

Current options for prophylactic treatment of hereditary angioedema in the United States: patient-based considerations

Richard G. Gower, M.D.,¹ William R. Lumry, M.D.,² Mark A. Davis-Lorton, M.D.,³ Douglas T. Johnston, D.O.,⁴ and Paula J. Busse, M.D.⁵

ABSTRACT

Hereditary angioedema (HAE) results from mutations in the C1-esterase inhibitor (C1 INH) gene that decrease production of C1 INH or render it dysfunctional. HAE is characterized by recurrent, unpredictable, bradykinin-mediated edema of the extremities, face, genitalia, trunk, gastrointestinal tract, or upper airway. Attacks causing laryngeal edema can be fatal. Patients with HAE need medications for acute attacks; some also require prophylaxis. Management requires consideration of the patient's disease burden and effect on the patient's quality of life. This review examines an individualized approach to identifying HAE patients who may benefit from prophylaxis. A literature search was performed for HAE and prophylaxis. HAE guidelines, case reports, safety studies, and randomized, controlled clinical prophylaxis trials were selected. Authors provided cases demonstrating individualized prophylaxis. U.S. Food and Drug Administration-approved options for prophylaxis of HAE include attenuated androgens and nanofiltered C1 INH (C1 INH-nf). In other countries, pasteurized C1 INH and purified C1 INH are also available. Alternative therapies include fresh frozen plasma for preprocedural prophylaxis and antifibrinolytics for long-term prophylaxis. Attenuated androgens reduce attack frequency in many patients. Adverse effects include weight gain, virilization, increased hair growth, hypercholesterolemia, depression, and liver adenomas. C1 INH-nf reduces frequency of attacks and is well tolerated. Each patient with HAE has unique needs, based on the nature and frequency of past attacks, proximity to a medical center, occupation, and the patient's wishes. These factors should be used to create a patient-centered approach to management of HAE.

(Allergy Asthma Proc 33:235–240, 2012; doi: 10.2500/aap.2012.33.3573)

Hereditary angioedema (HAE) is an autosomal-dominant disease resulting from a mutation in the C1-inhibitor gene that causes a deficiency in C1-esterase inhibitor (C1 INH) in 85% of patients and dysfunction of the protein in all patients.^{1,2} The defective genes have 1 of more than 200 different described mutations. HAE is rare, with prevalence estimated at 1 in 50,000 people worldwide.³ Patients experience recurrent episodes of localized subcutaneous nonpruritic angioedema of the extremities, face, genitalia, or trunk or submucosal edema of the upper airway or abdomen.⁴ Pain typically accompanies these episodes. Edema in the gastrointestinal tract can cause intestinal

blockage and severe nausea, vomiting, and in some patients, diarrhea. Laryngeal edema is a potentially fatal manifestation of HAE because without proper management, it can lead to asphyxiation. Limitations at work, school, and leisure activities from HAE attacks, as well as adverse effects of some medications used to treat HAE prophylactically, may cause patients to report a poor quality of life and depression.⁵ In a web-based study conducted to assess the effect of HAE on quality of life, patients with HAE scored significantly lower than a normal population on a standardized health survey.⁵ The 457 patients surveyed reported a mean of 26.9 attacks per year; approximately half missed at least 1 day of work, school, or leisure activities because of their most recent attack.

The triggers of an HAE attack are not entirely clear or predictable. Many attacks occur spontaneously, but there are known triggers, such as stress, trauma, or infection, that may provoke an attack, albeit not consistently.⁶ After a triggering event, activation of the contact pathway is ineffectively inhibited due to insufficient functional C1 INH (Fig. 1).^{4,7} Overproduction of bradykinin results, increasing vascular permeability and extravasation, leading to angioedema. Although the physical presentation may resemble allergic angioedema, bradykinin is the major mediator producing

From the ¹University of Washington, Marycliff Allergy Specialists, Spokane, Washington;

²University of Texas Southwestern Medical School, Asthma and Allergy Research Associates, Dallas, Texas; ³Winthrop Rheumatology, Allergy, and Immunology, Mineola, New York; ⁴Edward Via College of Osteopathic Medicine, Carolina Campus, and Allergy Partners, PA, Greenville, South Carolina; and ⁵Department of Medicine, Allergy and Immunology, The Mount Sinai Medical Center, New York, New York

