Meeting the Challenges and Burdens Associated With Hereditary Angioedema

With the advent of new disease-specific agents, some patients with HAE may find relief from its enormous physical and psychological toll

Michael Toscani, PharmD, senior fellow, Jefferson School of Population Health, Philadelphia, and Marc Riedl, MD, MS, assistant professor of medicine and section head of clinical immunology and allergy, David Geffen School of Medicine, University of California–Los Angeles

ABSTRACT

Purpose: Because little is known about the burden of illness associated with hereditary angioedema (HAE), this article reviews the challenges in identifying and managing this rare disease and its humanistic and economic burdens.

Design: We identified studies examining the burdens associated with HAE. Conducting larger studies using claims analyses for HAE is particularly challenging, owing to the rarity of the disease in health plans and to diagnostic/coding challenges. Because the data have been limited, larger surveys of patients have been conducted. They are explored here.

Methodology: We searched for studies addressing attack characterization, acute treatment, chronic disease management, adverse events, psychosocial burden, effect on work, and patient costs.

Principal findings: HAE may result in physical and/or psychological disability because of the lack of effective treatments and the unpredictability of symptom severity. The reported average annual total costs per patient are approximately $42,000, ranging from approximately $14,000 for mild cases to approximately $96,000 for severe disease. It is not known how much of this is paid by the patients, although it can be assumed that it is substantial for some.

Conclusion: The appropriate use of disease-specific treatments for HAE may improve patients' quality of life and reduce HAE-associated morbidity and mortality while also reducing costs associated with hospitalizations and other interventions. Future cost-effectiveness studies are needed to examine these issues. Disease-specific agents are expected to significantly change the HAE treatment paradigm in the United States and dramatically improve the efficacy of medical care for these patients.

Key words: hereditary angioedema, humanistic burden, economic burden

INTRODUCTION

Hereditary angioedema (HAE) is a rare, debilitating, life-altering, and potentially life-threatening autosomal dominant disease caused by a deficiency in functional C1 esterase inhibitor (C1-INH) (Donaldson, 1963; Zuraw, 2008; Davis, 1988). HAE causes variable and unpredictable recurring episodes of nonpruritic, non-pitting, subcutaneous, or submucosal edema affecting the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, or larynx (Zuraw, 2008). Depending on the site of the edema, the effect of these attacks can range from moderate interference with daily activities to profound, acute disability to life-threatening events. The incidence and prevalence of the disease are unknown, but it is estimated that the disease occurs in as few as 1 in 150,000 people to as many as 1 in 10,000. Ethnicity is not a determinant (Nzeako, 2001).

Little is known about the burden of illness, but it is clear that many patients suffer from the physical, psychological (social, emotional, mental health), and, at times, the financial costs associated with the disease. Because there is a paucity of information, we wrote this paper to review the clinical challenges in identifying and managing this rare disease and the various burdens that HAE places on patients, caregivers, providers, and payers.

GENETICS AND PATHOGENESIS

HAE is an autosomal dominant genetic disorder caused by a mutation in the C1-INH gene (Donaldson, 1963; Zuraw, 2008; Davis, 1988). HAE can be divided into two clinically indistinguishable types, depending on the nature of the mutation. Type I HAE is the consequence of a quantitative deficiency in C1-INH production; type II HAE results from the production of abnormal, nonfunctional C1-INH protein. A third type, not associated with C1-INH deficiency, has been identified in a small subset of patients, with mutations in factor XII the likely underlying cause in some people (Bork, 2000; Bork, 2006; Duan, 2009).
C1-INH, a serine protease, provides regulatory effects for the complement, contact, and fibrinolytic systems (Levy, 2006; Davis, 2005). Thus, C1-INH deficiency results in abnormal activation of these systems, with the contact or kallikrein-kinin system recognized as critical in the pathophysiology of HAE symptoms (Davis, 2005). The kallikrein-kinin system produces mediators such as bradykinin, which enhances vascular permeability (Levy, 2006; Shoemaker, 1994). C1-INH normally inhibits both factor XIIa and kallikrein activity within this system, thereby regulating the production of the vasoactive mediators (Levy, 2006; Davis, 2005). In the absence of normal C1-INH function, unimpeded activation of factor XIIa results in an increasing positive feedback loop wherein factor XIIa cleaves prekallikrein to the active enzyme kallikrein (Levy, 2006). Uninhibited kallikrein activity further converts high-molecular-weight kinogen to bradykinin, resulting in increased local tissue bradykinin levels (Levy, 2006; Nussberger, 1999). The effects of bradykinin on endothelial cells are mediated through the bradykinin-2 receptor, resulting in fluid extravasation and tissue edema (Levy, 2006; Kaplan, 2002; Schmaier, 2008).

