

Current Medical Management of Hereditary Angioedema: Follow-up Survey of US Physicians

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What is already known about this topic? A previous survey conducted in 2009 to 2010 revealed wide variability in hereditary angioedema (HAE) management practices in the United States. Since then, this field has undergone numerous advancements, including several new therapies and updates to clinical guidelines.

What does this article add to our knowledge? This updated survey found several important trends in HAE care over recent years, including significantly more patients with HAE being treated at home, fewer HAE-related hospitalizations, reduced androgen usage, and greater patient satisfaction with HAE treatment.

How does this study impact current management guidelines? This study demonstrated changes in HAE treatment paradigms over the past 5 years as reported by US physicians. Analysis of such findings indicates recent therapeutic advances, and published consensus recommendations are improving the clinical management of HAE.

BACKGROUND: A physician survey conducted in the United States between October 2009 and February 2010 revealed wide variability in hereditary angioedema (HAE) management.

OBJECTIVE: A follow-up survey was conducted to assess the impact of newly available treatment options and investigate changes in HAE care patterns.

METHODS: Between March and June 2013, 6570 physicians were contacted, of whom, 245 HAE-treating physicians responded.

Participants completed a 46-question online survey that was closely patterned after the initial survey. Although most data were analyzed descriptively, selected questions underwent statistical analysis to evaluate differences in treatment patterns between the 2 surveys.

RESULTS: Compared with the prior survey, this follow-up survey found that the proportion of physicians who reported danazol as

the preferred long-term prophylaxis agent declined from 56% to 23% ($P < .00005$); conversely, C1-esterase inhibitor increased in this category (20% to 57%; $P < .00005$). The percentage of attacks self-treated at home increased from 8% to 27% ($P < .00005$).

Decreases were observed in emergency department visits (61% to 54%; $P =$ not significant) and hospitalizations (13% to 3%; $P = .0001$) for HAE attacks. The percentage of patients perceived by physicians to be very satisfied with HAE treatment increased from 13% to 40% ($P < .00005$). In 2013, convenience was reported more frequently as an important patient factor that drove long-term prophylaxis choice (27% vs 10%; $P < .00005$), whereas adverse effects were cited less frequently (16% vs 42%; $P < .00005$); in both surveys, cost and/or insurance coverage was the greatest driver in this category (43% and 46%).

CONCLUSION: Analysis of these findings suggests that the change in HAE treatment has increased self-treatment at home, decreased emergency department visits and/or hospitalizations, and provided greater patient satisfaction. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:220-7)

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Hereditary angioedema (HAE) is a rare (approximately 1/50,000 persons) autosomal dominant disorder caused by a deficiency of C1 esterase inhibitor (C1-INH), a serine protease inhibitor involved in regulation of the complement and contact systems.^{1,2} The most common variant of HAE is type I, characterized by genetic mutations that result in reduced production of endogenous C1-INH; type II HAE is distinguished by normal levels of a dysfunctional form of C1-INH.³ Clinically, these 2 types of HAE are indistinguishable.¹ A more recently defined type of HAE (type III, or preferably “HAE with normal C1-INH”) has been identified in patients with clinical HAE, despite having normal, functional C1-INH levels.⁴⁻⁶

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Abbreviations used

C1-INH- C1-esterase inhibitor

ED- Emergency department

FDA- US Food and Drug Administration

FFP- Fresh frozen plasma

HAE- Hereditary angioedema

NS- Not significant

Experience with this new variant is limited, and optimal treatment has not yet been well defined.⁶ Patients with HAE experience periodic attacks of nonpruritic, nonpitting edema, which most commonly affects the skin and gastrointestinal tract; attacks that affect the airway are potentially fatal.^{1,2} Attack patterns vary considerably among patients with regard to both frequency and severity. Onset is typically during childhood, worsens around puberty, and persists throughout life.^{1,2} The physical distress and lifestyle interruptions associated with HAE have a substantial impact on quality of life for both patients and their families.⁷⁻¹⁵