Supported by by ViroPharma Inc., Exton, PA
RG Gower, WR Lumry, and PJ Busse have received research and grant support, and have consulted for Viropharma. MA Davis-Lorton is a consultant for Viropharma and DT Johnston has received research support from Viropharma

Address all correspondence and reprint requests to Richard G. Gower, M.D., Marycliff Allergy Specialists, 823 West 7th Avenue, Spokane, WA 99204
E-mail: rgower@marycliffallergy.com

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

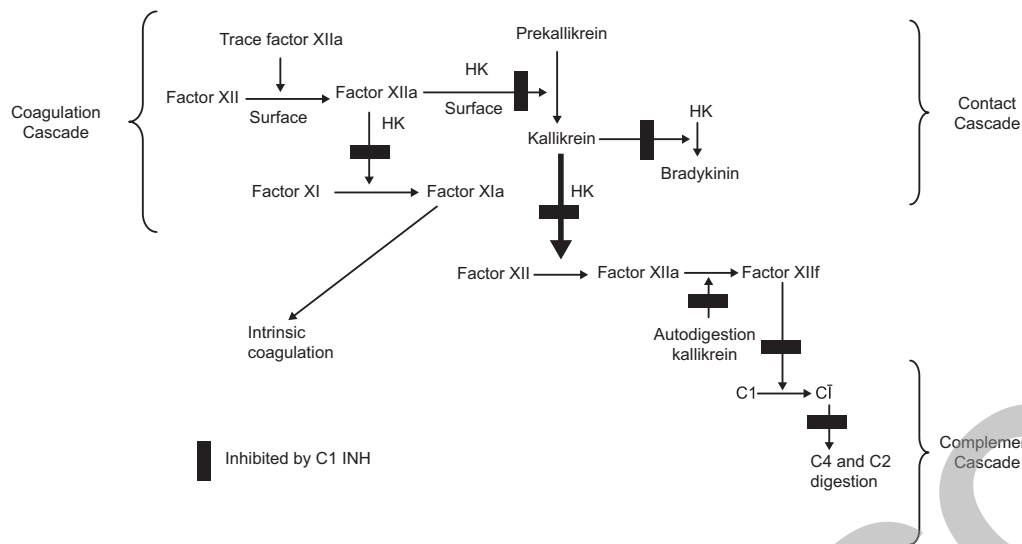


Figure 1. Effect of C1 INH on bradykinin formation (reproduced from Ref. 7, with permission). C1i, Activated C1; HK, high-molecular-weight kininogen.

Table 1 Laboratory diagnostic criteria for hereditary angioedema^{4,9,10}

Parameter	HAE type I	HAE type II
C4 level	Low	Low
C1 INH level	Low	Normal
C1 INH functional activity	Low	Low
C1q level	Normal	Normal

angioedema in HAE, whereas an IgE-mediated response releasing histamine, leukotrienes, and other proinflammatory mediators is central to allergic angioedema. These two entities are also distinguished by response to medications. Symptoms of an allergic reaction are reversed by epinephrine, antihistamines, and corticosteroids; however, they will have little effect on an HAE attack.⁸

Diagnosis of HAE should be initially considered based on symptoms as described previously, including a lack of response to medications used for treatment of allergic angioedema, and in individuals with a family history of angioedema. Diagnosis is confirmed by laboratory evaluation of serum complement factor 4 (C4), C1 INH antigenic and functional levels, and C1q (Table 1).^{4,9,10} The clinical presentation and treatment of the swelling cannot be differentiated between type I (~85% of patients) and type II HAE. Type III HAE is very rare and will not be discussed in this article. There is a positive family history of HAE in ~75% of patients.¹¹ In 25% of cases, there is a spontaneous mutation in the C1 INH gene, and in these patients, there is no previous family history suggesting HAE. Because HAE is a rare disease, it may not be considered in the initial differential diagnosis of patients, and this contributes to delays in diagnosis.¹² Undiagnosed patients

with HAE frequently undergo unnecessary medical treatments, such as exploratory abdominal surgery during an acute abdominal attack, and are not given appropriate medications to treat HAE but instead medications traditionally used to treat histamine-mediated angioedema.¹³

Each patient with HAE has a unique clinical course, defined by varying frequency, severity, and anatomic location of attacks.⁵ Disease characteristics may also vary throughout a patient's life. For example, a patient may never have experienced an airway attack but later in life may have his or her first attack. Similarly, the frequency of attacks may vary with age. These changes in disease presentation cannot be predicted.

