Allergy Immunology, Dallas, Texas, ⁵CSL Behring GmbH, Marburg, Germany, and ⁶Pulmonary, Allergy, and Critical Care Medicine, Penn State University College of Medicine, Hershey, Pennsylvania

Funded by CSL Behring LLC

R.J. Levy is a medical consultant for CSL Behring and Dyax and a principal investigator for CSL Behring, Dyax, ViroPharma, Pharming, and Shire. R.L. Wasserman is a consultant for CSL Behring, Baxter, Talecris; an investigator for CSL Behring; and on the Board of Directors of the American Academy of Allergy, Asthma and Immunology. T. Machnig is an employee of CSL Behring. T.J. Craig is a speaker for ViroPharma, CSL Behring, and Dyax; a researcher with Dyax, CSL Behring, Shire, and Pharming; an interest section leader for the American Academy of Allergy, Asthma and Immunology; and a board member of the American College of Allergy, Asthma and Immunology. The remaining authors have no conflicts of interest to declare pertaining to this article

Address correspondence and reprint needs to Againdra K. Bewtra, M.D., Creighton University School of Medicine, 601 North 30th Street, Suite 3M100, Omaha, NE 68131

E-mail address: AGAINDRABEWTRA@creighton.edu

Copyright © 2012, OceanSide Publications, Inc., U.S.A.

Recently, results were reported from the International Multicenter Prospective Angioedema C1-Inhibitor Trial 1 (I.M.P.A.C.T.1), a phase II/III study conducted at 36 centers worldwide with 125 subjects ≥ 6 years of age with laboratory-confirmed C1-INH deficiency.¹⁴ Subjects were randomized to double-blind treatment with an infusion of C1-INH at 10 U/kg body weight (BW), C1-INH at 20 U/kg BW, or placebo in response to an acute abdominal or facial HAE attack. A C1-INH dose of 20 U/kg was found to provide significantly faster onset of symptom relief (median time of 0.5 hours) compared with placebo-treated patients.¹⁴ After completion of I.M.P.A.C.T.1, study participants were given the opportunity to continue receiving a single injection of C1-INH at 20 U/kg BW treatment for successive acute HAE attacks at any body site in an open-label extension study, I.M.P.A.C.T.2.^{15,16}

The survey described in this article was conducted among a subgroup of patients participating in the I.M.P.A.C.T.2 study. The purpose of the survey was to prospectively solicit patient comments about the effectiveness of C1-INH for the treatment of acute HAE attacks, the effect on HRQoL, and the impact of its availability. Treatment-related responses were submitted by patients in "real time" using an automated self-reporting system with the intention of minimizing recall bias.

METHODS

All patients who entered the C1-INH concentrate open-label I.M.P.A.C.T.2 study were eligible to participate in this companion survey, and, per the open-label study protocol, to receive a single injection of C1-INH at 20 U/kg for acute HAE attacks. Survey participation was voluntary. The survey protocol was approved by the Institutional Review Board of Creighton University (Omaha, NE), and written informed consent was obtained from all subjects or from a parent or caregiver of subjects < 14 years of age.

Responses were collected *via* an interactive voice response service or online with a personal computer. Data were recorded in a centralized database (Clarix Informatics, Conshohocken, PA). On survey entry, subjects completed a one-time questionnaire about the characteristics of their disease (age of onset, age when diagnosis of HAE was confirmed, average number of annual hospitalizations and emergency room visits in the year before study entry, current use of anabolic steroids, and family members with HAE). At the time of each acute HAE attack, patients submitted data relevant to the nature of the attack. In every quarter (approximately every 13 weeks) during their participation in the study, subjects had the opportunity to complete a survey measuring the impact of the availability of C1-INH on overall HRQoL and specific lifestyle and

mental health domains. The quarterly questionnaires included the short form (SF) 12, a multipurpose generic measure of HRQoL.¹⁷ The SF-12 measures eight domains commonly represented in widely used surveys: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and well-being). Subjects were asked to respond to each question with regard to his/her QoL over the previous 4 weeks. The SF-12 survey scores can range from 0 to 100 (higher scores indicate a better perceived HRQoL) and are normalized so that scores > 50 represent above average health status.¹⁷