The general goals of HAE management include minimizing the overall morbidity of the condition and preventing fatalities. Specific strategies include long-term prophylactic drug administration, short-term prophylaxis before potential triggers, and on-demand treatment of attacks when they occur. Before 2009, there were no specific treatments approved by the US Food and Drug Administration (FDA) to treat acute HAE attacks. A plasma-derived, pasteurized, nanofiltered C1-INH was approved in 2008 for prophylaxis only (Cinryze; ViroPharma, Exton, Pa). Other agents used for HAE included attenuated androgens (danazol, stanozolol) and antifibrinolytic agents for prophylaxis, and fresh frozen plasma (FFP) for HAE attacks. In recent years, the FDA has approved 3 new HAE therapies for acute treatment, including another pasteurized, nanofiltered formulation of C1-INH (Berinert; CSL Behring, Marburg, Germany); a plasma kallikrein inhibitor, ecallantide (Kalbitor[®] Dyax Corp, Cambridge, Mass); and a bradykinin β_2 receptor antagonist, icatibant (Firazyr; Shire Orphan Therapies, Lexington, Mass). With the availability of these new agents, the US HAE community has access to highly effective and safe treatments, including the option to self-administered treatment at home (ecallantide requires health care professional oversight).¹⁶

Given the rare nature of HAE, most physicians have little experience with treating the condition. A physician survey conducted in the United States between October 2009 and February 2010 revealed wide variability in HAE management and limited awareness of the newer therapies, which were either not available or became available coincident with conduction of the survey.¹⁷ In addition, a number of recently published treatment guidelines for HAE have continued to refine clinical practice standards, including recommendations for home-based treatment whenever possible.¹⁸⁻²³ The objectives of this follow-up survey were to evaluate the impact of the newly available treatment options and identify current trends in HAE care patterns among HAE-treating physicians in the United States as well as assess changes in HAE management practices since the initial survey (referred to as "2010 survey" hereafter).

METHODS

Data collection

This was a voluntary, Web-based survey that targeted physicians who treat patients with HAE. Potential participants were

identified by using mailing lists obtained from the US Hereditary Angioedema Association and the American College of Allergy, Asthma and Immunology, the latter was based on analysis of previous findings that suggested that the majority of patients with HAE are managed by allergists.¹⁷ The 2010 survey relied on mailing lists from the American College of Allergy, Asthma and Immunology, and the American Medical Association.

Between March 2013 and June 2013, 6570 physicians were contacted via postal mail, with up to 3 reminder e-mails to request their participation in the survey. Participants were asked to complete a 46-question online survey (hosted by SurveyMonkey; Palo Alto, Calif) that was closely patterned after the initial survey from 2009 to 2010. Thirty-five questions were taken directly from the original survey, and 11 new questions were added that pertained to HAE treatments not available in 2009. Respondents were given a \$25 honorarium for participating. Data collection was closed and the survey was taken offline at midnight on July 1, 2013. The study protocol and survey questionnaire were reviewed by the Chesapeake Institutional Review Board (Columbia, Md), which granted an exemption for institutional review board approval.

Data analysis

De-identified data were analyzed by us, and descriptive statistics were generated for each survey question. Not all respondents provided an answer for every single question; thus, percentage values were calculated based on the number of respondents who answered a particular question. Selected questions underwent statistical analysis to evaluate trends in prescribing habits or differences between the 2 surveys. The χ^2 test of independence was used to determine the statistical significance of all relationships. In some cases, adjacent levels of certain variables were combined to satisfy the underlying assumptions of the test and to ensure the validity of the test. All tests were performed at the 5% level of significance. In those instances when a statistically significant relationship was discovered, the precise nature of the relationship was established through examination of the pattern of contributions to the overall χ^2 value by the individual cells.

RESULTS

A total of 277 physicians responded to the survey (response rate, 4.2%), and 245 respondents indicated that they treated patients with HAE. These 245 comprised the analysis population. In comparison, the 2010 survey had a response rate of 3.1% (184 respondents of 5859 contacted), with 172 physicians who treated patients with HAE. Demographics and practice characteristics of the current survey population are provided in Table I. Overall, physician and practice characteristics were similar between the 2013 and 2010 surveys. Compared with 2013, the 2010 survey included a notably higher percentage of physicians with a specialty described as "other" (10.5% vs 0.4%), likely attributable to the use of an American Medical Association mailing list in 2010, which included a broader specialty audience.

Epidemiology

The volume of patients with HAE per physician in the 2013 survey was consistent with the 2010 survey (Table I). In the year before the survey, most respondents reported having treated 1 to 5 (70.4%) or 6 to 10 (19.3%) patients with HAE. Most

TABLE 1. Demographic and practice characteristics of respondents (HAE-treating physicians)