TREATMENT

Treatment of HAE is traditionally classified into three approaches: acute treatment, short-term (preprocedural) prophylaxis, and long-term prophylaxis.^{4,9,10} The practical application of the latter two approaches is the focus of this article. All patients with HAE must have ready access to at least one medication to treat acute attacks, which includes replacement C1 INH or medications that inhibit the actions of bradykinin, such as icatibant and ecallantide.⁴ Fresh frozen plasma has been used during acute attacks, but it may exacerbate an ongoing attack.^{4,9,10} For this reason, it is generally not recommended as an acute therapy, especially during an airway attack. A 2009 survey reported that only 20–30% of U.S. physicians who treat patients with HAE were familiar with C1 INH, and less than 50% prescribed C1 INH for acute attacks.¹⁴ Improving awareness of HAE and the availability of C1 INH as well as the other new therapeutic options to treat acute attacks will potentially improve outcomes for patients with HAE.

In a short-term prophylaxis strategy, treatment is administered before a medical, surgical, or dental procedure (potential triggers of an HAE attack) and consists of C1 INH (first choice, 1000 units given within 1–6 hours before procedure), fresh frozen plasma (2 units within 6 hours of the procedure), or high-dose attenuated androgens (up to 600 mg danazol daily).^{4,9,10} Attenuated androgens should be administered for 5 days before and 2–5 days after the procedure. In some patients, long-term prophylaxis of HAE should be considered. U.S. Food and Drug Administration-approved options for long-term prophylaxis include routine administration of attenuated androgens or nanofiltered C1 INH.^{4,9,10} Antifibrinolytics may be used for long-term prophylaxis but are less effective than androgens and are not approved for this use in the United States.

CASE STUDIES

The approach to prophylaxis will vary with each patient's disease characteristics and lifestyle. Healthcare providers should consider each patient's disease burden, quality of life, and outcome of previous treatments when constructing a strategy for prophylaxis and treatment of acute attacks. The following case studies describe the individualized approach to prophylaxis and treatment in several patients with HAE and demonstrate that an individual approach with discussion between the patient and physician is needed for the selection of therapy that accommodates the patient.

Patient Satisfaction with Attenuated Androgens

Case. A 28-year-old female presented with acute facial edema and abdominal pain, which was attributed to a milk allergy that she had since childhood. She continued to have intermittent extremity swelling, abdominal pain, vomiting, and loose stools, which occurred most months, often requiring emergency department (ED) visits. No improvement in gastrointestinal symptoms was noted after cholecystectomy. A dental procedure precipitated swelling around the mouth and lips that lasted several days. She developed laryngeal swelling several years later, and intubation was considered. At age 51 years, she was seen in the ED for facial swelling and found to have C4 <10 mg/dl (normal 16–47 mg/dl), C1 INH <3.5 mg/dl (normal 7.8–23.4 mg/dl), and C1 INH function of 45% (normal >67%). Her family history includes a father with mild facial swelling that was never evaluated and a son with HAE. She was diagnosed with HAE and began danazol 200 mg/day, subsequently decreased to 150 mg/day. A further attempt at dose reduction resulted in an abdominal attack, and there has been reluctance to reduce the dose since then.

Six years after her diagnosis, she reported increased hair growth and fatigue, deepening of the voice, and weight gain. Comorbidities included hypertension and hypercholesterolemia. Physical exam was remarkable for obesity and elevated blood pressure (140/88 mm Hg). Total cholesterol was 216 mg/dl (high-density lipoprotein 24 mg/dl, low-density lipoprotein 177 mg/dl); liver enzymes were normal.

Nanofiltered C1 INH (C1 INH-nf) was discussed as an alternative prophylactic therapy in an effort to decrease side effects of danazol, which included weight gain, hypertension, elevated cholesterol, hair growth, and deepening of the voice. The patient elected to continue danazol therapy because she had been free of attacks for several years. She feared that a change in therapy could lead to an HAE attack and felt the side effects of danazol were more tolerable than the risk of swelling. The plan is to continue danazol at a decreased dose if it is tolerated and to treat acute attacks with C1 INH. Medications to control her hypertension are carvedilol and triamterene-hydrochlorothiazide, and she is compliant with laboratory testing and ultrasounds to monitor liver function.

