Modeling Cost-Effectiveness of On-Demand Treatment for Hereditary Angioedema Attacks

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ABSTRACT

BACKGROUND: Hereditary angioedema (HAE) is a rare C1-inhibitor (C1-INH) deficiency disease. Low levels of functional C1-INH can lead to recurrent attacks of severe swelling occurring in areas such as the limbs, face, gastrointestinal tract, and throat. These attacks are both painful and disabling and, if not treated promptly and effectively, can result in hospitalization or death. Agents targeting the specific physiologic pathway of HAE attacks can offer improved outcomes with limited side effects compared with nonspecific therapies. However, these treatments display varying efficacy in HAE patients, including the need to redose or seek additional care if the treatment does not resolve symptoms effectively.

OBJECTIVE: To analyze the expected cost and utility per HAE attack when treated on-demand with HAE therapies indicated for the treatment of acute attacks.

METHODS: A decision-tree model was developed using TreeAge Pro software. Four on-demand HAE treatments were included: ecallantide, icatibant, plasma-derived (pd)C1-INH, and recombinant human (rh)C1-INH. The model uses probabilities for redosing, self-administration versus health care provider administration, and risk of hospitalization. Costs within the model consisted of the HAE treatments and associated health care system expenses. Nonattack baseline utility and attack utility were implemented for effectiveness calculations; time to attack resolution was considered as well. Effectiveness and overall costs per attack were calculated and used to estimate cost per quality-adjusted life-year (QALY). Variability and ranges in cost-effectiveness were determined using probabilistic sensitivity analyses. Finally, a budget impact model for a health plan with 1 million covered lives was also developed.

RESULTS: The base case model outputs show costs and calculated effectiveness per attack at \$12,905 and 0.806 for rhC1-INH, \$14,806 and 0.765 for icatibant, \$14,668 and 0.769 for pdC1-INH, and \$21,068 and 0.792 for ecallantide, respectively. Cost per QALY was calculated using 26.9 attacks per person-year, leading to results of \$420,941 for rhC1-INH, \$488,349 for icatibant, \$483,892 for pdC1-INH, and \$689,773 for ecallantide. Sensitivity analyses demonstrate that redose rates (from 3% for rhC1-INH to 44% for icatibant) are a primary driver of variability in cost-effectiveness. Annual health plan costs from the budget impact model are calculated as \$6.94 million for rhC1-INH, \$7.97 million for icatibant, \$7.90 million for pdC1-INH, and \$11.33 million for ecallantide.

CONCLUSIONS: Accounting for patient well-being and additional cost components of HAE attacks generates a better estimation of cost-effectiveness than drug cost alone. Results from this model indicate that rhC1-INH is the dominant treatment option with lower expected costs and higher calculated effectiveness than comparators. Further analyses reinforce the idea that low redose rates contribute to improved cost-effectiveness.

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What is already known about this subject

- Hereditary angioedema (HAE) is a rare disease that causes painful and potentially fatal episodes of swelling (attacks).
- Effective treatment of such attacks using on-demand therapies is a crucial component of disease management for HAE patients.
- On-demand therapies present varying costs and efficacies that may correspond to additional health care resources required to fully treat an attack.

What this study adds

- A cost-effectiveness model that considers downstream variables beyond the medication alone produces a more complete evaluation of resource utilization and patient well-being.
- Redosing rates can vary widely among on-demand therapies and contribute significantly to overall cost-effectiveness.
- Model outputs show recombinant human C1-inhibitor (C1-INH) as the most cost-effective option, followed by plasma-derived C1-INH, icatibant, and ecallantide in decreasing cost-effectiveness.

Hereditary angioedema (HAE) is a rare, serious disease caused by a mutation in the gene encoding for the plasma protein C1 esterase inhibitor (C1-INH).¹ Because of low levels of functional C1-INH, patients with HAE experience intermittent, unpredictable episodes of swelling (termed angioedema attacks) that can be painful, disabling, and life-threatening.² Treatments for HAE are divided into on-demand medication that is provided at the onset of the acute attack symptoms and prophylactic therapy that is given at regular intervals to prevent attack symptoms before they occur. Due to the heterogeneity of the disease, the frequency and severity of attacks vary greatly among patients with hereditary angioedema, even those in the same family.³ In spite of the recent availability of newer agents for prophylaxis treatment, on-demand treatment may remain an appropriate and effective option for many patients, dependent upon the patients' attack frequency and severity. The use of these therapies is also not mutually exclusive; although some patients may be sufficiently treated with on-demand treatment alone, other patients may need both prophylaxis and on-demand treatments. Because no prophylactic therapy is completely effective at preventing

FIGURE 1 Diagram of Decision-Tree Model

Note: This figure presents a schematic diagram of the decision-tree model for this investigation. From the acute attack node, there are 4 treatment paths with the same structure for each.