**CLINICAL PRESENTATION AND DIAGNOSIS**

HAE symptoms typically begin in childhood and persist throughout life with unpredictable severity. Although some triggers, such as stress and minor trauma, have been identified, the factors initiating many acute attacks are unknown. On average, untreated patients have attacks every 1 to 2 weeks, but the frequency of angioedema is highly variable, ranging from almost no episodes to the occurrence of symptoms approximately every 3 days (Zuraw, 2008; Bork, 2006).

HAE attacks usually follow a progressive course and may be preceded by a prodromal phase of localized sensory disturbance (such as a tingling sensation), with approximately one third of the attacks accompanied by erythema marginatum. Cutaneous and/or mucosal swelling follows, with increasing symptoms during the first 24 hours and then gradual resolution over the next 2 to 3 days (Zuraw, 2008). Attacks may start in any area of the body and spread to other regions before resolution. Most commonly, the hands, arms, legs, feet, face, and gastrointestinal (GI) tract are affected (Bork, 2006).

GI edema causes abdominal manifestations, including severe nausea, vomiting, and intense pain. Bowel sounds may be diminished or absent, and guarding and tenderness may be present on physical examination, which may lead to unneeded surgical procedures. Clinically significant hypotension may also occur because of fluid shifting into the peritoneal cavity (Zuraw, 2008). Laryngeal attacks of angioedema are less common, but more than 50% of all patients have at least one episode of laryngeal angioedema in their lifetime, which can lead to asphyxiation and death (Zuraw, 2008; Bork, 2006).

Diagnostic delays are frequent and can be significant in patients with HAE. One study showed that the average time between symptom onset and diagnosis was more than 10 years in a registry cohort of patients from Spain (Roche, 2005).

Causes of angioedema in the general population may include medications, such as angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs). Given the variety of etiologic factors associated with angioedema, differentiating HAE from other causes and confirming the diagnosis requires laboratory testing for levels of complement components (Zuraw, 2008). All patients with HAE have low functional C1-INH levels, and nearly all have a low antigenic complement component 4 level with normal antigenic C1 and complement component 3 levels. This results in overactivation of the kallikrein-kinin cascade and elevates levels of tissue bradykinin, a potent activator of vascular permeability and the primary mediator of the clinical manifestations of HAE (Davis, 2006).

Management of HAE includes genetic counseling, treatment of acute episodes, short-term prophylaxis to prevent attacks, and long-term prophylaxis to reduce the frequency and severity of recurrent attacks (Zuraw, 2008; Nzeako, 2001; Prematta, 2008). Prevention of HAE attacks may include avoidance of trauma and other triggers known to provoke episodes. Patients should avoid the use of ACE inhibitors and estrogens, since these are known to trigger acute attacks in some patients. Treatment of comorbidities such as Helicobacter pylori infection may also be important in reducing or preventing attacks (Prematta, 2008). However, many HAE attacks occur spontaneously without an identifiable trigger, thus limiting the effectiveness of avoidance measures (Zuraw, 2008).

Purified plasma-derived C1-INH therapy has been the primary therapy for HAE in many countries outside the United States and has been shown to be safe and efficacious for acute and prophylactic treatment (Zuraw, 2008; Farkas, 2007). In 2008, the U.S. Food and Drug Administration (FDA) approved Cinryze (C1 esterase inhibitor [human], ViroPharma Inc.) for routine prophylaxis against angioedema attacks in adolescents and adults with HAE (Cinryze PI, 2008). Cinryze is supplied as a freeze-dried powder that is reconstituted with diluent for intravenous (IV) administration (Cinryze PI, 2008) In the United States and other countries, additional agents useful for short-term or long-term prophylaxis include attenuated androgens, 17-alpha alkylated agents such as danazol, and less commonly used antifibrinolytics such as epsilon-aminocaproic acid.
All agents used for the prophylactic treatment of HAE must be carefully monitored for adverse effects because serious adverse events have been reported (Gompels, 2005). Because of the historical absence of FDA-approved products for the treatment of acute HAE attacks, acute therapy in the United States has consisted of supportive care with analgesics, antiemetics, IV fluids, and airway management as necessary (Zuraw, 2008). Although fresh-frozen plasma contains C1-INH and has some reported success in terminating attacks, its use in treating acute episodes of HAE is controversial because it contains contact system proteins that may stimulate bradykinin production and worsen the condition (Rosen, 1969). Antihistamines and corticosteroids are not effective for the treatment of HAE. Epinephrine is frequently administered as a temporary measure for laryngeal edema but does not effectively alter the natural course of HAE episodes (Zuraw, 2008).

