

Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: Implications for future therapies

Jaison Jose, D.O., Erik B. Lehman, M.S., and Timothy Craig, D.O.

ABSTRACT

Background: Ever-expanding armamentarium of treatments for hereditary angioedema (HAE) are associated with various adverse effects, issues with vascular access, or lack of self-administration.

Objective: To understand patients' impressions and confidence in their past and present treatments, and identifying adverse events while also directly asking patients to reveal their hope for the future of HAE management and treatments.

Methods: After institutional review board approval, all subjects with laboratory-confirmed HAE were mailed a survey that they completed and returned to the researchers, and data were collected and entered into a secure online web application for surveys. Medication confidence data were summarized and expressed as means, medians, standard deviations, and quartiles by using a 5-point Likert scale. Analyses were performed by using statistical software.

Results: Of 150 surveys, 38 (25.3%) were completed. Among 36 subjects, 27 (75.0%) were female subjects, and the mean age was 50.1 years. Cinryze and Berinert (both C1-esterase inhibitors) had the highest median scores (5.0) for patient confidence, followed by ecallantide (4.5), icatibant (4.0), and androgens (2.0). For Cinryze, 64.3% selected it as the most effective and 57.1% tolerated it best. For Berinert, 50% of the subjects found it to be most effective and 59.1% tolerated it best. Some subjects listed androgens as most effective (33.3%) or best tolerated (16.7%), and many reported that this class caused the most adverse effects (44.4%). Among those who answered, 50% preferred a noninvasive method of administration, such as oral (24%), subcutaneous (18%), or not intravenous (8%) routes.

Conclusion: Determining patient predilections and the reasoning behind them can be valuable for determining specific therapies to achieve each individual's personal goals.

(Allergy Asthma Proc 39:74–80, 2018; doi: 10.2500/aap.2018.39.4095)

Hereditary angioedema (HAE) was initially described in 1888 by William Osler when he was a staff physician in Philadelphia.¹ Over time, it was determined that HAE is caused by a deficiency in functional C1 inhibitor and is transmitted in an autosomal dominant fashion. HAE involves all ethnic groups equally, without a well-defined prevalence, with some estimates that indicate ~1 case per 50,000 individuals; there are possibly 6000 patients in the United States living with HAE.^{2,3} HAE manifests with recurrent episodes of nonpruritic, nonpitting, subcutaneous and submucosal edema that involves various parts of the body, especially arms, legs, hands, feet, intestines, genitalia, trunk, face, tongue, and larynx.² Before an attack, there can be prodromal symptoms, such as fatigue,

muscle aches, and rash (*i.e.*, erythema marginatum).⁴ Symptoms are considerably variable among individuals and can begin in early childhood (50% by 10 years of age, nearly all by 20 years of age), worsen during puberty, and persist throughout life.^{2,3}

Over the past few decades, analysis of the research has revealed the importance of C1 inhibitor involvement in various pathways. It is the major inhibitor of complement proteases (C1r, C1s, and mannose-binding lectin-associated serine proteases 1 and 2), contact system proteases (plasma kallikrein and coagulation factor XIIa), and a minor inhibitor of the fibrinolytic protease plasmin and the coagulation protease factor XIa.² This cascade of events leads to the overproduction of bradykinin that potently binds to the bradykinin B2 receptor on vascular endothelial cells, which results in increased permeability. Understanding HAE and the pathways involved created a renaissance in treatment development for acute attacks and short- and long-term prophylaxis for this disease over the past few years. There have been several expert panel meetings and published consensus statements to clarify and provide algorithms for the diagnosis and management of this complex disease.^{5–12} In fact, because of the inconsistency in available medications around the

From the Department of Medicine, Division of Pulmonary, Allergy & Critical Care Medicine, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, Pennsylvania

No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Jaison Jose, D.O., Department of Medicine, Division of Pulmonary, Allergy & Critical Care Medicine, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Mail Code H041, 500 University Drive, P.O. Box 850, Hershey, PA 17033-0850

E-mail address: jjose@geisinger.edu

Copyright © 2018, OceanSide Publications, Inc., U.S.A.

world, recommendations vary by country.^{13–17} An effort has been made to summarize all of these documents,¹⁸ but there will be difficulty in doing so in the coming years because of newer agents and the uniqueness of each patient with HAE, which will lead to a more patient-centered approach to management.