HAE=hereditary angioedema; HCP=health care provider; pdC1-INH=plasma-derived C1 inhibitor; rhC1-INH=recombinant human C1 inhibitor.

all attacks, treatment guidelines strongly emphasize that all patients need access to on-demand treatment.⁴ Given the physiologic evolution of the attack, the guidelines also encourage self-administration of the on-demand therapy to reduce symptom burden and improve outcomes.⁴

There are several on-demand treatment options available that have been approved by the U.S. Food and Drug Administration (FDA). Because of their differing mechanisms of action, as well as the clinical idiosyncrasies of the disease, these treatments have varying efficacy in HAE patients. Among the most pronounced differences between the treatments is the variable need for redosing, in which patients may require a second dose—or, for certain therapy, even a third dose—within a 24-hour period to control symptoms from a single attack.⁵ In addition, some patients may be hospitalized due to the lack of efficacy of the on-demand therapy. Together, these factors can have a profound effect on the disease burden and cost to treat an HAE attack. Furthermore, although prophylaxis therapy can help reduce the number of attacks, breakthrough attacks still occur; so even with prophylaxis, the need for cost-effective on-demand treatment exists.

Given the remaining importance of an on-demand treatment option, cost and utility analysis for on-demand therapies taking into account redosing rates, administration, and associated health care costs were evaluated to compare the cost-effectiveness per attack across the on-demand treatment options.

Methods

Cost-Effectiveness Modeling

To estimate the cost-effectiveness of on-demand treatment for HAE attacks, a decision-tree model from the U.S. commercial payer perspective was developed using TreeAge Pro 2018 R1 release (TreeAge Software, Williamstown, MA; Figure 1). The 4 comparators included were plasma-derived (pd)C1-INH (Berinert, CSL Behring GmbH)⁶; icatibant (Firazyr, Shire Orphan Therapies LLC)⁷; ecallantide (Kalbitor, Dyax Corp)⁸; and recombinant human (rh)C1-INH (Ruconest, Pharming Americas BV).⁹ The variables considered within the model can be seen in Table 1, along with the sources from which the values have been extracted. Beginning with variables that influence both cost and utility, we included proportion of redosing rates, self-administration, and risk of hospitalization. The latter variable was derived from an investigation in which HAE subjects were followed as they moved from health care provider (HCP) administration of rescue medication to self-administration; a rate of 22.8% for hospitalization when treatment was administered by an HCP compared with 3.6% when the subjects were able to self-administer.¹⁰

On-Demand Redosing Assumptions Based on Literature Review

Redosing and self-administration rates were obtained for each of the on-demand therapies from the research literature. A phase 3 study for pdC1-INH reported 18.6% of subjects in

TABLE 1 Input Values and Sources for Model Variable

Variable = Value, Reference (Range)	rhC1-INH	Icatibant	Ecallantide	pdC1-INH
Distribution unit	2,100 U ⁹	3 mL 10 mg/mL ⁷	1 mL 10 mg/mL ⁸	500 U ⁶
Distribution unit wholesale cost, ³⁰ \$	5,965 (5,070-6,263)	11,148 (9,475-11,705)	4,923 (4,184-5,169)	2,955 (2,512-3,103)
Dosing	50 U/kg ⁹	30 mg ⁷	30 mg ⁸	20 U/kg ⁶
Redosing rate, %	3 ²³ (2-10)	29 ¹⁹ (7-44)	12 ²¹ (6-18)	19 ¹¹ (8-30)
Self-administration rate, %	95 ²⁶ (80-98)	100 ⁷	0 ⁸	95 ²⁶ (85-98)
Time to resolution, hour	4.4 ³² (4.0-15.0)	6.0 ³² (2.2-24.3)	3.1 ³² (2.8-3.8)	8.4 ³² (6.2-21.5)
Body weight, kg (SD; range)	81 (24; 38-122)			
Nonattack utility	0.83 ²⁷ (0.62-1.00)			
Attack utility	0.51 ²⁷ (0.21-0.1)			
Hospitalization risk, self-administration, %	3.6 ¹⁰ (2.0-6.0)			
Hospitalization risk, HCP administration, %	22.8 ¹⁰ (15.0-30.0)			
Cost, home nurse, \$	184 ³³ (156-212)			
Cost, outpatient administration, \$	272 ³³ (231-313)			
Cost, ED visit/administration, \$	2,081 ³⁴ (1,769-2,393)			
Cost, hospitalization, \$	11,794 ³⁵ (10,025-13,563)			