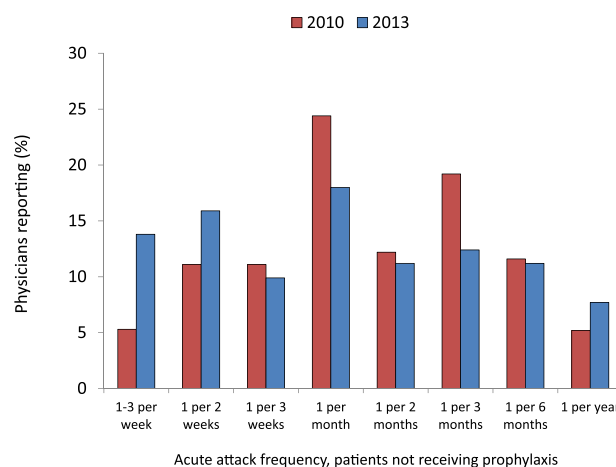
Characteristic	Respondents (HAE treaters), no. (%)	
	2010 (n = 172)	2013 (n = 245)*
Degree		
MD	156 (90.7)	213 (86.6)
MD, PhD	8 (4.7)	10 (4.1)
DO	8 (4.7)	13 (5.3)
Other	0	10 (4.1)
In practice		
<1 y	20 (11.6)	14 (5.7)
1-10 y	60 (34.9)	115 (46.7)
11-20 y	45 (26.2)	49 (19.9)
21-30 y	33 (19.2)	35 (14.2)
>30 y	14 (8.1)	33 (13.4)
Medical specialty		
Allergy/immunology	145 (84.3)†	236 (96.7)
Dermatology	17 (9.9)	NA
Family practice	2 (1.2)	2 (0.8)
Internal medicine	4 (2.3)	2 (0.8)
Pediatrics	3 (1.7)	3 (1.2)
Other	18 (10.5)	1 (0.4)
Practice setting		
Academic medical center	64 (37.2)	71 (29.0)
Community hospital	3 (1.7)	4 (1.6)
Office-based, multispecialty group practice	27 (15.7)	46 (18.8)
Office-based, single specialty group practice	48 (27.9)	85 (34.7)
Office-based, solo practice	30 (17.4)	39 (15.9)
Population size of practice location		
<10,000	NA	1 (0.4)
10,000-100,000	NA	41 (16.7)
100,000-500,000	NA	81 (33.1)
500,000-1,000,000	NA	52 (21.2)
>1,000,000	NA	70 (28.6)
No. patients with HAE treated in the past year		
1-5	127 (73.8)	171 (70.4)
6-10	30 (17.4)	47 (19.3)
11-15	6 (3.5)	12 (4.9)
16-20	6 (3.5)	5 (2.0)
≥20	3 (1.7)	8 (3.3)

NA, Not applicable (information not gathered).

*One non-HAE treating physician provided answers to degree and years in practice questions, thus these categories total 246 responses; not all respondents provided answers to "Population size of practice location" and "No. patients with HAE treated in the past year" questions, thus these categories have fewer than 245 responses (244 and 243 responses, respectively).

†In the 2010 survey, some physicians indicated more than 1 specialty.

respondents (70.4%) reported seeing between 0 and 1 new patients with HAE per year, and only 2.1% of respondents reported seeing 6 or more new patients with HAE per year. Most referrals were reported to come from primary care physicians (48.3%) and patient self-referral (25.0%), similar to 2010 findings. The majority of respondents reported an average age range for their patients with HAE of 26 to 35 years (32.7%) or 36 to

**FIGURE 1.** The proportion of physicians who reported an average frequency of acute HAE attacks in patients who did not receive prophylaxis, 2010 vs 2013.

45 years (31.0%). The most frequently reported average age range for onset of HAE symptoms was 11 to 17 years (48.7%), followed by 18 to 25 years (20.5%) and 6 to 10 years (17.9%).

Clinical symptoms

Physicians were asked to rank the 3 most common HAE symptoms that prompted referral or evaluation. Facial swelling was selected by 85.2% of respondents in 2013, followed by throat swelling (51.7%), tongue swelling (51.7%), abdominal pain (47.9%), and hand swelling (40.7%). Physicians reported facial swelling (72.8%), throat swelling (66.8%), tongue swelling (61.3%), and abdominal pain (60.0%) when asked to select 3 HAE symptoms most reported by patients with HAE to be problematic. These reported patterns were remarkably similar to those reported in the 2010 survey.