Comment. As is true for many patients with HAE, diagnosis and proper treatment were delayed for many years in this case, possibly because of lack of recognition of HAE on the physician's part. When the patient and physician communicate freely about symptoms and frequency of swelling episodes and family history, a diagnosis of HAE may be reached and a plan for management of the disease may be made. Further consultation between the patient and physician is necessary to determine the patient's expectations regarding long-term management. Patients may be willing to tolerate the adverse effects of attenuated androgens to prevent acute attacks, and they may be satisfied enough with the efficacy of this drug class to look no further for prophylaxis.

Attenuated androgens, such as danazol, stanozolol, and oxandrolone, were the only option for prophylactic treatment of HAE in the United States before C1 INH-nf became available. According to a survey conducted in 2009 (administered shortly after the U.S. Food and Drug Administration approval of C1 INH for prophylactic treatment), attenuated androgens were prescribed for more than 80% of patients who required long-term prophylaxis.¹⁴ They are readily available and inexpensive, but tolerability is variable due to their potential side effects, which include weight gain, headache, depression, virilization, menstrual irregularities, and the potential for liver adenomas. In one study, 111 of 118 patients with HAE had decreases in attack frequency while taking danazol; however, 93 experienced adverse effects, and 30 discontinued danazol because of the adverse effects.¹⁵ It is recommended that pa-

tients on long-term attenuated androgens have a laboratory evaluation every 6 months to assess liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and a complete lipid profile), complete blood cell count, and urinalysis.^{4,9,10} An abdominal liver and spleen ultrasound is recommended annually for patients taking ≤ 200 mg/day of danazol or every 6 months for patients taking > 200 mg/day of danazol. There may be an increased risk of adverse effects when > 200 mg/day of danazol is given long term; however, therapy must be individualized, and doses above this level may be effective and well tolerated in some patients.

Attenuated androgens may impair growth; therefore, they are contraindicated in childhood.⁴ Likewise, attenuated androgens are contraindicated in pregnancy and breastfeeding because of potential adverse effects such as masculinization of the fetus or child.^{4,9,10}

Patient Satisfaction with C1 INH

Case. A 41-year-old female was diagnosed with HAE at age 32. At 8 years of age, she developed episodes of swelling of her hands and feet that occurred every few months, lasted a few days, and resolved spontaneously. In her early teenage years, she had occasional episodes of severe abdominal pain and abdominal bloating, sometimes with nausea and vomiting. Episodes of extremity swelling were more frequent during her two pregnancies at ages 17 and 19. After delivery, abdominal attacks increased in frequency and severity, with occasional swelling of her face but no airway involvement. At age 26, she experienced laryngeal edema that required hospitalization without intubation. None of these episodes responded to treatment with corticosteroids, antihistamines, or epinephrine. At age 32, she was hospitalized with severe abdominal pain, nausea, and vomiting. Laboratory testing revealed a C4 of 6 mg/dl (normal 14–45 mg/dl), C1 INH of 7 mg/dl (normal 10–25 mg/dl), and C1 INH function of 20% ($< 41\%$ abnormal), and she was diagnosed with HAE type I. Her family history was significant in that her maternal grandmother (at age 40) and two maternal aunts (at ages 20 and 32) died from airway swelling.

The patient was prescribed danazol for prophylaxis, with subsequent trials of stanozolol and oxandrolone. Danazol had the best tolerability; however, side effects included weight gain, headaches, depression, and anxiety. In 2006, the patient was enrolled in a clinical trial of C1 INH for HAE attacks. During the open-label portion of the trial, the patient used C1 INH for routine prophylaxis. Her HAE attacks decreased in frequency and severity, and her mood improved after discontinuation of danazol. She discontinued participation in

the open-label portion of the trial because her work schedule prevented her from visiting the study site every 3–4 days. She resumed danazol 400 mg/day but continued to have breakthrough attacks, resulting in hospitalizations and ED visits for abdominal attacks. The side effects of danazol (i.e., increased irritability and depression) continued to affect her work and family life. She resumed prophylaxis with C1 INH, which allowed her to discontinue danazol. Her HAE attacks have decreased in number and severity, and her depression has improved. She self-administers C1 INH for prophylaxis and attacks.