For now, the influx of new treatments since 2008 has been welcome news for patients with HAE who have this chronic, incapacitating, and disfiguring disease. Attacks that involve the hands and feet can restrict a patient's ability to work and perform activities of daily living, and result in constant fear, anxiety, and depression.¹⁹ In fact, one survey conducted in 2004 by using a website of 63 patients with HAE, revealed that their three greatest fears were sudden airway closure (85%), intolerable pain (65%), and transmission of HAE to their children (55%).²⁰ Another aspect to consider is the economic burden of HAE, in which the average annual cost per patient is \$42,000 with hospitalizations, which accounts for 67% of direct medical costs.³ This is exacerbated by patients' dissatisfaction of the care they received during an HAE attack in the emergency department,²¹ which results in reduced confidence in the ability of the medical community to adequately treat them.²²

In the present climate of managed care and personalized medicine, patient-driven management of disease will become a viable and more satisfying option. However, the treatments that are available are associated with uncomfortable adverse effects, issues with vascular access, or a lack of self-administration. We performed a survey to understand patients' impressions and confidence in their past and present treatments, while also directly asking them to reveal their hope for the future of HAE management and treatments, especially in light of the new therapies that are expected to be available in the next few years. In addition, we wanted to focus on adverse events of therapies without biasing the patient; we achieved this by having all known adverse events for all the medications listed under each medication. Also, it was our impression that comparing therapies such as we did was important because determining patient predilections and the reasoning behind them can be valuable for determining specific therapies to achieve each individual's personal goals.

METHODS

Data Collection

This study was approved by the institutional review board of Penn State University, Hershey, Pennsylvania. Study team members developed and queried an established HAE data base for potential subjects diagnosed with HAE types I and II. All the patients had laboratory-proven HAE type I (HAE with C1 inhibitor

deficiency) and HAE type II (HAE with C1 inhibitor dysfunction), and were diagnosed by an allergist/immunologist with expertise in this area. All the subjects were mailed the survey which included a self-addressed return envelope *via* the U.S. Postal Service. Once completed, the subjects mailed the surveys back to the researchers without their identifying information, and data were collected and entered into RED-Cap.²³

Survey

The survey and questions were developed in collaboration with HAE experts (T.C.), a statistician (E.B.L), and the institutional review board. The first section was an explanation of the study, which was voluntary, and consent was implied when the questionnaire was completed and received by us. The next section was for demographic and patient characteristics, such as gender, age, years with HAE, and type of HAE. The subjects were then requested to list HAE medications that they were taking or had taken in the past. For each medication they listed, there was a section in which the subjects had to mark adverse effects, from a list inclusive of all known HAE drug adverse effects, that they experienced for each specific therapy. They then were requested to answer questions about which medications were most effective, tolerated best, and had the most adverse effects. The last question inquired about what development in HAE therapy would the subject like to see or have in the future.

Statistical Analysis

All analyses were performed by using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Medication effectiveness, toleration, overall adverse effects, and individual adverse effects data were summarized by using percentages and frequencies. Medication confidence data were summarized by means, medians, standard deviations, and quartiles. Because this study was observational, with the subjects having multiple medications at times but not the same medications, no inferential analysis with comparisons among medications was possible.

RESULTS

Patient Characteristics

A total of 150 surveys were sent to the subjects, and 38 (25.3%) were completed and returned. There were two subjects who did not select a gender and so, among 36 subjects, 27 were female subjects (75.0%). The mean age of the subjects was 50.1 years. Of the 35 subjects who answered the question for type of HAE, 30 (85.7%) self-identified as type I and 5 (14.3%) as type II (Table 1).

Table 1 Patient characteristics

	No. (%)
Surveys	
Total mailed	150
Total completed	38 (25.3)
Sex (<i>n</i> = 36)	
Male	9 (25.0)
Female	27 (75.0)
HAE types (<i>n</i> = 35)	
I	30 (85.7)
II	5 (14.3)
Age of subjects, y	
Mean	50.1
Median	52

HAE = Hereditary angioedema.