Assessment was also made of the impact of the availability of C1-INH concentrate on physical health; emotional state; outlook on the future; feelings of security in being able to treat life-threatening attacks; normal functioning at work, home, and social activities; and comfort with regard to the need for steroids. Subjects compared the impact of HAE before entry into the study with how they felt at the time of survey completion and rated each issue as "much better," "somewhat better," "about the same," "somewhat worse," or "much worse." Subjects were also asked to indicate what they would have done for an attack if C1-INH concentrate had not been available. Subjects received a small financial compensation for completing each attack-related survey and each quarterly HRQoL survey.

Data were analyzed using descriptive statistics.

RESULTS

Between January 2007 and August 2008, 28 patients (mean age, 33.5 years; range, 12–54 years) from 7 study sites in the United States enrolled in the survey. Mean age of HAE onset was 13.4 years (range, 1–45 years). The subjects reported having a mean of 5 family members with HAE (range, 0–12). Ten subjects (35.7%) were on anabolic steroids during the clinical study.

Data collection continued through August 2009. The 28 survey subjects reported a total of 384 attacks treated with C1-INH concentrate. The median number of attacks reported per patient was 3.0 (range, 1–106). The majority of attack sites were the abdomen ($n = 261$; 68.0%) or extremities ($n = 71$; 18.5%). Patients also reported laryngeal ($n = 17$; 4.4%), facial ($n = 8$; 2.1%), genitourinary ($n = 6$; 1.6%), and other site ($n = 21$; 5.5%) attacks.

HRQoL (SF-12 Questionnaire)

Eighteen subjects submitted a total of 60 quarterly SF-12 questionnaires (range, 18 questionnaires per subject), and 13 (46.4%) submitted SF-12 assessments for > 1 quarter. Figure 1 is a scatterplot portraying mean total SF-12 scores reported by 18 subjects as a function

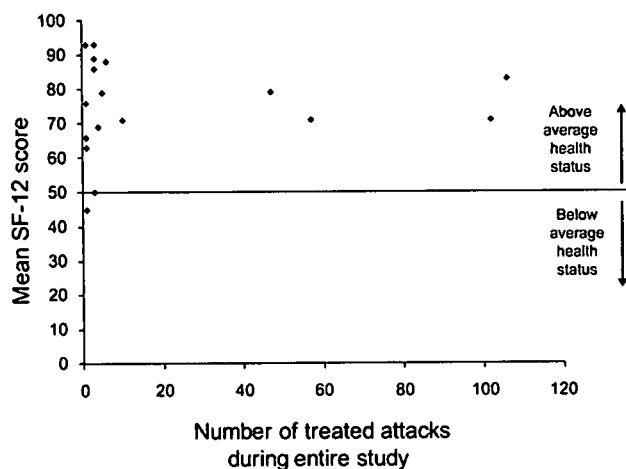


Figure 1. Scatterplot of mean short form 12 (SF-12) scores for 18 respondents, plotted by number of total treated hereditary angioedema (HAE) attacks during the survey period. Each data point represents the mean SF-12 score for each subject for the entire study period (number of submitted SF-12 questionnaires ranged from one to eight per subject). SF-12 questionnaires could be completed during any quarter, even if no attacks were treated during that quarter. Only 17 data points are apparent in the figure because two subjects had the same plot values (one treated attack and mean score of 76).

of the total number of treated HAE episodes. Mean SF-12 scores ranged from 44.8 to 93.2, with only one subject having an SF-12 score of <50. Mean SF-12 scores among the four subjects with the greatest number of treated attacks (47–106 attacks per subject) ranged from 70.6 to 82.7.