Comment. This case demonstrates the problems of delayed diagnosis and selection of appropriate treatment. Even after diagnosis of HAE and provision of attenuated androgens for prophylaxis, the patient continued to suffer from acute attacks and tolerated the attenuated androgens poorly. C1 INH was a better choice for her because it allowed her to discontinue danazol and improve her quality of life.

In the United States, human C1 INH-nf (Cinryze; ViroPharma Inc., Exton, PA) was approved in 2008 for routine prophylaxis against HAE attacks.¹⁶ In a randomized, double-blind clinical trial, 22 patients received C1 INH-nf or placebo via i.v. infusion every 3–4 days for the first of two 12-week periods. Each patient crossed over to the other study treatment for the second 12-week period. When patients received C1 INH-nf, they had fewer attacks than when they received placebo (6.26 versus 12.73 attacks; $p < 0.001$).¹⁷ During the subsequent open-label extension phase of this trial, C1 INH-nf was administered to 146 patients every 3–7 days.¹⁸ Duration of participation in the open-label phase of the study ranged from 8–959 days; however, C1 INH-nf was administered to 73% of patients for at least 6 months. The baseline (before C1 INH prophylactic therapy) median attack rate was 3.0 cases/month; during prophylaxis with C1 INH-nf, the median attack rate decreased to 0.2 attacks/month. In the double-blind portion of this trial, three patients had adverse events that were considered to be possibly related to the study drug; these included pruritus and rash, lightheadedness, and fever.¹⁷ In the open-label phase, headache (eight patients, 5.5%), nausea (six patients, 4.1%), rash (four patients, 2.7%), erythema (three patients, 2.1%), and diarrhea (three patients, 2.1%) were reported to be related to study drug in at least one patient.

Other C1 INH products have long been used for acute treatment and preprocedural prophylaxis in Europe and other parts of the world.^{19, 20} Although these products are derived from human plasma, they carry a low risk of viral transmission because of advanced manufacturing processes as well as strict screening and testing of donors.^{16,19, 20} Furthermore, no cases of viral

transmission with these products have been documented since these strict manufacturing steps were implemented.²¹ A disadvantage of C1 INH products is the requirement of i.v. administration; however, self-administration at home may be possible if a patient is using a product approved for self-administration and is able to learn how to safely reconstitute the product and perform venipuncture.^{22,23}

Prophylaxis Not Necessary

Case. A 24-year-old female in nursing school with a past medical history of Crohn's disease with type II HAE who had attacks 10 times a month received prophylaxis with C1 INH, which had markedly decreased the frequency and severity of her attacks. She discontinued C1 INH when she lost her health insurance after finishing nursing school. She did not have an attack for more than 3 months. A previous trial of attenuated androgens had precipitated serious psychiatric problems, weight gain, and acne. She and her physician opted against prophylaxis, deciding instead to treat acute HAE attacks only.

Comment. In this case, a patient in whom prophylaxis with C1 INH was at one time necessary because of frequent HAE attacks was able to discontinue prophylaxis when the attacks began to occur less often. Current HAE guidelines suggest long-term prophylaxis for patients who experience at least one severe attack per month, have a history of laryngeal attacks, do not respond well to acute treatment, or do not have immediate access to healthcare or on-demand treatment.^{4,9,10,24} When determining appropriate long-term prophylaxis, healthcare providers should bear in mind that past attacks do not predict severity or location of future attacks. Laryngeal edema may occur at any time, regardless of whether the patient has previously experienced an airway event. In addition, this case clearly exemplifies how stressful living situations can increase the number of attacks in HAE patients and how the reduction of such stressors may reduce the frequency of angioedema attacks. Every HAE patient should have on-demand therapy available for acute attacks and this may be the only treatment necessary.