In October 2009, the FDA approved Berinert (CSL Behring) (C1 esterase inhibitor [human]) for the treatment of acute abdominal or facial attacks of HAE in adults and adolescents. Berinert is supplied as a freeze-dried powder that is reconstituted with diluent for IV administration (Berinert PI, 2009). In December 2009, a plasma kallikrein inhibitor, Kalbitor (ecallantide, Dyax Corp.), received approval from the FDA for the treatment of acute attacks of HAE in patients 16 years of age and older. Kalbitor is formulated as a solution and is administered subcutaneously in three 10-mg (1-mL) injections (Kalbitor PI, 2009). In August 2011, Firazyr (icatibant), a subcutaneous bradykinin B2 receptor antagonist was approved by the FDA for the treatment of acute HAE attacks in adults 18 years and older and Rhucin (recombinant human C1-INH) is in the late stages of clinical development. Current and emerging therapies for acute HAE attacks differ in production methods, mechanism of action, pharmacokinetics, and method of administration (Table 1) (Cinryze PI, 2008; Berinert PI, 2009; Kalbitor PI, 2009; European Medicines Agency, 2008; Firazyr, 2008). Consensus guidelines have been prepared for the diagnosis and management of HAE; however, newer therapies have only recently been incorporated into guidelines and recommendations. (Gompels, 2005; Bowen, 2010).

**BURDEN OF ILLNESS**

HAE is a debilitating, life-altering, and potentially life-threatening disease that can be highly variable and unpredictable for patients and caregivers. The unpredictability and frequency of attacks in some patients may have both an immediate and long-term effect on health-related quality of life (QoL).

Because of the low incidence of the disease, little is known about the humanistic and economic burden of HAE on patients, caregivers, and the health care system. Studies involving small numbers of patients with HAE have reported QoL results associated with the disease and its treatments.

One study evaluated the effect of self-administration of IV C1-INH replacement therapy in seven patients whose severe, debilitating HAE affected their physical, psychological, and social functioning. The two instruments used were the 36-Item Short Form Survey and the Dermatology Life Quality Index. Both scales showed significant treatment-associated improvements in QoL scores with changes in both physical and

### TABLE 1

A comparison of FDA-approved and emerging treatments for HAE

<table>
<thead>
<tr>
<th>Method of production</th>
<th>Mechanism of action</th>
<th>Method of administration</th>
<th>Half-life</th>
<th>FDA-approved indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinryze</td>
<td>Human plasma-derived concentrate</td>
<td>C1-INH replacement</td>
<td>IV infusion</td>
<td>56 ± 36 h</td>
</tr>
<tr>
<td>Berinert</td>
<td>Human plasma-derived concentrate</td>
<td>C1-INH replacement</td>
<td>IV infusion</td>
<td>18.4 ± 3.5 h</td>
</tr>
<tr>
<td>Kalbitor</td>
<td>Recombinant protein</td>
<td>Plasma kallikrein inhibitor</td>
<td>SC injection</td>
<td>2.0 ± 0.5 h</td>
</tr>
<tr>
<td>Rhucin</td>
<td>Recombinant protein</td>
<td>C1-INH replacement</td>
<td>IV infusion</td>
<td>Approximately 2 h</td>
</tr>
<tr>
<td>Firazyr</td>
<td>Synthetic peptide</td>
<td>Bradykinin type 2 receptor antagonist</td>
<td>SC injection</td>
<td>1–2 h</td>
</tr>
</tbody>
</table>

C1-INH indicates C1 esterase inhibitor; FDA, US Food and Drug Administration; HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous.
Another study involved 22 patients with severe HAE who were intolerant or nonresponsive to danazol and who received pasteurized, human plasma-derived C1-INH concentrate as replacement therapy. This study used an adapted version of the Pain Disability Index and focused on domains of life-activity items such as family/home responsibility, social activities, occupation, general condition, and others. All QoL areas improved significantly, compared with danazol prophylaxis, and were confirmed by objective measures such as work or school absence and days of hospitalization (Kreuz, 2009).

Conducting larger studies using claims analyses for HAE is particularly challenging because of the rarity of the disease in health plans, diagnostic challenges, and coding of clinical episodes. Because of delays in proper diagnosis of HAE and lack of recognition by health care providers, episodes may be miscoded as other diseases (idiopathic or allergic urticaria/angioedema, laryngeal edema, abdominal pain, food allergy, drug allergy, or anaphylaxis) based on signs and symptoms (Zilberberg, 2010). Because of the limited data associated with the understanding about the burden of illness of HAE, larger surveys of patients have been con-

FIGURE 1
Scores for the physical and mental components of 12-item Short-Form Health Survey (SF-12): HAE population compared with normative population
Standardized (z-score transformed) SF-12 values are shown. Normative population values based on Ware et al. (Ware 2002) Patients with HAE reported decreased physical and mental health vs. the normative population (P < 0.001) for all subscales and overall summary components, based on t-tests. Adapted with permission from Lumry et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc.* 2010;31(5):407–414.
HAE indicates hereditary angioedema.
ducted.