Table 2 HAE medications past or present use (*n* = 38)

Medication	No. (%)
Icatibant	29 (76.3)
Berinert	22 (57.9)
Androgens	18 (47.4)
Cinryze	14 (36.8)
Ecallantide	6 (15.8)
Ruconest	2 (5.3)
Tranexamic acid	1 (2.6)

HAE = Hereditary angioedema.

HAE Medications

The majority of the respondents (76.3%) used icatibant (Firazyr; Shire, Dublin, Ireland) at some point in their lives. A smaller number had used Berinert (CSL Behring, King of Prussia, PA) (57.9%), androgens (danazol, stanozolol, and oxandrolone) (47.4%), Cinryze (Shire, Lexington, MA) (36.8%), ecallantide (Kalbitor; Dyax Corp., Boston, MA) (15.8%), Ruconest (Pharming Group NV, Liden, the Netherlands) (5.3%), and tranexamic acid (2.6%), as presented in Table 2. Because of orphan drug rules, we were obliged to use the “brand name” of the C1-esterase inhibitor drugs because they are administered for unique indications. For this reason, C1-inhibitor were referred to as either Berinert (indicated for on-demand therapy) or Cinryze (indicated for prophylaxis); however, because both drugs are biosimilar, they can be used interchangeably.

HAE Medication Known Adverse Effects

Patients who were on androgens reported the most adverse effects (Table 3), including weight gain (59.0%), abnormal liver enzymes (40.9%), depression (36.4%),

menstrual abnormalities (36.4%), acne (27.3%), altered libido (22.7%), fatigue (18.2%), hypertension (9.1%), muscle pain and/or cramps (4.5%), and redness or flush (4.5%). For icatibant, the main adverse effect was injection-site pain (41.4%). Anaphylaxis was only reported by one subject (16.7%), who had used ecallantide. Ecchymoses were reported with the C1 inhibitor products: Berinert (18.2%) and Cinryze (14.3%).

Patient Confidence

Summary statistics of the confidence (1, not at all confident; 2, not confident; 3, equivocal; 4, somewhat confident; 5, completely confident) for each medication by using the pictures that patients selected for each medication were calculated (Fig. 1). Cinryze and Berinert had the highest median scores (5.0) for patient confidence, followed by ecallantide (4.5), icatibant (4.0), and androgens (2.0). Tranexamic acid and Ruconest were not included because each had only one response and a comparison could not be made.

Patient Impression of Medications

Among those who used Cinryze, 64.3% marked it as the most effective and 57.1% marked it as the best tolerated medication (Table 4). For Berinert, one-half of the patients found it to be most effective and 59.1% tolerated it best. For ecallantide and icatibant, as revealed in Fig. 2, there was a similar percentage of patients who found that these were most effective (33.3% versus 31.0%) and best tolerated (50.0% versus 37.9%). Very few subjects listed androgens as most effective (33.3%) or best tolerated (16.7%), and most reported that this drug class caused the most adverse effects (44.4%).

Patient Treatment Preference

More than one-third (34%) did not respond to the question that asked for the main development that the subject would like to see or have with regard to HAE medications. However, 50% of those who responded preferred a noninvasive method of administration, such as oral (24%), subcutaneous (18%), or not intravenous (8%) routes (Fig. 3).

DISCUSSION

Patients with HAE experience significant physical, emotional, and financial burdens with their disease, which can be unpredictable, debilitating, disfiguring, and life-threatening. Therefore, an individualized HAE treatment plan is necessary for all patients, and taking into account parameters such as location, rate, and severity of attacks; patient preference; age; gender; pregnancy; access to medical facilities; geography; comorbid conditions (*i.e.*, prostate and breast cancer); and chronic medication use (*i.e.*, angiotensin-converting en-