ED=emergency department; HCP=health care provider; pdC1-INH=plasma-derived C1 inhibitor; rhC1-INH=recombinant human C1 inhibitor; SD=standard deviation.

the treatment group received rescue medication due to “insufficient or no symptom relief” 4 hours after initial treatment¹¹; this frequency compares with FDA labeling that indicates 30.2% of pdC1-INH patients receiving rescue study medication, analgesics, or antiemetics subsequent to treatment and before initial relief of symptoms.⁶ A follow-up study reports a much lower redose rate,¹² but the protocol expressly disallowed use of additional pdC1-INH beyond the initial 20 U/kg dose, and therefore such an estimate is not considered valid.

In 6 clinical trials with icatibant, a frequent adverse event was worsening or recurrence of the HAE attack within 48 hours after symptom onset requiring patients to often redose with icatibant.¹³⁻¹⁷ A wide range of redosing rates for icatibant have been reported, from 2.5% in Germany/Austria and 21.6% in France to a more recent U.S. survey indicating a retreatment rate of 29% and a smaller comparative study of on-demand treatments finding a 44% retreatment rate with icatibant.¹⁸⁻²⁰ It is also worth noting that the FDA label allows for up to 3 doses of icatibant in 24 hours to treat a single HAE attack.⁷

According to its label, ecallantide is administered for up to 2 doses within a 24-hour period and has a redosing frequency of 12% drawing from a pooled analysis of clinical trials.²¹ A phase 3 study independently found 15.7% of patients received a second dose for incomplete or relapsing symptoms between 4 and 24 hours after initial dosing.²²

For rhC1-INH, a redose rate of 3% has been reported,²³ while a phase 3 open-label extension found that 4% of attacks were treated with a second dose.²⁴ Similarly, a recent study of rhC1-INH in the pediatric population reported a 4% rate of redosing.²⁵

Rates of self-administration for pdC1-INH were extracted from the Berinert registry,²⁶ because rhC1-INH is administered by the same route as pdC1-INH, it was assumed that

rhC1-INH has similar self-administration rates in the absence of any published literature suggesting otherwise. Icatibant is labeled for self-administration exclusively,⁷ whereas ecallantide is only administered by a health care provider.⁸

Cost-Analysis Assessment

Cost variables within the model included the drug wholesale acquisition costs, administration costs for home nurse, outpatient, or emergency department, and finally the typical cost for hospitalization of an HAE patient. All costs are dated to 2019, either directly or by inflation using the medical-care inflation subset of the Consumer Price Index for All Urban Consumers. Utility values were drawn from the literature,²⁷ citing a utility of 0.51 when experiencing attack symptoms and 0.83 without symptoms. The time to resolution from treatment administration until attack symptoms have subsided was included to calculate effectiveness more precisely. Additionally, it was assumed that any patient requiring redosing experienced recurrent attack symptoms within 24 hours of the initial attack onset; in the context of clinical trials, redosing is often specified as requiring another dose of medication for the same attack. Our model then estimates the base case cost and effectiveness per attack.

When extrapolating a per attack cost-effectiveness to cost per QALY, as well as the budget impact model, the assumption was made that an HAE attack refers to a 72-hour period of time in which the primary attack initially occurs and during which follow-up attacks can occur because of ineffective treatment. Thus, the calculation of cost per QALY from per attack cost-effectiveness requires subtracting the number of annual hours during which the patient is experiencing attack symptoms (attack hours) from annual nonattack hours. As an example, a patient using a treatment with 7.5-hour time to resolution who

