



Perspective

Management of hereditary angioedema in 2012: scientific and pharmacoeconomic perspectives

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent episodes of edema involving the skin, gastrointestinal tract, and/or airway. With a prevalence of approximately 1 in 50,000, HAE is rare, affecting fewer than 10,000 people in the United States.¹ There is a range of severity and frequency of symptoms in patients with HAE. Some patients experience relatively mild symptoms on rare occasions, others have symptoms 1 or more times each month, and still others have recurrent debilitating attacks that may lead to tragic outcomes, including narcotic addiction and/or inappropriate surgery due to recurrent acute abdominal pain from intestinal edema. Laryngeal edema leading to death or near-death from asphyxiation may also occur, sometimes in patients who had not previously had severe symptoms.² As a group, HAE patients are more likely to require frequent emergency department visits and hospitalizations, consistently miss work or school, and endure the negative psychosocial effect of HAE as a chronic disease.³ The morbidity and potential mortality of HAE, if untreated, are therefore profound, especially for those with moderate or severe symptoms.

Pathophysiology

In 1963 Donaldson and Evans⁴ demonstrated that the pathophysiology of HAE involves a deficiency of a protein called C1 esterase inhibitor (C1INH). Over the years, additional forms of HAE have been described, including a poorly functional C1INH produced in normal quantities (type 2 HAE)⁵ and a rare and still poorly understood form involving a normal C1INH level and a presentation that primarily affects females (type 3 HAE).⁶ As a serine protease inhibitor, the C1INH protein is an important regulator of complement, thrombin, and kallikrein. It is via disruption of its role as a kallikrein inhibitor that C1INH deficiency leads to excessive bradykinin formation, increased endothelial cell permeability, and

the resultant attacks of angioedema. Multiple mutations in the *C1INH* gene have been described, and HAE patients are heterozygotes; that is, they have one copy of the normal *C1INH* gene and another mutated copy⁷ that is either not translated (type 1 HAE) or results in a dysfunctional protein (type 2 HAE). HAE patients therefore produce at least some of their own normal C1INH. Serine protease inactivation by C1INH involves “suicide” inactivation (ie, the C1INH protein is destroyed in the process). HAE has an autosomal dominant inheritance pattern despite the presence of some normal C1INH protein because at times of increased demand (such as dental work or surgery) the smaller quantity of normal C1INH protein is overwhelmed, and this “suicide” inactivation leads to its disappearance. Because only a few patients report a family history of angioedema, spontaneous mutations likely account for many cases of HAE.

Treatment Before 2008

Supportive care (eg, intravenous fluids, pain control, and airway management) has been the mainstay of the management of acute symptoms because HAE attacks resolve within several days and no intervention was ever been found to alter that natural history. Fresh frozen plasma was also commonly used because it contains normal C1INH protein, although this was often not a reliable treatment because in rare cases it results in worsening of angioedema. This finding was thought to be due to concomitant administration of additional kiningen substrate. Although effective as a preventive treatment, anabolic steroids even at much higher than normal doses were not found to attenuate acute attacks of HAE.

Before 2008 the main options for prophylactic treatment of HAE were antifibrinolytics, such as ϵ -aminocaproic acid,^{7–12} and attenuated androgens, such as danazol.^{13–16} Of these, the attenuated androgens have a clearer scientific rationale and have proven to be more practical. In 1976, after observing that HAE symptoms often worsen in female patients during their menstrual periods and when taking oral contraceptives and reasoning that attenuated androgens, by opposing estrogen effects, may be beneficial for HAE

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patients, Frank and colleagues^{17,18} published a placebo-controlled trial evaluating the effects of the attenuated androgen danazol. During 46 courses of danazol only 1 angioedema attack occurred compared with 44 attacks during 47 placebo treatment courses. The authors also observed an increase in both C4 and C1INH levels during treatment. The presumed mechanism of attenuated androgens in HAE is the upregulation of hepatic synthesis from the normal C1INH gene, although this has not been proven, and the clinical course of patients does not correlate well with C1INH levels.