Recently, a Web-based survey was undertaken by investigators who collaborated with the U.S. Hereditary Angioedema Association (HAEA) to evaluate the humanistic (Lumry, 2010) as well as the economic (Wilson, 2010) burden of the disease. The results of this study have several limitations, such as selection bias, and must be interpreted carefully regarding generalizability to all patients with HAE. Nevertheless, in lieu of other methods and data sources, the results can be representative of a large subset of patients with the disease.

The study evaluated 457 adult patients with HAE (overall mean age, 41 years); the average age at diagnosis was 22 years (range 1–72 years). Most respondents (92.1%) were Caucasian, and 75.5% of respondents were female. Although the number of attacks per year was highly variable, the average number was 26.9 (median 12), with an average duration of symptoms resulting from attacks lasting approximately 2.5 days. Most respondents (56%) rated the average severity of attacks over the previous year as moderate, 28.4% rated it as severe, and 15.5% rated it as mild. Approximately 16% of respondents indicated they were employed less than full time because of the complications of HAE. Fifty-eight percent of respondents reported that HAE had adversely affected their career advancement, and 48% reported a hindrance to educational attainment (Lumry, 2010).

The study included three standardized instruments to compare HAE patient data with normative (healthy) and chronic disease populations: the 12-Item Short-Form Health Survey (SF-12), the Hamilton Depression Inventory-Short Form (HDI-SF), and the Work Productivity and Activity Impairment–General Health (WPAI-GH) Questionnaire. (Lumry 2010)

**RESULTS**

Results from the SF-12 Health Survey indicated that patients with HAE reported significantly decreased physical (functioning, role physical, bodily pain, general health, vitality) and mental (social functioning, role emotional, mental health) scores compared with the normative population for all subscales and summary components (Figure 1) (Lumry, 2010; Ware, 2002). The mean scores on the SF-12 physical component summary were 43.7 for the HAE population and 49.6 for the normative population ($P<0.001$). The mean scores on the mental component summary were 42.6 for the HAE population compared with 49.4 for the normative population ($P<0.001$). Scores from the HDI-SF showed that HAE patients had higher mean HDI-SF scores than the normative population (8.1 vs. 3.1, $P<0.001$) and 42.5% of patients had scores greater than 8.5, indicative of at least mild depressive symptomatology.

The percentage of HAE patients receiving psychotropic medications was almost double that of the normative population (Lumry, 2010). Patients who reported receiving chronic androgen therapy for HAE also reported more adverse effects of the medications, higher scores associated with depression, and larger decrements in work productivity than those not receiving androgen therapy. This finding could also indi-

<table>
<thead>
<tr>
<th>TABLE 2 Annual direct medical costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical resource</td>
</tr>
<tr>
<td>Total direct medical costs</td>
</tr>
<tr>
<td>Direct medical costs of acute attacks (N=419)§</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Emergency room visit</td>
</tr>
<tr>
<td>Clinic/doctor’s office treatment</td>
</tr>
<tr>
<td>Hospital stay</td>
</tr>
<tr>
<td>Treatment costs</td>
</tr>
<tr>
<td>Medication costs</td>
</tr>
<tr>
<td>Direct medical costs for chronic disease management (treatment outside of acute attacks) (N=457)¶</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Routine visit costs</td>
</tr>
<tr>
<td>Medication costs</td>
</tr>
</tbody>
</table>

*Number of patients reporting utilization of the listed resource.
†Total annual cost of the resource listed in U.S. dollars.
‡Percentage of the total direct medical costs (percentages do not add up to 100 because of rounding).
§Analysis excludes patients who received only experimental treatment during most recent attack. A total of 47 patients received experimental treatment, 9 of whom received additional treatment.
Treatment costs include costs for procedures or tests, including intubation, MRI, ultrasound, x-ray, endoscopy, blood work, and abdominal surgery.
¶Analysis based on the entire survey population, including those who received only experimental treatment during most recent attack.

48 MANAGED CARE / SEPTEMBER 2011
cate that patients treated with androgens had more serious disease, which contributed to depression and decreases in work productivity (Blaustein, 2008).