CONCLUSIONS

As demonstrated in these case reports, prophylactic therapy for HAE depends on several patient-specific factors, including the nature, severity, and frequency of attacks, efficacy and tolerability of prophylactic therapies, impact of the disease on quality of life, and patient expectations. Frequent, severe HAE attacks can prevent patients from participating in work, school, and leisure activities. These patients are candidates for long-term prophylaxis; however, it is important to note

that even patients with mild attacks may experience laryngeal edema. Some patients tolerate attenuated androgens better than others; those who recognize improvement in attack frequency and accept the potential adverse effects may elect long-term prophylaxis with attenuated androgens. Alternatively, patients who tolerate attenuated androgens poorly may be candidates for long-term prophylaxis with C1 INH-nf. For some, on-demand therapy for acute attacks is appropriate management. The approach to prophylactic treatment in an individual patient should be revisited regularly, because changes in a patient's life may influence the appropriateness of prophylactic treatment.

The acute and prophylactic therapies for HAE in the United States have provided many management options where there previously were few. These advances are expected to decrease deaths caused by laryngeal edema secondary to HAE as well as improve quality of life for patients with HAE.

ACKNOWLEDGMENTS

Jennifer L. Darby, Pharm.D., of Scientific Therapeutics Information, Inc., Springfield, NJ, provided editorial assistance on this manuscript. Funding for editorial assistance was provided by ViroPharma Inc.

REFERENCES

1. Bock SC, Skriver K, Nielsen E, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. *Biochemistry* 25:4292–4301, 1986.
2. Ferraro MF, Moreno AS, Castelli EC, et al. A single nucleotide deletion at the C1 inhibitor gene as the cause of hereditary angioedema: insights from a Brazilian family. *Allergy* 66:1384–1390, 2011.
3. Agostoni A, and Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 71:206–215, 1992.
4. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 6:24, 2010.
5. 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.
6. Frank MM, Gelfand JA, and Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 84:580–593, 1976.
7. Kaplan AP, and Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol* 104:193–204, 2010.
8. Zuraw BL. HAE therapies: past present and future. *Allergy Asthma Clin Immunol* 6:23, 2010.
9. 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(1 Suppl 2):S30–S40, 2008.
10. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 139:379–394, 2005.
11. Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1 inhibitor gene of pa-

- tients with angioedema. *J Allergy Clin Immunol* 106:1147–1154, 2000.
12. Füst G, Farkas H, Csuka D, et al. Long-term efficacy of danazol treatment in hereditary angioedema. *Eur J Clin Invest* 41:256–262, 2011.
 13. Cicardi M, Bergamaschini L, Marasini B, et al. Hereditary angioedema: an appraisal of 104 cases. *Am J Med Sci* 284:2–9, 1982.
 14. Riedl M, Gower RG, and Chrvala CA. Current medical management of hereditary angioedema: results from a large survey of US physicians. *Ann Allergy Asthma Immunol* 106:316–322, 2011.
 15. Bork K, Bygum A, and Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol* 100:153–161, 2008.
 16. Cinryze [package insert]. Exton, PA: ViroPharma Biologics, Inc.; viropharma.com/physicians/cinryze%20overview/cinryze%20package%20insert.aspx; 2010.
 17. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 363:513–522, 2010.
 18. Zuraw B, Baker J, Hurewitz D, et al. Open-label use of nanofiltered C1 esterase inhibitor (human) (Cinryze™) for the prophylaxis of hereditary angioedema (HAE) attacks. Abstract Book of the 2010 Annual Meeting of the American College of Allergy, Asthma and Immunology, Phoenix, AZ, November 11–16, 2010, A100 (Abs 262).
 19. Berinert [package insert]. Marburg, Germany: CSL Behring GmbH; www berinert.com/professional/prescribinginformation.aspx; 2009.
 20. Ceter [package insert]. Amsterdam, The Netherlands: Sanquin; www.sanquin.nl/repository/documenten/en/prod-en-dienst/plasmaproducten/139660/Package_Leaflet.pdf; 2010.
 21. Morgan BP. Hereditary angioedema: therapies old and new [published correction appears in *N Engl J Med* 363:2673, 2010]. *N Engl J Med* 363:581–583, 2010.
 22. Aygören-Pürsün E, Martinez-Saguer I, Rusicke E, et al. On demand treatment and home therapy of hereditary angioedema in Germany: the Frankfurt experience. *Allergy Asthma Clin Immunol* 6:21, 2010.
 23. Bygum A, Andersen KE, and Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol* 19:147–151, 2009.
 24. Craig T, Riedl M, Dykewicz MS, et al. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol* 102:366–372, 2009. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.