In both 2010 and 2013, the average HAE attack frequency in their patients cited by most physicians was "1 per month" (Figure 1). In 2013, there were higher percentages of responses in the highest frequency categories of "1 to 3 per week" and "1 per 2 weeks." When asked what percentage of patients' attacks would be considered "moderate to severe," which implies a significant interference with daily activities, the majority of physicians (58.4%) responded that 25% to 50% of their patients' attacks would fall into this category, which was similar to 2010. Another 16.3% of respondents answered that 75% of attacks fall into this category. Approximately 1 in 5 respondents indicated that 10% or fewer of their patient's attacks were moderate to severe. Very few respondents (4.7%) indicated that 90% or more of all attacks were moderate to severe. When asked how frequently their untreated patients presented to an emergency department (ED) or who were admitted to a hospital for HAE symptoms, the most common response was once every 12 months (35.7% of respondents), once every 6 months (21.3%), once every 3 months (15.2%), and once every 2 months (12.2%). Again, no major shifts were seen in these parameters compared with the 2010 physician survey.

Diagnosis

Physicians were asked to rate 3 factors on their level of importance for making a diagnosis of HAE; laboratory testing

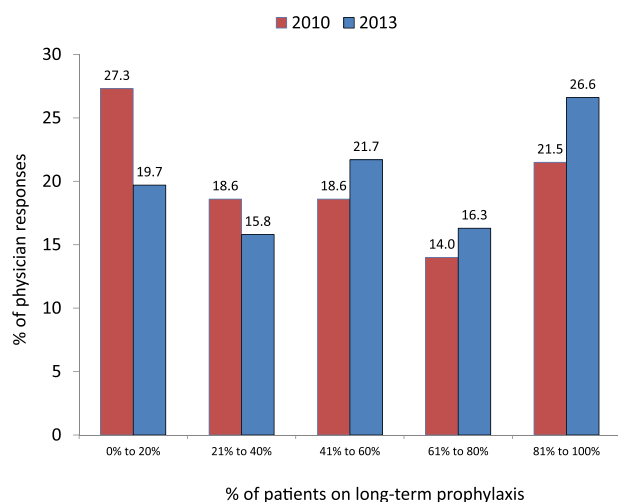


FIGURE 2. Reported percentages of patients with HAE who received long-term prophylaxis.

was ranked as very or somewhat important by 88.4% of physicians, followed by presenting symptoms (84.9%), then family history (58.0%); in comparison, these same factors were rated as important in the 2010 survey by 84.3%, 73.3%, and 97.1%, respectively. When asked to choose the most useful laboratory test to screen for HAE, C4 level was selected most frequently (68.8% vs 51.7% in 2010). Compared with 2010, fewer physicians cited C1-INH level (13.9% vs 15.7%) or C1-INH function (15.2% vs 28.5%) as the most useful screening test. The reported average time from onset of first symptoms to diagnosis of HAE ranged from 0 to 6 months (8.2% of respondents) to >10 years (5.2% of respondents). Overall, the pattern of average reported diagnostic delay was fairly similar in 2013 versus 2010, with the most-frequent categories reported in both surveys being 1 to 3 years and 4 to 7 years. A slight trend was observed that suggested relatively longer reported delays between symptoms and diagnosis in 2013 versus 2010.

Long- and short-term prophylaxis

Responses regarding percentages of HAE patients who use long-term prophylaxis showed a great deal of variability among HAE-treating physicians (Figure 2), with a trend that suggests a higher percentage of patients on long-term prophylaxis in 2013 compared with 2010. Physicians were asked to rank the 3 most important factors (of 12 possible) influencing their decision to recommend long-term prophylaxis (Figure 3). Response patterns were strikingly similar between 2013 and 2010 with the most frequently cited factors, including attack severity (96.1% vs 95.3%), attack frequency (93.6% vs 86.6%), and laryngeal attack frequency (50.7% vs 48.9%). In both surveys, attack severity was rated most frequently as “1” (most important). Certain prescriber characteristics were found to correlate with prophylaxis prescribing patterns as discussed next.

Patterns of agents used for prophylaxis showed differences between the 2010 and 2013 surveys (Figure 4). The reported use of C1-INH for long-term prophylaxis was significantly higher in 2013 compared with 2010 (56.7% vs 20.4%; $P < .00005$). Likewise, danazol use dropped significantly, from 55.8% in 2010 to 23.4% in 2013 ($P < .00005$). Other prophylaxis agents also

were reported less frequently in 2013 versus 2010, including a decrease in other attenuated androgen (stanozolol, oxandrolone) usage, from 13% to 6%; epsilon aminocaproic acid use was reported by 2% of physicians in 2010 but not at all in 2013. When choosing an agent for long-term prophylaxis, the most commonly cited (nonefficacy) factor as being important to prescribers in 2013 was cost and/or insurance coverage (40.5% vs 24.4% in 2010).