The effect of HAE on worker productivity is significant and comparable to patient impairments associated with chronic severe asthma or Crohn’s disease (Lumry, 2010; Chen, 2008; Reilly, 2008). Productivity was markedly impaired in all WPAI-GH Questionnaire categories, including 33.6% overall work impairment (a weighted combination of missed work and reduced productivity while working) and 45% nonwork activity impairment because of health. Greater than 50% of patients with HAE indicated that their last attack caused them to miss work. Patients reported missing a mean of 3.3 days of work as a result of their most recent HAE attack. These effects correlated with most recent attack severity; patients experiencing a mild attack missed 2.2 days of work, those experiencing moderate attacks missed 1.8 days, and those experiencing severe attacks missed 5.5 days (Lumry, 2010).

The economic burden of HAE was also assessed by the HAEA survey (Wilson, 2010). Again, the information obtained must be carefully evaluated because patients participating in the survey might not be fully representative of the overall HAE population with regard to disease demographics, severity, or treatment received. Also, their recollection of the economic burdens associated with therapy might not be accurately or completely described by the models used. It is important to note that this survey was conducted before the 2008 FDA approval of Cinryze as prophylactic therapy and the 2009 FDA approvals of Berinert and Kalbitor for the acute treatment of HAE attacks. Nevertheless, these estimates are a good starting point for understanding the economic burdens associated with HAE management.

The total annual costs associated with HAE are significant but vary with self-assessed disease severity. Costs include direct treatment costs of acute attacks and routine care as well as indirect costs, such as travel, child care, missed work, and reduced productivity incurred from both acute attacks and chronic effects associated with the disease. The reported average annual total costs (direct and indirect) per patient were estimated at $42,000 for the entire population, ranging from about $14,000 for mild cases to approximately $27,000 for moderate cases and about $96,000 for severe cases (Figure 3) (Wilson, 2010).

As expected, the largest component of all direct medical costs associated with acute attacks was hospitalizations (67%), followed by emergency department care (10.1%) and routine care visits (9.8%) (Table 2) (Wilson, 2010). It is not known how many of these costs are paid by patients or by third-party payers, but it can be assumed that for some, the costs are substantial.

In terms of indirect costs, respon-
HAE is a rare, genetic disorder resulting from a deficiency in functional C1-INH activity. It is characterized by periodic episodes of angioedema affecting different parts of the body throughout an individual’s lifetime. Symptom frequency and intensity are highly variable among and within patients, and symptom severity may change over time in individual patients, ranging from mild to life-threatening.

Limited data indicate that HAE poses a significant humanistic and economic burden for patients and caregivers. HAE may result in physical and psychological disability because of the historical lack of effective treatments and the unpredictability of symptom severity, factors that may lead to significant anxiety, depression, and a reduced QoL. These vitally important challenges experienced by HAE patients are difficult to measure, although recent progress has been made in the development of an international health-related QoL questionnaire specific for HAE adults using qualitative methodology and cross-cultural validation. The substantial economic effect of HAE is more quantifiable and also contributes to the difficulties faced by patients.

FDA-approved therapies are now available for prophylaxis against HAE attacks and for the treatment of acute attacks. In addition, emerging therapies are under investigation. Each of these medications possesses unique qualities, including mechanism of action, risk–benefit profile, route of administration, and convenience of use for patients. For the first time in the United States, disease-specific agents offer the possibility of effective acute therapy to reduce the morbidity, mortality, and disability associated with frequent episodes of angioedema. Prophylactic therapy provides hope for the most severely affected people to resume work, school, and return to “normalcy” in their daily lives. Additional benefits may be realized through the avoidance of adverse effects from chronic androgen therapy. Therapeutic options will ideally allow medical therapy to be tailored to a patient’s disease severity, access to medical care, and comorbidities.

Although yet to be quantified, the...
appropriate use of these treatments may improve patients’ QoL, reduce morbidity and mortality, and decrease costs associated with hospitalizations and other therapeutic interventions. Future cost-effectiveness studies are needed to examine these issues. However, these therapeutic agents are expected to significantly change the HAE treatment paradigm in the United States and dramatically improve the efficacy of medical care for people affected by HAE.

ACKNOWLEDGMENTS

The authors wish to acknowledge the medical affairs department of Dyax Corp, for its assistance in identifying the unmet educational need that this article addresses.

REFERENCES

Berinert [prescribing information]. Kankakee, IL: CSL Behring LLC; 2009.
Ware JE Jr, Kosinski M, Turner-Bowker D, Gandek B. How to score version 2 of the SF-12 Health Survey (with a supplement documenting version 1). Lincoln, RI: QualityMetric, Inc; 2002.