TABLE 2 Results of Decision-Tree and Budget Impact Models

	rhC1-INH	Icatibant	Ecaltantide	pdC1-INH
Base case results				
Cost per attack, \$	12,905	14,806	21,068	14,668
QALH (per 72)	58.03	55.06	57.03	55.37
Effectiveness	0.806	0.765	0.792	0.769
Annualized extrapolation				
Mean attacks per year	26.9 ²⁹			
Mean cost per year, \$	347,145	398,281	566,729	395,107
Mean QALYs per year	0.825	0.816	0.822	0.817
Overall cost/QALY, \$	420,941	488,349	689,773	483,892
Budget impact model				
Covered lives	1,000,000			
Prevalence	1/50,000 ²⁸			
HAE patients	20			
Overall cost to plan, \$	6,942,890	7,965,628	11,334,584	7,902,144
Cost PMPM, \$	0.58	0.66	0.94	0.66

HAE = hereditary angioedema; QALH = quality-adjusted life-hours; QALY = quality-adjusted life-year; pdC1-INH = plasma-derived C1 inhibitor; PMPM = per member per month; rhC1-INH = recombinant human C1 inhibitor.

experiences 26 attacks in 1 year and requires redosing in 6 of those attacks would have 363 total attack hours in that year $[(26 \text{ attacks} \times 7.5 \text{ hr}) + (6 \text{ redosings} \times 24 \text{ hr})]$, and 8,397 total nonattack hours in that year. The utility can then be calculated as $[(0.51 \times 363) + (0.83 \times 8,397)] \div 8,760 = 0.816$ for that year.

For the budget impact model, a total of 1 million covered lives was assumed along with an HAE prevalence of 1 in 50,000 individuals.²⁸ An overall average attack rate of 26.9 times per person-year (or 2.24 per month) was used.²⁹ From these assumptions, the budget impact model can be calculated by finding the product of the cost per attack and the total number of attacks per year. The QALY method described above can then be used to estimate the effectiveness of treatment for patients in the plan. For the budget impact model, all calculations were carried out with a single therapy; no combination therapies (use of multiple different drugs) were explored in this work.

Sensitivity Analyses

To validate the robustness of the model and to examine the assumptions made, several sensitivity analyses were performed. Ranges for each variable were established by consideration of publicly available literature for reasonable maximum and minimum values (Table 1). Probability distributions were assigned to model variables: for probability and utility values, the beta distribution was implemented; gamma distributions were used for time to resolution variables; and normal distributions were used for body weight, redose time, and the various general health care costs. Because drug costs are not randomly dispersed, but rather controlled by the manufacturer, we have used a triangular distribution for them. Therapies for rare

diseases are not significantly discounted in comparison with those for more common conditions, thus a 15% discount was applied to the low end of the drug costs in accordance with expert consensus.

We first performed 1-way sensitivity analyses examining each variable for each comparator across the range of the variable from minimum to maximum. The results from this analysis show the resultant change in overall treatment cost per attack due to the change in each variable; percentage change from the base case attack cost is calculated as well. Second, a probabilistic sensitivity analysis (PSA) was performed with a 5,000 trial Monte Carlo sampling simulation. In the PSA, every value in the model is randomly drawn from the assigned variable distributions discussed previously. These randomly drawn values are then used to calculate costs and effectiveness for that single trial, and the process is repeated 5,000 times. From the PSA simulation a cost-effectiveness scatter plot was generated for all 5,000 trials with 90% confidence ellipses as well as the means. Finally, the PSA results were used to develop cost-effectiveness acceptability curves comparing the likelihood of each comparator being more cost-effective than the others at various levels of willingness to pay.

Results

Outputs from the decision-tree model evaluated per attack are shown in Table 2. Beginning with the base case results, the model indicates that rhC1-INH is the dominant therapy; rhC1-INH is the least expensive treatment per attack at \$12,905 and has a higher calculated effectiveness score than the other therapeutic options. Ecaltantide is highly effective but also the most expensive, resulting in the least cost-effective therapy in the model at a per attack cost of \$21,068. Driven by higher redosing rates, icatibant exhibits a greater per attack cost of \$14,806 and comparatively poor effectiveness measures. In terms of quality of life metrics, we looked to the derived effectiveness that was obtained from the number of quality-adjusted life-hours per each 72-hour attack period. Effectiveness is compared with a nonattack baseline of 0.83; thus the model indicates that rhC1-INH can provide effectiveness of 0.806, with ecaltantide next at 0.792, followed by pdC1-INH and icatibant at 0.769 and 0.765, respectively.