The most commonly cited factor in 2010 was the adverse effects profile (55.8%), which dropped to 29.5% in 2013. Other factors cited in the 2013 survey included convenience (16.0%), route of administration (6.0%), and personal experience with medication (7.5%). The type of product (synthetic or plasma derived) was cited as important by only 0.5% of respondents. Physicians also were asked to rank the top factors considered to be important to patients when choosing long-term prophylaxis therapy (Figure 5). Cost and/or insurance coverage was cited most frequently in both 2013 and 2010 (45.5% and 43.0%, respectively), with convenience cited as the second highest factor (27.2% vs 9.9% in 2010; $P < .00005$). Adverse effects were ranked third (15.8%) and a much less important factor than in the 2010 survey (41.9%; $P < .00005$ vs 2013).

The reported percentages of patients on long-term prophylaxis who experienced breakthrough attacks showed generally similar patterns for androgens, antifibrinolytics, and C1-INH. The lowest frequency category of breakthrough attacks (1% to 10% of patients) was cited by 41.0% of physicians for C1-INH, 34.0% for androgens, and 26.8% for antifibrinolytics. The category that indicated the highest frequency of breakthrough attacks (>40% of patients) was reported by 15.6% of physicians for androgens, 12.4% for C1-INH, and 7.3% for antifibrinolytics. Most physicians (89.3%) reported prescribing some type of short-term prophylaxis to prevent acute HAE attacks in high-risk situations, such as invasive medical procedures. Although this was essentially unchanged from 2010, C1-INH was the most frequently reported short-term prophylaxis agent (66.7% of respondents), an increase from 30.2% in 2010, followed by FFP (9.3% vs 34.9% in 2010) and high-dose androgens (8.9% vs 18.6% in 2010).

A significant association was found between years in practice and the proportion of managed patients with HAE using long-term prophylaxis ($P = .0283$); physicians with >20 years of experience were less likely to report low prophylaxis usage ($\leq 20\%$ of patients), although physicians with ≤ 10 years of experience were more likely to report low prophylaxis usage ($\leq 20\%$) of patients. Physicians with >20 years' practice experience were more likely to have many patients (>60%) who used attenuated androgens compared with physicians who had fewer years of practice ($P = .0199$). Physicians who reported the highest percentages of patients with moderate-to-severe HAE attacks also had significantly higher percentages of patients using C1-INH for long-term prophylaxis ($P = .001$). Although use of antifibrinolytics for long-term prophylaxis was low overall (81.7% reported no use), physicians in practice for >30 years appeared more likely to have at least 1 patient using an antifibrinolytic agent compared with physicians with fewer years of experience ($P = .0142$).

Management of HAE attacks

Physicians were asked to indicate all treatments that they use for treating acute HAE attacks (Figure 6). C1-INH was cited most

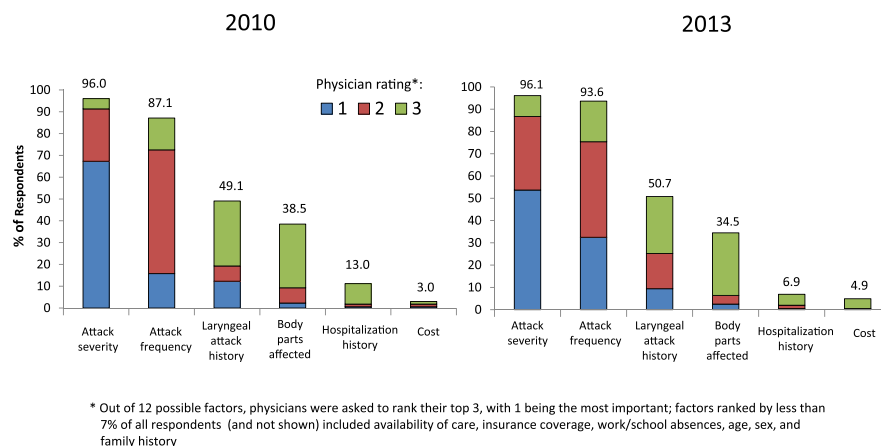


FIGURE 3. Factors reported as influencing physicians' decisions to recommend long-term prophylactic therapy for HAE (2010 vs 2013). Physicians were asked to rank their top 3 in order of importance, 1 being the most important. Bars reflect the percentage of physicians who rated each factor.