Table 1 outlines the average quarterly SF-12 values reported for specific domains. Mean physical functioning scores per quarter varied between 45.4 and 53.6, and mean quarterly bodily pain scores ranged from 39.6 to 50.2. General health scores and vitality scores per quarter varied from 47.4 to 59.8 and from 46.1 to 54.5, respectively. Among the 13 subjects with at least two quarterly SF-12 assessments, the mean changes between first and last observations showed that scores remained fairly stable for mental health (mean change, +4.2) and physical functioning (mean change, -1.1).

Assessment of the Impact of C1-INH Availability

A total of 60 quarterly assessments were submitted over the course of the study reporting subjects' opinions on the impact of having C1-INH concentrate available. For five of the six domains, the vast majority of responses indicated feeling much or somewhat better with the availability of C1-INH compared with prior experience without it (Fig. 2). The one exception was comfort level about the need for anabolic steroids, which was reported most commonly as "about the same" (53%). Only 5 of 360 individual domain ratings

Table 1 Mean SF-12 component scores reported over 10 study quarters among hereditary angioedema patients treated with C1-INH for acute attacks*

SF-12 Component	Overall Mean, Quarters 1–10	Range of Quarterly Averages
Physical functioning	51.1	45.4–53.6
Role physical	47.1	41.4–52.6
Bodily pain	45.5	39.6–50.2
General health	52.8	47.4–59.8
Vitality	51.2	46.1–54.5
Social functioning	45.5	39.3–53.2
Role emotional	49.8	44.9–52.9
Mental health	50.2	43.6–56.7
Mental health summary score	49.6	44.6–54.5
Physical health summary score	48.8	42.7–52.5

*Value of 50 representative of normal for general U.S. population.

SF-12 = short form 12; C1-INH = C1 inhibitor.

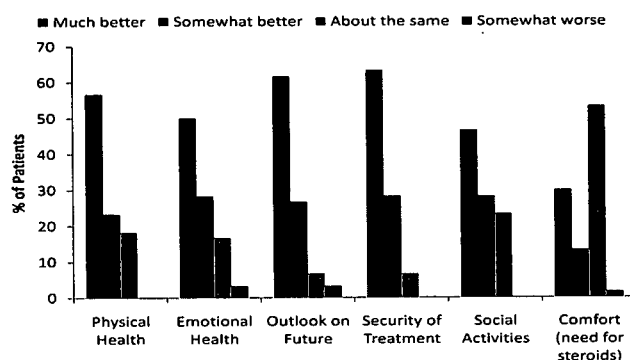


Figure 2. Subjective impact of C1-inhibitor (INH) availability on various quality of life (QoL) domains—opinions as reported by 18 HAE patients in 60 quarterly survey completions. The option of "much worse" was also offered in the survey. There were no responses in that category.

(6 domains rated for each of 60 quarterly assessments completed) were reported as "somewhat worse," and there were no responses of "much worse." Subjects' feeling of security about being able to treat life-threatening attacks was rated as much or somewhat better in almost 92% of assessments, and their ability to function normally at home/work/social activities was rated as much or somewhat better in 75% of responses.

Responses provided by 18 patients at the end of study participation indicated that without C1-INH availability, 7 would have tolerated the acute HAE attack without medical intervention, 6 would have sought emergency medical treatment, 3 would have

self-treated with analgesics, and 2 would have consulted a physician.

DISCUSSION

This prospectively designed survey reports the effects on HRQoL of a single injection of C1-INH at a dose of 20U/ kg BW for the treatment of HAE and the impact of its availability. The cohort of 18 of 28 HAE patients whose responses to the questionnaire are reported here is sizable for this rare and poorly studied condition, the number of treated attacks is substantial (384 for all patients), and the data were gathered under generalizable "real-world" conditions. The data have a number of limitations related to study design. Being open label in nature, the study did not include an active or placebo control group for comparison. Because the questionnaires were voluntary, they were not completed by all patients or during every quarter. Furthermore, the SF-12 is certainly not disease specific for HAE, and we did not attempt to account or control for concomitant illnesses and how they might impact QoL. We were also not able to capture direct or indirect financial burdens imposed by HAE. Despite these limitations, the data added to our knowledge base and provide insight into patient perceptions of treatment and the impact of treatment availability on mental status and physical functioning.