Table 3 HAE medication adverse effects

Adverse Effect	HAE Medication, no. (%)						
	Cinryze (n = 14)	Berinert (n = 22)	Ecallantide (n = 6)	Icatibant (n = 29)	Ruconest (n = 2)	Androgens (n = 22)	Tranexamic Acid (n = 1)
Abnormal liver enzymes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (40.9)	0 (0)
Acne	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (27.3)	0 (0)
Altered libido	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	5 (22.7)	0 (0)
Anaphylaxis	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)
Black and blue spots	2 (14.3)	4 (18.2)	0 (0)	10 (34.5)	1 (50.0)	0 (0)	0 (0)
Bleeding	0 (0)	0 (0)	0 (0)	2 (6.9)	0 (0)	0 (0)	0 (0)
Blood clots	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Depression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (36.4)	0 (0)
Fatigue	1 (7.1)	2 (9.0)	0 (0)	4 (13.8)	0 (0)	4 (18.2)	0 (0)
Headaches	1 (7.1)	0 (0)	0 (0)	2 (6.9)	0 (0)	0 (0)	0 (0)
Hypertension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9.1)	0 (0)
Infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Menstrual abnormalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (36.4)	0 (0)
Muscle pain and/or cramps	0 (0)	0 (0)	0 (0)	1 (3.4)	0 (0)	1 (4.5)	0 (0)
Nausea	1 (7.1)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pain	0 (0)	2 (9.0)	1 (16.7)	12 (41.4)	0 (0)	0 (0)	0 (0)
Redness or flush	0 (0)	1 (4.5)	0 (0)	7 (24.1)	0 (0)	1 (4.5)	0 (0)
Viral infections	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Weight gain	0 (0)	0 (0)	0 (0)	1 (3.4)	0 (0)	13 (59.0)	0 (0)

HAE = Hereditary angioedema.

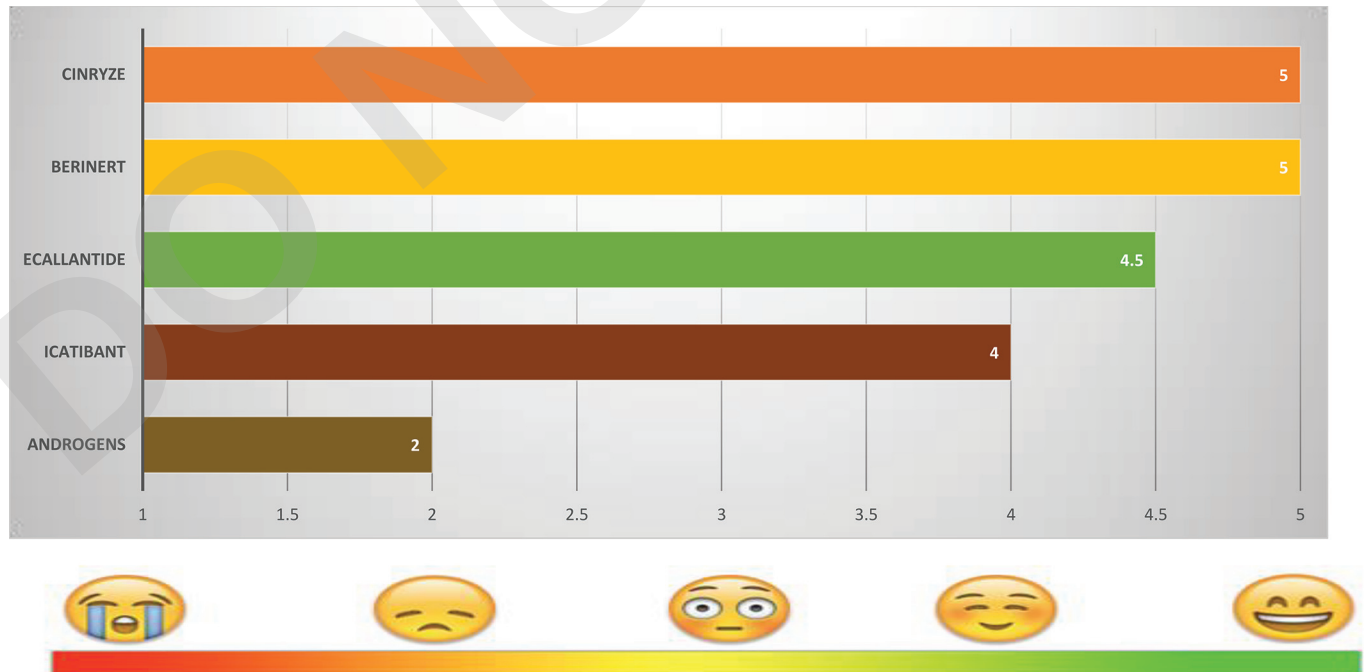


Figure 1. Patients' confidence with medications, with median scores.