In 1980 these authors reported a longer-term experience with a series of 69 HAE patients with relatively severe disease who were treated with danazol for up to 6 years.¹⁹ The starting dose was 600 mg/d, and this was decreased every 6 to 12 weeks until the lowest effective dose was found. Control of attacks was achieved in all patients. However, only roughly 30% were controlled with a daily dose of 200 mg or less, and unfortunately many of the patients experienced dose-dependent adverse effects, the most common of which were weight gain, menometrorrhagia, myalgias, headaches, anxiety, and liver function test result abnormalities. Most adverse effects occurred in patients maintained with a daily dose greater than 400 mg, and only 2.5% of the reported adverse effects occurred in patients taking 200 mg or less. On rare occasions, hematuria, cholestasis, hemorrhagic cystitis, or hepatocellular adenomas have occurred, and for this reason when attenuated androgens are used, consensus guidelines recommend regular monitoring of laboratory values and performing annual liver and spleen ultrasonography.²⁰

As a classic single-gene mendelian disease whose missing protein is readily available from donated plasma, HAE would appear to be curable or at least lend itself to normalization of life quality in all patients via prophylactic replacement of the deficient C1INH protein. In fact, a notable clinical response to C1INH replacement therapy was demonstrated as early as 1980,²¹ and within several years of that report C1INH replacement therapy became available in Europe. However, in the United States this treatment was not available until 2008, and at about the same time several other exciting new therapies simultaneously emerged for the short-term treatment of HAE symptoms. Priced in excess of \$5,000 per dose,²² these new medications are expensive relative to previous HAE treatments, which raises several questions. Have these new treatments, in fact, essentially cured HAE? Why did the availability of C1INH replacement therapy in the United States take so long? Why are these drugs so expensive? Is there still a place for attenuated androgens? The remainder of this Perspectives article will attempt to answer these questions by examining the scientific and pharmacoeconomic issues relevant to the management of HAE in 2012.

Prophylactic Treatment

Pasteurized, nanofiltered C1INH replacement therapy (Cinryze; Viropharma, Downingtown, Pennsylvania) was approved for intravenous administration for HAE prophylaxis in the United States in 2008. Currently, a volume-reduced subcutaneous formulation of C1INH is also under development.²³ The qualifying trial involved 22 patients with moderate to severe HAE defined as an attack frequency of at least twice each month.²⁴ In two 12-week treatment periods, each patient received twice-weekly intravenous infusions of either C1INH (1,000 units) or placebo before crossing over to the other agent. Zuraw and Kalfus²⁵ recently reported an open-label extension study involving 146 patients (16 from the initial trial) treated for a mean of 340 days. This study enrolled patients reporting either an attack frequency of more than once per month or a history of laryngeal angioedema. Nearly 90% of patients reported a decrease in attack frequency to less than once

a month; however, only roughly one-third reported having no HAE attacks while being treated. Furthermore, no decrease in attack frequency was found in 7.5%. Remarkably, during the crossover study 1 patient reported markedly worse control with C1INH than with placebo.²⁴

The results of these studies suggest that C1INH replacement therapy reduces but does not eliminate HAE attack frequency and severity in most patients, effectively ends attacks in some, but surprisingly has no apparent effect in others. Neither clinical characteristics nor baseline C1INH level predict a response to this treatment, although those with normal functional activity of baseline C1INH were more likely to respond well during the open-label study. Given what is known about the pathogenic mechanism of HAE, the basis for failure to achieve comprehensive prophylaxis with replacement C1INH remains enigmatic. An important finding in these studies was that C1INH replacement therapy appears to be safe because no significant drug-related adverse effects were reported. Two fatalities occurred, neither of which was due to HAE symptoms or study drug administration,²⁵ although the inherent risk of long-term intravenous access is illustrated by the fact that one of these fatalities resulted from pulmonary arterial embolization due to inappropriate infusion of an oral medication.