Extrapolating a per attack cost-effectiveness to an annual basis allows estimation of cost per QALY for each therapy (Table 2). Using an attack rate of 26.9 per year, we calculated outright costs per year for each therapy as well as QALYs using the approach discussed in the methods section. Although the cost results vary from \$347,145 per year for rhC1-INH to \$566,729 for ecaltantide, the QALYs for each therapy are much closer with rhC1-INH at 0.825 down to icatibant at 0.816. From the cost and QALY values, we can derive a cost per QALY of \$420,941 for rhC1-INH that represents the most cost-effective

FIGURE 2 Probabilistic Sensitivity Analysis Scatter Plot

Note: A scatter plot of 5,000 trial probabilistic sensitivity analysis (PSA) is presented in this figure. Each pale dot represents 1 of the 5,000 trials. A 90% confidence ellipse is shown with the dashed line, while the overall mean cost-effectiveness is plotted with the large diamond.

pdC1-INH = plasma-derived C1 inhibitor; rhC1-INH = recombinant human C1 inhibitor.

therapy in this analysis, compared with \$488,349 for icatibant, \$483,892 for pdC1-INH, and, finally, \$689,773 for ecallantide.

Results of the budget impact model are also shown in Table 2. A plan with 1 million covered lives may have 20 HAE patients and with those patients experiencing a mean attack rate of 26.9 per year, an overall cost to the plan would be \$6.94 million with rhC1-INH, or \$0.58 per member per month (PMPM), representing the lowest cost to the plan among the comparators. In contrast, the overall cost of icatibant is \$7.97 million (\$0.66 PMPM) and pdC1-INH is \$7.90 million (\$0.66 PMPM), whereas ecallantide is the most expensive at \$11.33 million overall cost per year (\$0.94 PMPM).

One-way sensitivity analyses for each therapy are presented in the Appendix (available in online article) showing the 5 most influential variables of each comparator in terms of overall treatment costs per attack.

Within the sensitivity analysis, redosing rates represent a significant influence in treatment costs for all therapies. For icatibant, redosing rates as high as 44% have been reported,²⁰ which could lead to treatment costs surpassing \$16,000 in spite of a fixed self-administration rate and fixed dose volume.

A range of redosing rates from 0.08 to 0.30 for pdC1-INH could represent changes in cost per attack of more than \$1,300 from the base case. Ecallantide and rhC1-INH both have

narrower redosing ranges that limit the cost variability due to redosing to less than \$1,000 from the base case.

The cost of the therapy itself is either the first or second most important factor in determining treatment cost per attack for all therapies. For pdC1-INH and rhC1-INH, the drug cost is second whereas the population weight is first with regards to influencing costs. Because both therapies are dosed by body weight, a patient with lower (or higher) weight will use less (or more) of the drug. For pdC1-INH, this can alter the cost of treating any 1 attack from less than \$8,000 to more than \$20,000. This breadth of cost for pdC1-INH represents the largest range of treatment costs in the model.

Although ecallantide and icatibant are exclusively labeled for HCP administration or self-administration, respectively, both rhC1-INH and pdC1-INH are labeled for either administration route; thus the percentage of patients that self-administer these 2 therapies is a relevant factor in overall costs. Finally, we note that associated health system costs (such as outpatient service costs or emergency department costs) play a bigger role in overall cost of treatment for ecallantide than for the other therapies.

In Figure 2 the results of the PSA are shown. Compared with the 1-way analyses in which a single variable is changed over a range, the PSA results show what happens when all variables are simultaneously altered from the base case assumptions. The small pale dots represent each single trial while the large diamond is the mean of all 5,000 trials, and the 90% confidence range is indicated by the dashed ellipse for each therapy. The mean cost and effectiveness, respectively, for each therapy within the PSA simulation follows: rhC1-INH, \$12,170 and 0.805; icatibant, \$14,323 and 0.764; ecallantide, \$20,478 and 0.791; pdC1-INH, \$13,349 and 0.769. We further note that based on the general shape and scale of the 90% confidence ellipses, pdC1-INH represents the largest variance in overall cost-effectiveness compared with the others.

Finally, in Figure 3 the PSA simulation results are used to plot cost-effectiveness acceptability curves. Based on rare disease guidelines that extend willingness to pay to \$500,000 per QALY,³⁰ rhC1-INH offers a greater than 60% probability to be more cost-effective than the other therapies. In contrast, the willingness-to-pay threshold for having the greatest probability for being the most cost-effective therapy is 0% for ecallantide, less than 40% for pdC1-INH, and less than 5% for icatibant.