Replacement with C1-INH concentrate has long been a recommended treatment of choice for acute HAE attacks and short-term prophylaxis in Europe and Canada.^{10,11} Before the availability of C1-INH in the United States, symptomatic treatment was the basis of acute HAE attack management, and patients reported a high level of dissatisfaction with the management of their disease.⁸ Pharmacologic interventions were limited mainly to fresh frozen plasma or ϵ -aminocaproic acid, neither of which has been well studied or shown to have consistent efficacy.⁵

The open-label study, which was the parent study for this companion survey, evaluated efficacy and safety data of C1-INH concentrate at 20 U/kg in 57 patients and 1085 acute HAE attacks.¹⁷ The C1-INH concentrate treatment was associated with a median time to relief onset of 0.5 hours, which was similar for all attack sites. Median time to complete resolution of HAE attack symptoms was 15.5 hours. There were no safety concerns and no detection of inhibitory anti-C1-INH antibodies.

Neither overall HRQoL nor the impact of the availability of effective treatment has been well studied in patients with HAE. However, a recent study confirmed the physical and emotional burden of HAE, with patients who were not treated with C1-INH reporting clinical depression and marked impairments in work productivity.⁶ HAE patients had a mean SF-12 physical

component summary score of 43.7 and a mental component summary score of 42.6, both of which were significantly lower than the historic population norm values of 49.6 and 49.4, respectively (both, $p < 0.0001$). Our survey was limited in its capacity to detect changes in HRQoL because there was no control group or baseline data with which to compare SF-12 scores before and after C1-INH treatment. Nonetheless, SF-12 scores obtained throughout the survey were within the range of healthy people.¹⁷ Only 1 subject had a mean SF-12 score < 50 , and 13 subjects' mean scores were ≥ 70 . Similarly high scores were noted among the four subjects with the greatest number of treated attacks, a subgroup who, intuitively, might have been expected to exhibit the poorest HRQoL. For individual SF-12 domains, average values for all 10 reporting quarters were generally within several points of the population norm of 50.

The relatively high SF-12 scores in the survey population might be caused by self-selection bias in that the patients who volunteered for the survey may have been those with a more positive outlook on their disease. These scores may also indicate that these patients had become so accustomed to living under the constant burden of HAE that even small benefits of C1-INH were dramatic enough to improve substantially their sense of well-being.

The positive SF-12 scores were mirrored by the more subjective but possibly even more insightful portion of the survey about the impact of C1-INH availability on various physical and emotional domains. Almost all survey participants reported having a better outlook on the future and having a greater level of security in their disease treatment. Opinions of physical and emotional health were also improved in the majority of patients. The category that showed the least improvement in attitude was that of being able to function normally at work, home, and social activities, with about one-half of patients feeling better in this regard and approximately one-half feeling about the same. This may reflect the fact that social functioning can be impaired by the constant threat of or onset of an acute HAE attack, neither of which would have been minimized in this study, even with rapid and effective treatment when attacks occurred.

Many patients reported an increased comfort level about the need for anabolic steroids. Long-term anabolic steroid use has often been a mainstay of prophylactic treatment, but this treatment has troubling side effects¹⁸ that limit its usefulness and patient acceptance. Given that almost one-half of survey subjects reported that before C1-INH availability they would have simply tolerated acute HAE attacks without any kind of medical attention, having access to a rapidly effective intervention would likely be a major advance in the management of their disease.