A comparison between prophylactic C1INH therapy and attenuated androgens is problematic because there are no published studies comparing them and the published data were accumulated using vastly different study designs separated by decades. It is reasonable to conclude that C1INH replacement therapy is much safer than attenuated androgens at doses required to control symptoms in most HAE patients. However, in some patients attenuated androgens may be more efficacious than C1INH, and this observation deserves further study.

Treatment of Acute HAE

Three medications have been recently approved for treatment of acute attacks, each targeting a different component of the dysfunctional kallikrein regulatory pathway in HAE patients. Human pasteurized, nanofiltered C1INH (licensed as Berinert; CSL Behring, King of Prussia, Pennsylvania) is administered as an intravenous dose of 20 U/kg. The other 2 available agents are administered subcutaneously, including a recombinant protein competitive inhibitor of kallikrein called ecallantide (Kalbitor; Dyax, Burlington, Massachusetts) and a synthetic decapeptide bradykinin receptor antagonist called icatibant (Firazyr; Shire, Dublin, Ireland). In controlled clinical trials, a variety of patient-reported clinical assessment tools were used to establish the efficacy of these agents^{26–32}; therefore, comparing individual agents is difficult. Each of these agents has been reported to result in a clinical response within 4 hours in approximately 60% to 85% of patients, and many patients report improvement in 30 minutes or less. Complete resolution of symptoms is often achieved in 8 to 12 hours. Although there is a 3% risk of anaphylaxis when administering ecallantide (and therefore it must be administered under medical supervision), the adverse events reported with these agents were otherwise minor and similar to adverse events with placebo injections.

Although these agents are effective, as with prophylactic administration of C1INH, none of them completely controlled symptoms of HAE. Failure to achieve comprehensive control with agents given as short-term treatment may reflect, in part, their inability to ameliorate an established reaction. That is, in some patients inhibition of kinin-related pathways may no longer provide efficacy once angioedema has developed. As with preventive treatment with C1INH, this may also reflect our current incomplete appreciation of the pathogenic pathways driving this disease.

HAE as an Orphan Disease

Historically, regulatory burdens and high costs associated with bringing a drug to market discouraged sponsors from developing products for diseases affecting small numbers of patients. Rare disease populations were therefore “orphaned” by pharmaceutical companies and given few approved treatment options. To address this public health need, in 1983 the US federal government passed the Orphan Drug Act (ODA) with the intent of stimulating the development of orphan drug products.³³ With its promise of 7-year market exclusivity, development tax credits, and a shorter and less rigorous Food and Drug Administration (FDA) approval process, the ODA lowers barriers to innovation and fosters development of treatments for diseases that affect fewer than 200,000 individuals. As such, the law has been an unequivocal success. For example, in the decade before 1983 only 34 orphan products went on the market, whereas between 1983 and 2009 there were FDA approvals of an astounding 275 orphan drugs for 337 orphan indications.³⁴ In fact, during the 2000s, orphan products comprised 22% of all new molecular entities and 26% of all biologics receiving FDA approval.^{35,36} Because HAE affects only approximately 6,000 individuals in the United States, all of the recently approved HAE treatments were developed under the auspices of the ODA program.

Extended market exclusivity for orphan products is a particularly powerful feature of the ODA because it creates an effective monopoly during a 7-year period. This exclusivity enables companies to establish and maintain relatively high prices, subject to little if any market competition from competitor products, which facilitates generation of sufficient revenue in a small market to recoup the costs of research and development while also earning a profit. In practice, even after expiration of their market exclusivity, orphan drugs face less generic competition than nonorphan drugs.³⁷ This enhanced revenue potential likely explains why so many new molecular entities have been designated as orphan drugs.

Significant costs have been associated with HAE drug development and/or production. For example, with respect to the development of pasteurized, nanofiltered C1INH (Cinryze and Berinert), which did not require an investment in discovery, the pasteurizing and nanofiltering of human plasma into C1INH for treatment of HAE patients in the United States are labor-intensive and complex because the only available facilities for purifying C1INH from plasma are located in the Netherlands and Germany.³⁸ In addition, there is an FDA requirement that the donated plasma originate in the United States. This requirement means that plasma is collected in the United States, shipped overseas for processing, and then shipped back to the United States before it is available to HAE patients in the United States.