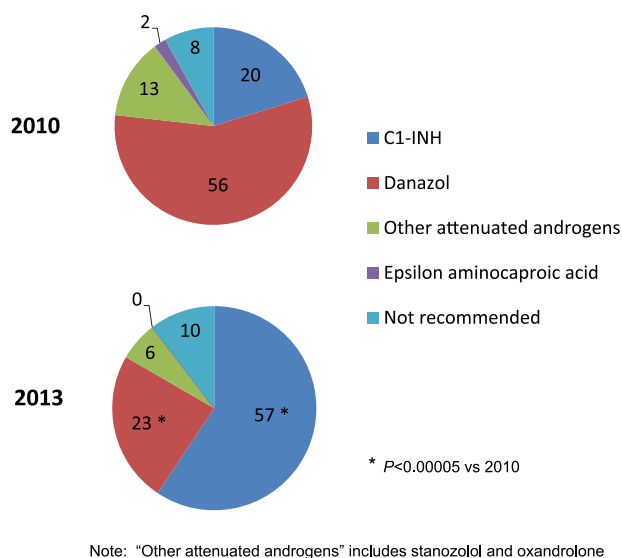


FIGURE 4. Long-term HAE prophylaxis, medications reported as used most frequently, 2010 vs 2013. Data represent percentage of physicians who reported.

frequently (68.9% vs 49.4% in 2010), followed by icatibant (53.9%) and ecallantide (47.0%), neither of which was reported in 2010. The use of FFP for acute HAE treatment dropped from 40.1% in 2010 to 17.8% in 2013, whereas the use of analgesics and hydration was not dramatically different between the 2 surveys. The percentage of physicians who reported "no treatment" decreased from 9.3% in 2010 to 1.4% in 2013. The most commonly reported setting for treatment of acute HAE attacks was the ED in both 2013 (53.9%) and 2010 (61.1%) (Figure 7). Reported self-treatment in a home setting increased significantly, from 8.1% in 2010 to 26.8% in 2013 ($P < .00005$). In addition, physician-reported hospital admission frequency for treatment of HAE decreased significantly, from 12.8% in 2010 to 2.6% in 2013 ($P = .0001$). More than two-thirds of respondents indicated that most of their patients treated with C1-INH use the product at

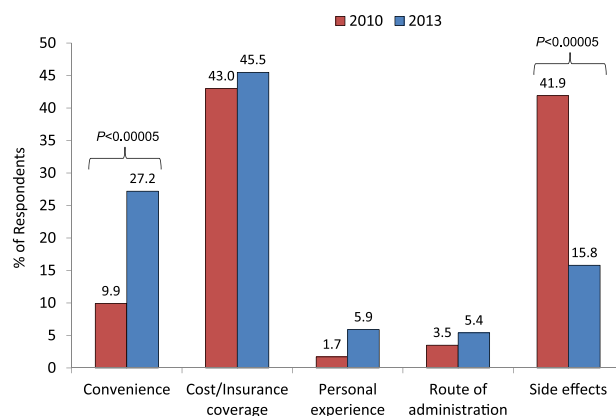


FIGURE 5. Physician perceptions of long-term prophylaxis treatment attributes considered most important by HAE patients, 2010 vs 2013.

home, either self-administered (46.7% of respondents) or with the assistance of home health care personnel (21.4%); other responses included administration at an outpatient center (15.9%), physician's office (7.7%), or ED (6.0%).

Physicians were asked to rate (1, very important; 2, somewhat important; 3, not important) various factors that influenced their choice of acute HAE treatment. Time to relief was rated as very important more often than any other factor (59.7% of respondents). Other responses rated as very important included patient preference (30.3%), product availability (29.0%), adverse events (20.4%), insurance coverage (19.9%), time to attack resolution (17.2%), and product cost (12.7%). Various non-efficacy factors relevant to acute treatment were rated for perceived level of importance to patients on a scale of 1 (most important) to 6 (least important); average rankings were as follows (lower score = higher importance), in descending order of importance rating: cost and/or insurance coverage (2.14), convenience (2.61), adverse effect profile (2.72), route of administration (3.22), personal experience with medication (4.24), and synthetic versus plasma-derived product (5.41).

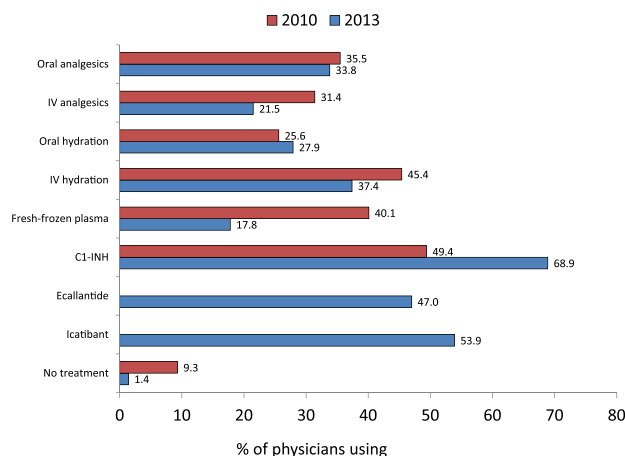


FIGURE 6. Physician-reported treatments used for acute HAE attacks, 2010 vs 2013 (physicians could choose more than 1 answer).