Recent studies suggest that training HAE patients to self-administer C1-INH at the immediate onset of an attack may provide further health and HRQoL benefits.^{7,19,20} Consensus guidelines encourage patient-administered C1-INH if there is proper training and protocol.^{10,11} Bygum *et al.*⁷ described the implementation of a home-based C1-INH administration program in seven patients, with follow-up ranging from 27 to 72 months. Both the Dermatology Life Quality Index and the SF-36 indicated significant improvement in patients' HRQoL. When questioned during follow-up visits, patients reported feeling that they had greater control of their disease and their lives and much less fear of life-threatening attacks.⁷

CONCLUSIONS

This prospectively designed patient survey provides information on the HRQoL benefits of C1-INH for acute HAE attacks and the positive impact of its availability on lifestyle and mental health. These data confirm that a high level of HRQoL is achievable for patients dealing with a chronic condition such as HAE when effective treatment is available.

ACKNOWLEDGMENTS

Editorial assistance in the development of this article was provided by S. Bala Dass, Ph.D., formerly of Churchill Communications, and Sandra Westra, Pharm.D., of Churchill Communications.

REFERENCES

1. Zuraw BL. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
2. Frank MM. Hereditary angioedema: The clinical syndrome and its management in the United States. *Immunol Allergy Clin North Am* 26:653–668, 2006.
3. Davis AE III. Hereditary angioedema: A current state-of-the-art review, III: Mechanisms of hereditary angioedema. *Ann Allergy Asthma Immunol* 100(suppl 2):S7–S12, 2008.
4. Bork K, Siedlecki K, Bosch S, et al. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc* 75:349–354, 2000.
5. Zuraw BL. Hereditary angioedema: A current state-of-the-art review, IV: Short- and long-term treatment of hereditary angioedema: Out with the old and in with the new? *Ann Allergy Asthma Immunol* 100(suppl 2):S13–S18, 2008.
6. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 31:407–414, 2010.
7. Bygum A, Andersen KE, and Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur Dermatol* 19:147–151, 2009.
8. Huang S-W. Results of an on-line survey of patients with hereditary angioedema. *Allergy Asthma Proc* 25:127–131, 2004.
9. Bernstein JA. Hereditary angioedema: A current state-of-the-art review, VIII: Current status of emerging therapies. *Ann Allergy Asthma Immunol* 100(suppl 2):S41–S46, 2008.
10. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: Consensus document. *Clin Exp Immunol* 139:379–394, 2005.
11. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: A current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 100(suppl 2):S30–S40, 2008.
12. Bork K, Meng G, Staubach P, and Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 45:1774–1784, 2005.
13. Farkas H, Jakab L, Temesszentandrási G, et al. Hereditary angioedema: A decade of human C1-inhibitor concentrate therapy. *J Allergy Clin Immunol* 120:941–947, 2007.
14. 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* 124:801–808, 2009.
15. Levy RL, Wasserman RL, Bewtra AK, et al. C1 esterase inhibitor concentrate (C1-INH)—Standard of care for the treatment of acute attacks of hereditary angioedema (HAE): Interim results of an ongoing, prospective, open-label study in North America after 640 attacks (I.M.P.A.C.T. 2). *J Allergy Clin Immunol* 123:S99, 2009.
16. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks—Final results of the I.M.P.A.C.T. 2 study. *Allergy* 66:1604–1611, 2011. (DOI: 10.1111/j. 1398-9995.2011.02702.x.)
17. Center for Outcomes Research, University of Massachusetts Medical School [Internet]. Interpretation guides to standardized questionnaires used in the ALS C.A.R.E database. Worcester (MA): University of Massachusetts; c1998–2010 [cited January 27, 2010]. Available from www.outcomes-umassmed.org/ALS/sf12.cfm.
18. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proc* 29:225–231, 2008.
19. Longhurst HJ, Carr S, and Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: A viable, effective treatment option. *Clin Exp Immunol* 147:11–17, 2006.
20. Levi M, Choi G, Picavet D, and Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 117:904–908, 2006. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.