zyme inhibitor and estrogens).²⁴ Choosing the best available medication that fits the patient's needs with few adverse effects has the potential to improve each patient's quality of life.

In an attempt to remain unbiased and to not directly solicit a known drug adverse effect from the subject, the adverse effects listed for each drug were inclusive of all known adverse effects for HAE medications. We

Table 4 Overall patient impression of medications*

	Cinryze (n = 14)	Berinert (n = 22)	Ecallantide (n = 6)	Icatibant (n = 29)	Androgens (n = 18)
Most effective, no. (%)	9 (64.3)	11 (50.0)	2 (33.3)	9 (31.0)	6 (33.3)
Tolerated best, no. (%)	8 (57.1)	13 (59.1)	3 (50.0)	11 (37.9)	3 (16.7)
Most adverse effects, no. (%)	0 (0.0)	0 (0.0)	1 (16.7)	8 (27.6)	8 (44.4)
Confidence, median (IQR)	5.0 (0.0)	5.0 (1.0)	4.5 (3.0)	4.0 (1.0)	2.0 (3.0)

IQR = Interquartile range.

*The Ruconest (n = 2) and tranexamic acid (n = 1) groups did not have enough subjects to warrant summary statistics.

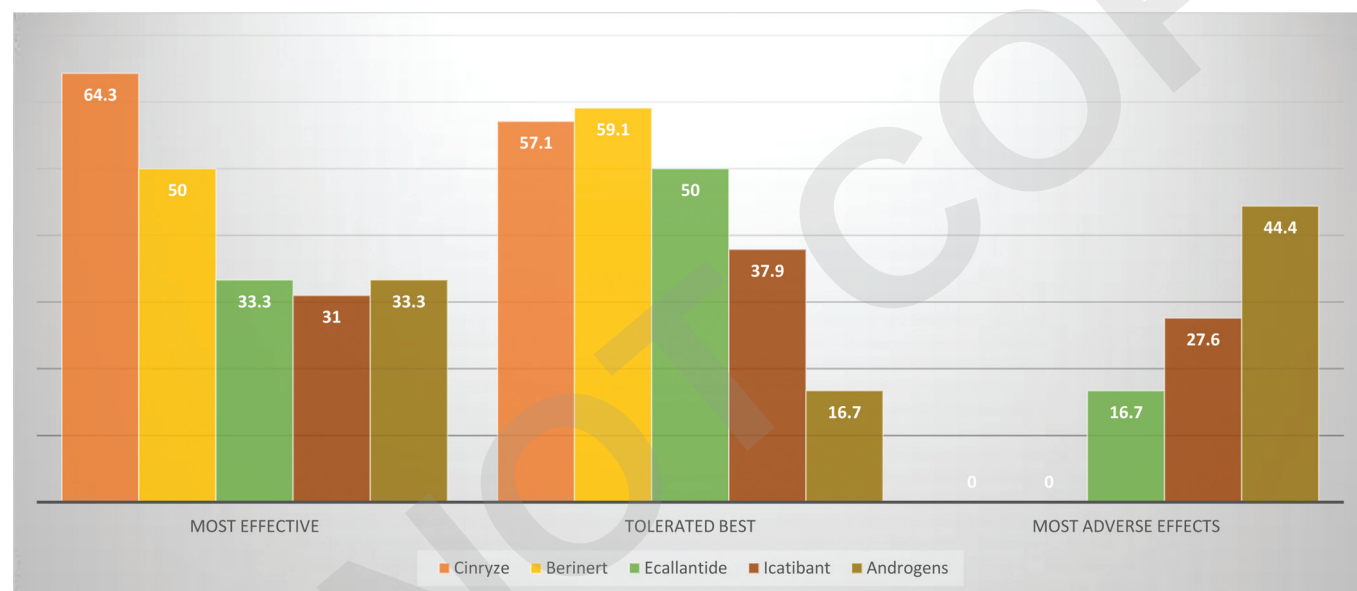


Figure 2. Overall patients' impression of medications.