Market availability does not, in and of itself, guarantee that patients will have access to a particular drug. The drugs have to be prescribed and paid for. Therefore, access to orphan drugs depends on physician prescribing patterns and payer reimbursement policies. With few if any alternative therapies available, payers have limited negotiating power in terms of price and formulary placement. This limited negotiating power combined with the relatively limited cost exposure in orphan disease markets (reflecting the small number of patients covered by any given payer) means that patient access is rarely denied.^{39,40} However, orphan drugs are not immune to payer formulary management and benefit design. Increased numbers of orphan drugs at high prices have caused payers to rethink their drug management strategies. For example, recent years have seen a marked shift from copayments to coinsurance, whereby the patient's obligation is determined as a percentage of the drug's cost. This shift was designed to control prescription use and spending for certain medication classes.⁴¹ In fact, coinsurance is virtually the exclusive cost-sharing mechanism

Table 1

Cost of drugs for treating acute hereditary angioedema attacks

Drug (trade name)	Cost per dose, \$ ²²
Pasteurized, nanofiltered C1 esterase inhibitor (Berinert)	5,796 (for 70-kg patient)
Ecaltantide (Kalbitor)	9,540
Icatibant (Firazyr)	6,800

for high-priced biologics, including orphans, and the coinsurance percentages have risen, on average, from approximately 15% to 28% in the past 10 years. Given the increases in already expensive drugs, this represents a significant shift of the cost burden onto the consumer.⁴²

As a way to keep the new HAE drugs affordable to patients, the manufacturers of these drugs have established programs to help patients with out-of-pockets costs from copayments, coinsurance, deductibles, and even transportation costs to have their treatment safely administered. These programs have enabled HAE patients to reduce their cost sharing. Because there are currently 3 approved therapeutic choices (human pasteurized, nonfiltered C1INH [Berinert], ecaltantide [Kalbitor], and icatibant [Firazyr]) for treatment of acute HAE, this market is not a monopoly. Manufacturers have incentives to consider their competitors when pricing their drugs. Because all of the options are orphan drugs, they will all be relatively expensive but perhaps less so than in a market without competitors. Table 1 lists the approximate costs of the drugs approved for treatment of acute HAE attacks. However, it is difficult to estimate the actual annual cost of drugs for acute attacks because attack frequency is variable.

The market for prophylactic treatment of HAE is different. Pasteurized, nanofiltered C1INH (Cinryze) is the only new drug approved for long-term continuous use to prevent HAE attacks and therefore would appear to enjoy a monopoly. However, within the HAE prophylaxis market, attenuated androgens are competitors with pasteurized, nanofiltered C1INH (Cinryze) and have an enormous price advantage, although these drugs are not safe in children, during pregnancy, or at the higher doses required to control moderate to severe HAE (especially in women). In addition, many patients are opposed to using attenuated androgens at any dose. The approximate cost of pasteurized, nanofiltered C1INH (Cinryze) relative to the other 5 highest priced orphan drugs is summarized in Table 2. To our knowledge, pasteurized, nanofiltered C1INH (Cinryze) has the highest annual cost of any drug on the market in the United States.

The pharmacoeconomics of HAE treatment presents a paradox. On the one hand, without the ODA and the ability to sell a drug at

Table 2

Six orphan drugs with annual costs of more than \$200,000 per patient^a

Orphan drug (trade name)	Indication	Annual cost per patient, \$
Agalsidase beta (Fabrazyme)	Fabry disease	239,000
Idursulfase (Elaprase)	Mucopolysaccharidosis I and II	300,000
Galsulfase (Naglazyme)	Mucopolysaccharidosis VI	441,000
Imiglucerase (Cerezyme)	Type 1 Gaucher disease	442,000
Ecilizumab (Soliris)	Paroxysmal nocturnal hemoglobinuria Atypical hemolytic uremic syndrome	486,000
C1 esterase inhibitor (Cinryze)	Hereditary angioedema prophylaxis	487,000

^aData are from Hyde and Dobrovolsky.⁴³ If all of the approximately 6,000 HAE patients were to take the drug, the annual budget effect to all payers would be $6,000 \times \$487,000 = \$2.9$ billion. Of course, this is an unrealistic ceiling estimate of the budgetary effect of C1 esterase inhibitor because only a small portion of HAE patients would be taking C1 esterase inhibitor at any given point.