Discussion

Although the drug costs for HAE-specific therapies tend to be expensive, the ability for a therapy to promptly and effectively resolve attack symptoms with the first dose can reduce further downstream costs that may arise. This model finds that rhC1-INH is both less costly and more effective than the remaining comparators and therefore represents the dominant therapy. Because icatibant has the highest reported rate of redosing

FIGURE 3 Cost-Effectiveness Acceptability Curves

Note: Derived from the 5,000 trial probabilistic sensitivity analysis, cost-effectiveness acceptability curves present likelihood that a treatment will be the most cost-effective for various thresholds of willingness to pay.

pdC1-INH = plasma-derived C1 inhibitor; QALY = quality-adjusted life-year; rhC1-INH = recombinant human C1 inhibitor.

among the therapies, this leads to comparatively poor effectiveness and higher per attack treatment costs. Furthermore, patients treating with icatibant may use up to the maximum 3 doses per 24-hour period and can exceed \$33,000 in drug costs alone to treat just 1 attack.³¹ Ecallantide, in spite of good effectiveness, maintains an overall poorer cost-effectiveness that is far behind the other comparators.

In terms of qualitative outcomes, this model shows that treating a single HAE attack can vary widely in cost-effectiveness due to the patient's ability to self-administer therapy and to avoid redosing. Although the drug cost for rhC1-INH is comparable with both pdC1-INH and icatibant per dose, the redose rate is lower, and thus the cost-effectiveness is better with rhC1-INH than the other therapies.

Ecallantide requires administration by a health care provider, and thus the cost-effectiveness for therapy is substantially worse than the other 3 comparators. Requiring a medication to be administered by a health care provider can delay treatment for symptoms that can be very painful and dangerous, while also exposing the patient to a higher risk of hospitalization, which is a costly occurrence.

Although the total cost outlay for HAE patients within a health care plan is significant, the ability to reduce the economic burden by hundreds or thousands of dollars per attack can be meaningful on an annual basis. To that end, the budget impact model demonstrates that on-demand treatment using rhC1-INH could represent cost savings of more than \$1 million

per year compared with icatibant and more than \$4 million compared with ecallantide. Those figures are outright costs, and when combined with better effectiveness, rhC1-INH may also contribute to a higher quality of life for patients due to a low redose rate.

For the sensitivity analysis, although both rhC1-INH and pdC1-INH are dosed by weight, that variable represents a more significant input for cost-effectiveness for pdC1-INH. Because the distribution unit for rhC1-INH is 2,100 U, compared with 500 U for pdC1-INH, any patient over 42 kg will use 2 vials of rhC1-INH. On the other hand, a 500 U distribution unit for pdC1-INH allows more stratification (every 25 kg of body weight) of medication use. This is evident in the PSA scatter plot of Figure 2, in which rhC1-INH has 2 groupings of points compared with 5 groupings for pdC1-INH, where these groupings correspond to the number of distribution units (vials) required for therapy.

The distribution of points from the PSA simulation and the shape of the confidence ellipses can provide some insight as well. Because both ecallantide and icatibant have a constant dose, the cost variance is lower than weight-based dosing of rhC1-INH and especially pdC1-INH. On the other hand, rhC1-INH has the lowest variance in effectiveness per attack, while icatibant and pdC1-INH maintain wide redosing ranges that contribute to variance in effectiveness. A strategy that emphasizes patient self-administration could also reduce variance in both cost and effectiveness for pdC1-INH and rhC1-INH.

Limitations

The most significant limitation to cost-effectiveness modeling of HAE is that as a rare disease there is not a large volume of research in general, and even less that examines costs and utilities associated with disease management. Therefore, a model such as this will necessarily have wide ranges for variables and at times require estimates in the place of empirical evidence. This lack of empirical evidence manifests as an inability to accurately model certain aspects of acute attack treatment. For instance, although icatibant is labeled for up to 3 doses—which would certainly worsen the calculated cost-effectiveness significantly—the quality of evidence surrounding that phenomenon is lacking and subsequently was not included in the model. Additionally, head-to-head comparison studies are essentially nonexistent and so we necessarily must assume that the populations studied are similar.