For patients who require redosing (second dose given <24 hours after the first dose) for an HAE attack, most respondents (64.7%) reported that they recommended redosing with the same drug; other responses included having patients seen at an ED or clinic (16.3%) or dosing with a different HAE agent (11.3%). Most respondents (44.3%) indicated a need for redosing in <5% of treated attacks; fewer respondents indicated redosing rates of 5% to 10% of attacks (30.5%), 11% to 20% of attacks (16.7%), 21% to 30% of attacks (4.9%), and >30% of attacks (3.4%).

Patient satisfaction

In 2013 versus 2010, a significantly higher percentage of physicians responded that they thought that their patients with HAE were very satisfied with their current treatment (40.3% vs 13.4%; $P < .00005$). Only 2.7% of the respondents indicated that their patients were not satisfied, a significant decrease from 2010 (21.5%; $P < .00005$).

Familiarity with HAE therapies

Physicians were asked to rate their level of familiarity with newer HAE therapies. The majority of respondents were very familiar with C1-INH, including both name brands, Cinryze (71.4%) and Berinert (65.9%). Approximately half of the respondents were very familiar with ecallantide (50.5%) and icatibant (52.9%). Only 9.7% of respondents were very familiar with recombinant C1-INH, not on the market in the United States. Response rates that indicated nonfamiliarity were the following: C1-INH (Cinryze) (3.2%), C1-INH (Berinert) (5.7%), ecallantide (9.9%), icatibant (11.0%), and recombinant C1-INH (52.6%). Reported rates for the likelihood of prescribing each therapy followed a similar pattern.

HAE other than type I or type II

Most physicians (49.8%) indicated having no patients diagnosed with HAE with normal C1-INH (type III); 43.0% of respondents stated having 1 to 5 such patients, 4.5% indicated having 6 to 10 patients, and 2.2% responded as having 11 to 15 such patients. One respondent (0.4%) noted having >15 patients with type III. With regard to the number of patients with

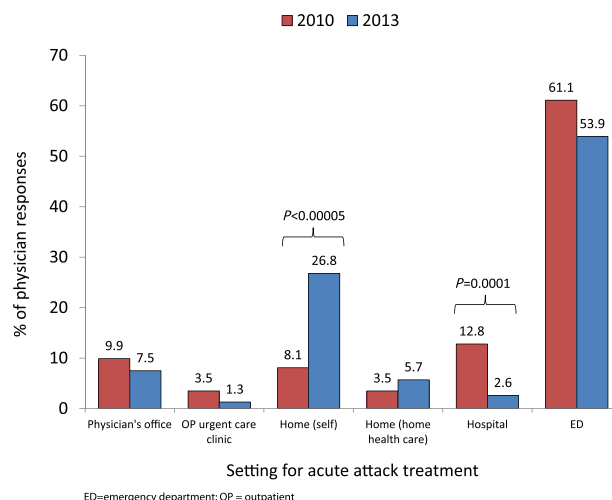


FIGURE 7. Physician-reported settings for HAE attack treatment, 2010 vs 2013.

recurrent idiopathic nonhistaminergic angioedema, responses were as follows: 0 patients (17.6% of respondents), 1 to 5 patients (41.0%), 6 to 10 patients (20.7%), and 11 or more patients (20.8%). For patients with HAE with normal C1-INH, idiopathic nonhistaminergic angioedema, or equivocal C1-INH laboratory values, most respondents (66.0%) indicated that they would always order additional laboratory tests, and another 26.8% would sometimes order additional laboratory tests; 43.7% responded that they would sometimes initiate a trial course of therapy with an HAE drug and observe the response; 22.1% responded that they would always do this. Approximately half of respondents indicated that they would always (15.9%) or sometimes (33.9%) refer such patients to an HAE specialist.