Table 3
Long-term prophylactic treatment for hereditary angioedema

C1INH replacement	Attenuated androgens
Advantages	
Replaces defective gene product	Oral once daily administration
Symptom control achievable in many patients	Symptom control achievable in nearly all patients ^a
Minimal adverse effects	Inexpensive
	Well tolerated by most patients at doses <200 mg/d
Disadvantages	
Ineffective in some patients	Multiple dose-dependent, potentially serious adverse effects: • Requires LFT, CBC, UA monitoring every 6 months • Requires liver and spleen ultrasonography every 12 months
	Less severe adverse effects may impair quality of life: • Myalgias (28%), hirsutism (8%), voice deepening (10%), altered libido (14%), anxiety (16%)
Requires twice weekly intravenous infusions	Contraindicated in pregnancy
Unprecedented high cost	Contraindicated in children

Abbreviations: C1INH, C1 esterase inhibitor; CBC, complete blood cell count; LFT, liver function test; UA, urinalysis.

^aAdverse effects limit long-term utility in patients whose symptoms require high-dose therapy to control symptoms.

a price reflective of what the market will bear, little incentive will exist to develop new HAE drugs. On the other hand, in the absence of a competitive market there is effectively no price ceiling. Third-party payers counter with shifts to coinsurance models. In the case of pasteurized, nanofiltered C1INH (Cinryze), even a 10% coinsurance obligation would reach a \$50,000 annual out-of-pocket expense for HAE patients, a scenario that has so far been largely avoided by aggressive assistance programs funded by the HAE drug manufacturers. It is unclear whether this cost protection for HAE patients will be viable in years to come.

Clinical Management of HAE in 2012

This is an exciting time for HAE patients and the physicians who care for them. Thanks to the unwavering dedication of basic and clinical scientists throughout several decades, our understanding of the pathophysiology of HAE has improved remarkably. In addition, because of the ODA and the willingness of several pharmaceutical companies to develop new products, there are now treatment options that have resulted in profound improvements in the lives of many HAE patients. However, despite these landmark accomplishments, there are several sobering truths that promise to perpetuate the scientific and pharmacoeconomic dialogue surrounding this orphan disease. The fact that C1INH replacement does not cure HAE is a stunning observation that suggests we still do not understand important elements of HAE pathophysiology. With regard to treatment algorithms, rather than encouraging more widespread prescriptions for prophylactic treatments, there has been a new focus on “on-demand” symptomatic treatment during HAE attacks.²⁰ The availability of safe and effective treatments for acute HAE attacks is no doubt an important reason for this paradigm shift. However, because replacement of the deficient gene product is now available and low-dose attenuated androgens remain a safe, convenient, and effective option for a significant minority of HAE patients, it is curious that these prophylactic options have been deemphasized

to some degree. To what extent factors such as efficacy, cost, convenience, safety, and perhaps marketing have influenced this shift remains to be explored.

Given the morbidity and mortality associated with HAE attacks and the availability of safe and effective treatment options, we believe that all HAE patients should have access to abortive therapy. With respect to prophylactic treatment, given the advantages and disadvantages inherent with both attenuated androgens and C1INH replacement therapy (Table 3), until comparative data are available we believe that both of these options should be discussed thoroughly with each HAE patient. Although the high cost of HAE drugs has resulted in both complex reimbursement logistics for patients and aggressive marketing by drug manufacturers, individual treatment decisions should result solely from a balanced discussion between HAE patients their physicians.

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