were concerned that past studies solicited specific adverse effects associated with androgens, while not soliciting specific adverse effects associated with some of the newer medications. Attenuated androgens, such as danazol, stanozolol, and oxandrolone, are routinely used to prevent the development of acute attacks of HAE, and they were the only effective option for prophylactic treatment in the United States before the availability of nanofiltered C1 inhibitor.^{25,26} As expected, in our study, androgens had the most adverse effects and intolerance.

For patients, adverse effects impact their impression of and confidence in medications, which play a large factor in their adherence and comfort.²⁷ However, despite our understanding of adverse effects,²⁸ confidence is difficult to interpret and has not been evaluated before in this way. Our study revealed that patients had the most confidence in Cinryze and Berinert, followed by ecallantide and icatibant; this same order applied to patients' overall impression of medications and what they felt were most effective and tolerated best. For patients, androgens had the most

adverse effects, the lowest median confidence, and the least overall positive impression of the medication, despite it being an oral medication.²⁹ The World Allergy Organization states that self-administration is the preferred method of treatment because of its proven benefit to decrease absenteeism, cost, disease burden, and potential morbidity and mortality.^{10,14,30} Currently, the only medication not able to be self-administered is ecallantide; however, despite this restriction, a fair number of patients were pleased with the medication, the adverse effect profile, and benefit, and had greater confidence in it than in icatibant.

One study, by Wang *et al.*,²⁷ reported that home was the patients' first choice for the most comfortable location to receive therapy. This is consistent with a work-group statement that self-administration and home therapy should be considered for every patient.³¹ Our subjects revealed that they prefer noninvasive routes of administration. In fact, of those who responded, 76% preferred a less-invasive route, of which 47% preferred an oral route and 37% preferred the subcutaneous route. As reported, the main challenge for self-admin-