DISCUSSION

In general, the findings of this updated survey confirmed the impact of several recently introduced new HAE treatments on clinical care in the United States. For acute treatment, the majority of physicians in the 2013 survey reported prescribing the newer treatments, including C1-INH (68.9%), ecallantide (47.0%), and icatibant (53.9%), and much lower use of FFP for acute treatment. Before 2009, FFP was considered a useful option for treating acute attacks,²⁴ despite concerns that other substrates found in FFP could potentially aggravate HAE.²⁵ A significant drop in the percentage of physicians who reported using “no treatment” for HAE attacks (9.3% in 2010 to 1.4% in 2013) is particularly encouraging. The percentage of physicians who reported patient self-administered treatment increased significantly from 2010 to 2013. Although this trend is encouraging, it should be noted that only approximately one-third of respondents in 2013 reported that their patients with HAE were being treated most frequently at home, either through self-administration or with the assistance of home health care, despite unanimous recommendations for home-based care for all patients with HAE whenever feasible¹⁸⁻²³ and a growing body of published evidence that supports its feasibility and benefits.²⁶⁻³¹ Our survey found a surprisingly high percentage of physicians who still reported treatment of HAE attacks in the ED (53.9%), although hospital admission for treatment was reported

significantly less in 2013 (2.6%). For C1-INH specifically, approximately two-thirds of use was characterized as administered in the home setting.

The recently FDA-approved HAE therapies are relatively costly, although comparable with other so-called orphan drugs developed for very small patient populations with rare life-threatening conditions. Analysis of our survey results suggests that physician treatment decisions appear most heavily driven by clinical issues. When rating various factors that influenced prescribing decisions, physicians rated "time to relief" most frequently, and "product cost" least frequently. Physicians did indicate that product cost is perceived to be an important consideration to patients when considering nonefficacy factors.

Both surveys confirmed a high degree of variability in the use of prophylaxis, which likely reflects both the heterogeneity of the disease and individual management strategy differences. Overall, there appeared to be a trend toward more patients being on long-term prophylaxis, with a significant decrease in the percentage of physicians who reported danazol use and a corresponding increase in reported C1-INH usage. There are no clear guidelines for determining which patients should be placed on long-term prophylaxis for HAE. All recent consensus statements cite attack severity and frequency as important determinants^{19,21,32-35} and many also mention a lack of efficient access to acute treatment^{21,32,33,35} and quality-of-life issues.^{19,21,33} Although attack severity and frequency consistently ranked as highly influential factors in long-term prophylaxis prescribing decisions, citing of cost and/or insurance coverage issues increased from 24.4% in 2010 to 40.5% in 2013, possibly attributed to wider prescribing of C1-INH prophylaxis and associated costs of this medication. Cost was cited as being important to patients by similar percentages of respondents in both surveys (2010, 43.0%; 2013, 45.5%). For both physicians and patients, an adverse effect profile was cited much less frequently as an important factor in 2013 compared with 2010, which may coincide with lower rates of danazol usage, given the number of potential undesirable effects, particularly in female patients. Convenience was cited significantly more frequently in 2013 compared with 2010 as a patient-specific important factor, an interesting finding given that the 4 recently FDA-approved HAE therapies are intravenous or subcutaneous injections. A relationship was observed between physician length of time in practice and prophylaxis patterns; physicians who reported a longer time in practice appeared to be more frequent users of antifibrinolytic agents and androgens, which possibly suggests slower uptake of new therapies on the part of the physicians and a greater familiarity with older therapies. Use of short-term prophylaxis was reported by high percentages of respondents in both surveys, although the pattern of agents used showed an increase in C1-INH use and corresponding decreases in use of androgens and FFP. Responses that pertained to perceived delays between the onset of HAE symptoms and diagnosis seemed to show little change from 2010 to 2013, with most physician estimates that suggested a time period between 1 and 7 years, with a slight trend that suggested longer delays in 2013. Analysis of these data suggests the ongoing existence of barriers to timely disease recognition or patient pursuit of appropriate care.

This analysis has certain limitations inherent to survey-based data. Many of the questions required estimations on the part of the respondent or having to select 1 categorical response that reflected his or her HAE population in general. As such, findings

that pertained to treatment-specific outcomes should be interpreted as based primarily on physician recall and/or opinion. In addition, although analysis of the data provides useful insight into changing trends between 2009 to 2010 and 2013, the physician populations that responded to each survey were not identical. However, the data analyzed in each survey were limited to physicians who treat HAE, with demographics and practice characteristics fairly similar between the 2 cohorts, and each respondent group was sizable enough to be reasonably representative of national practices on the whole. Overall, this updated survey reflects important changes in HAE management among US physicians over recent years. Observed trends suggest significantly more patients being treated at home for HAE attacks, fewer patients being hospitalized for HAE, greater use of long-term prophylaxis with a shift away from androgens, and overall higher patient satisfaction with treatment.

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