This deficiency of evidence is further compounded by the fact that HAE patients have vastly different characteristics in terms of attack severity and frequency. For this reason, specific treatment approaches for individual patients are likely to differ and establishing a singular cost-effectiveness estimate for a theoretical HAE patient is nearly impossible. Therefore, our work only examines the treatment of a single attack and then the implications of a large number of attacks within the scope

of a payer's patient population, and we do not propose cost-effectiveness calculations for an individual HAE patient.

Conclusions

HAE is a rare disease that represents a significant cost to the health care system and patient quality of life. Timely and effective treatments can help reduce this disease. This model reinforces the concept that redosing and self-administration are important factors to consider for on-demand treatment of HAE attacks. A treatment that can be quickly administered by the patient when attack symptoms arise and that does not require frequent redosing should offer lower overall costs to the health care system and improved patient outcomes. Model results indicate that rhC1-INH can offer those characteristics and is the dominant therapy with lower expected costs and a higher calculated effectiveness than the other comparators. Ecallantide is very effective but involves higher costs because of the requirement for health care provider administration. Icatibant's wide range for redosing leads to substantial uncertainty in effectiveness and total treatment cost, whereas pdC1-INH's weight-based dosing leads to a wide cost range. This work is relevant for HAE patients, practitioners caring for HAE patients and payers, as there are a number of HAE patients for whom on-demand treatment will continue to be sufficient to maintain a high quality of life, as well as for HAE patients treated prophylactically for whom breakthrough attacks would still require rescue medication intermittently.

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Modeling Cost-Effectiveness of On-Demand Treatment for Hereditary Angioedema Attacks

APPENDIX One-Way Sensitivity Analysis

Variable	Value Range		Attack Cost Range, \$	Change from Base Case Attack Cost, %
Ecallantide				
Cost of ecallantide (10-mg vial), \$	Min	4,184	18,436	-12.5
	Max	5,169	21,945	4.2
Proportion of ecallantide subjects requiring redose	Min	0.06	20,129	-4.5
	Max	0.18	22,008	4.5
Proportion hospitalization for HCP therapy	Min	0.15	20,149	-4.4
	Max	0.30	21,918	4.0
Cost of hospitalization, \$	Min	10,025	20,665	-1.9
	Max	13,563	21,472	1.9
Cost of ED visit, \$	Min	1,769	20,964	-0.5
	Max	2,393	21,172	0.5
Icatibant				
Proportion of icatibant subjects requiring redose	Min	0.07	12,353	-16.6
	Max	0.44	16,478	11.3
Cost of icatibant (30-mg dose), \$	Min	9,475	12,647	-14.6
	Max	11,705	15,524	4.8
Proportion of hospitalization for self-administration therapy	Min	0.02	14,617	-1.3
	Max	0.06	15,089	1.9
Cost of hospitalization, \$	Min	10,025	14,742	-0.4
	Max	13,563	14,869	0.4
Time to resolution (icatibant)	Min	2.2	14,806	0
	Max	24.3	14,806	0
pdC1-INH				
Population weight, kg	Min	38	7,634	-48.0
	Max	124	21,742	48.2
Cost of pdC1-INH (500-U vial), \$	Min	2,512	12,573	-14.3
	Max	3,103	15,395	5.0
Proportion of pdC1-INH subjects requiring redose	Min	0.08	13,384	-8.8
	Max	0.30	15,992	9.0
Proportion of pdC1-INH subjects self-administering therapy	Min	0.85	15,083	2.8
	Max	0.98	14,570	-0.7
Proportion hospitalization for self-administering therapy	Min	0.02	14,509	-1.1
	Max	0.06	14,957	2.0
rhC1-INH				
Population weight, kg	Min	38	6,742	-47.8
	Max	124	12,905	0
Cost of rhC1-INH (2,100-U vial), \$	Min	5,070	11,056	-14.3
	Max	6,263	13,521	4.8
Proportion of rhC1-INH subjects requiring redose	Min	0.02	12,785	-0.9
	Max	0.10	13,743	6.5
Proportion of rhC1-INH subjects self-administering therapy	Min	0.80	13,482	4.5
	Max	0.98	12,789	-0.9
Proportion hospitalization for self-administered therapy	Min	0.02	12,726	-1.4
	Max	0.06	13,174	2.1

Note: One-way sensitivity analysis results are shown for the 5 most significant variables for each comparator in terms of influencing overall treatment cost per attack.