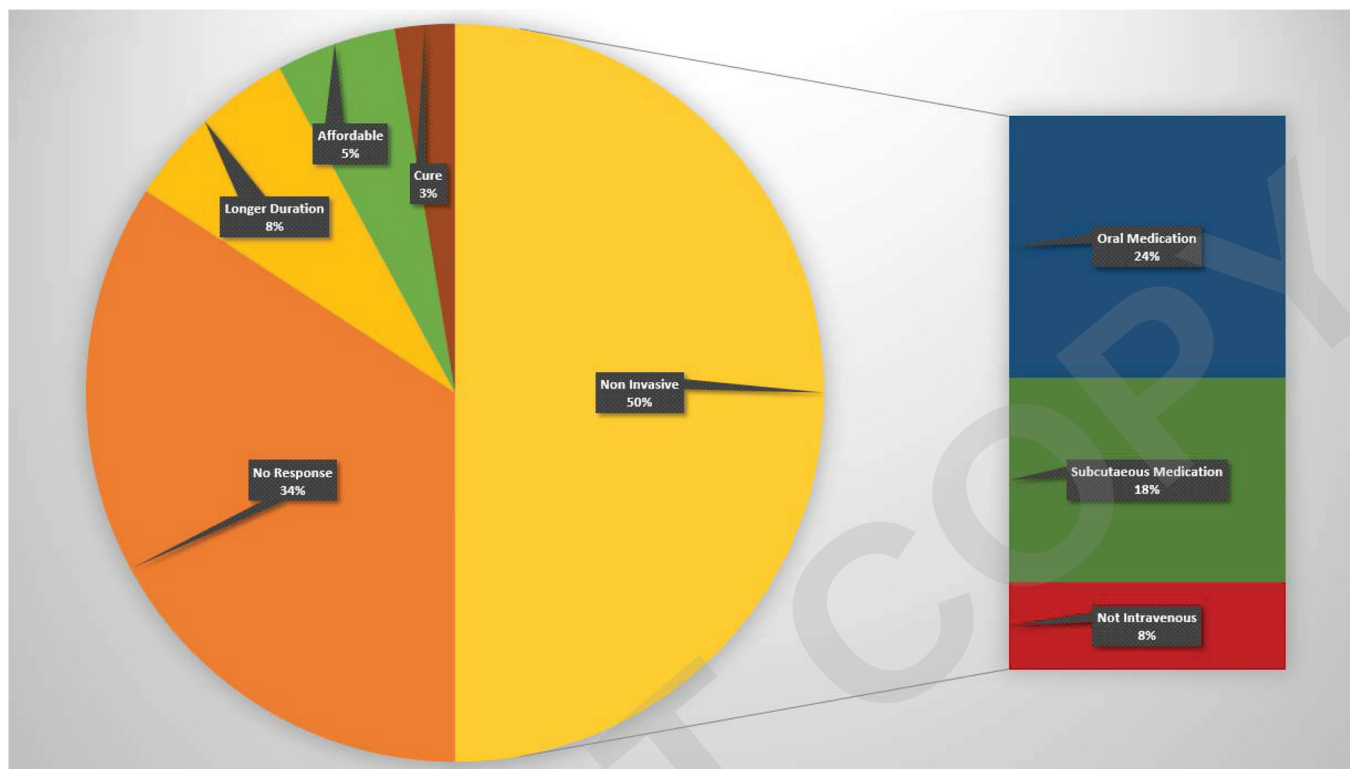


Figure 3. Patients' treatment preference.

istration is obtaining the necessary skill set, and this is especially true for intravascular administration and less so for subcutaneous administration.²⁹ However, independence can be associated with hazards, and, despite how effective a prophylactic agent is, an "on-demand therapy" is essential to have available at all times. In addition, if an attack does not respond to on-demand therapy, then the differential diagnosis of the symptoms and signs needs to be expanded. With the efficacy associated with the newer medications to be introduced to the HAE universe soon, it may be difficult for patients to remember to carry their on-demand therapy.

There were limitations to this study. The concern for any one-time survey done voluntarily is the risk of bias and, in this case, selection bias. Participation was based on self-selection, which can affect the representativeness of the study population. Not every patient answered all of the questions, which can affect the generalizability of the results. Most of the respondents were female patients (75.7%) who have been shown to experience more-severe symptoms, and this could indicate a bias as well.²⁶ Another consideration is that, because the patient information was retrieved from a university data base, there was the possibility of regional and geographic bias. There are several advantages to this study as well. We were able to collect data from a relatively large number of patients with a very rare disease. Even if the actual response rate seemed to

be small, the percentage was greater than expected for most random surveys.

CONCLUSION

Clinical trials and research of new treatments in various stages of development seem promising and could add to the armamentarium for HAE. These new treatments include the following: subcutaneous formulations of C1 inhibitor (Berinert and Cinryze³²); recombinant fully human monoclonal antibody against plasma kallikrein (lanadelumab),³³ factor XII inhibitor; orally administered small molecular kallikrein inhibitor (avoralstat)³⁴; an antisense drug designed to inhibit the production of prekallikrein (Ionis-PKKRx, Ionis Pharmaceuticals, Carlsbad, CA); and, possibly, genetic insertion of normal C1-inhibitor genes.³⁵ Because comparative studies are essentially impossible, studies similar to this will be important in the future to compare present, new, and evolving therapies.

REFERENCES

1. deShazo RD, Frank MM. Genius at work: Osler's 1888 article on hereditary angioedema. *Am J Med Sci.* 2010; 339:179–181.
2. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med.* 2008; 359:1027–1036.
3. Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol.* 2013; 111:329–336.
4. Prematta MJ, Kemp JG, Gibbs JG, Mende C, Rhoads C, Craig TJ. Frequency, timing, and type of prodromal symptoms associated

- with hereditary angioedema attacks. *Allergy Asthma Proc.* 2009; 30:506–511.
5. 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.* 2008; 100(suppl. 2):S30–S40.
 6. Caballero T, Baeza ML, Cabañas R, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. *J Investig Allergol Clin Immunol.* 2011; 21: 422–441; quiz 442–443.
 7. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol.* 2012; 129: 308–320.
 8. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents—A consensus on therapeutic strategies. *Eur J Pediatr.* 2012; 171:1339–1348.
 9. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. *Allergy Asthma Proc.* 2012; 33(suppl. 1): S145–S156.
 10. Craig T, Aygören-Pürsün E, Bork K, et al. WAO Guideline for the Management of Hereditary Angioedema. *World Allergy Organ J.* 2012; 5:182–199.
 11. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol.* 2004; 114:629–637.
 12. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: Consensus report of an International Working Group: HAE consensus report. *Allergy.* 2012; 67:147–157.
 13. Longhurst HJ, Tarzi MD, Ashworth F, et al. C1 inhibitor deficiency: 2014 United Kingdom consensus document. *Clin Exp Immunol.* 2015; 180:475–483.
 14. Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol.* 2014; 10:50.
 15. Giavina-Bianchi P, França AT, Grumach AS, et al. Brazilian guidelines for the diagnosis and treatment of hereditary angioedema. *Clinics (Sao Paulo).* 2011; 66:1627–1636.
 16. Horiuchi T, Ohi H, Ohsawa I, et al. Guideline for hereditary angioedema (HAE) 2010 by the Japanese Association for Complement Research—Secondary publication. *Allergol Int.* 2012; 61:559–562.
 17. Cicardi M, Bellis P, Bertazzoni G, et al. Guidance for diagnosis and treatment of acute angioedema in the emergency department: Consensus statement by a panel of Italian experts. *Intern Emerg Med.* 2014; 9:85–92.
 18. Jose J, Zacharias J, Craig T. Review of select practice parameters, evidence-based treatment algorithms, and international guidelines for hereditary angioedema. *Clin Rev Allergy Immunol.* 2016; 51:193–206.
 19. Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: Results from the Burden of Illness Study in Europe. *Allergy Asthma Proc.* 2014; 35:47–53.
 20. Huang SW. Results of an on-line survey of patients with hereditary angioedema. *Allergy Asthma Proc.* 2004; 25:127–131.
 21. Banerji A, Busse P, Christiansen SC, et al. Current state of hereditary angioedema management: A patient survey. *Allergy Asthma Proc.* 2015; 36:213–217.
 22. Fouche AS, Saunders EF, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol.* 2014; 112:371–375.
 23. Paul AH, Robert T, Robert T, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42:377–381.
 24. Gower RG. HAE update: Determining optimal patient specific therapy. *Allergy Asthma Proc.* 2013; 34:7–12.
 25. Gower RG, Lumry WR, Davis-Lorton MA, Johnston DT, Busse PJ. Current options for prophylactic treatment of hereditary angioedema in the United States: Patient-based considerations. *Allergy Asthma Proc.* 2012; 33:235–240.
 26. 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.
 27. Wang A, Fouche A, Craig TJ. Patients perception of self-administered medication in the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2015; 115:120–125.
 28. Kalaria S, Craig T. Assessment of hereditary angioedema treatment risks. *Allergy Asthma Proc.* 2013; 34:519–522.
 29. Boysen HB, Bouillet L, Aygören-Pürsün E. Challenges of C1-inhibitor concentrate self-administration. *Int Arch Allergy Immunol.* 2013; 161(suppl. 1):21–25.
 30. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract.* 2013; 1:458–467.
 31. Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol.* 2010; 6:22.
 32. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med.* 2017; 376:1131–1140.
 33. Banerji A, Busse P, Shennak M, et al. Inhibiting plasma kallikrein for hereditary angioedema prophylaxis. *N Engl J Med.* 2017; 376:717–728.
 34. Aygören-Pürsün E, Magerl M, Graff J, et al. Prophylaxis of hereditary angioedema attacks: A randomized trial of oral plasma kallikrein inhibition with avoralstat. *J Allergy Clin Immunol.* 2016; 138:934–936.e5.
 35. Bork K. A decade of change: Recent developments in pharmacotherapy of hereditary angioedema (HAE). *Clin Rev Allergy Immunol.* 2016; 51:183–192. □

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.