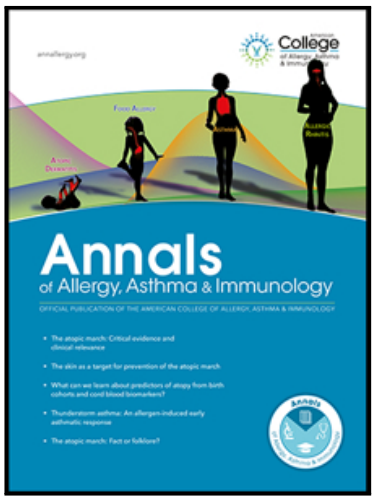

On-demand treatment of hereditary angioedema attacks: patient-reported utilization, barriers, and outcomes

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Original Article

On-demand treatment of hereditary angioedema attacks: patient-reported utilization, barriers, and outcomes

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CONFLICT OF INTEREST STATEMENT

Sandra Christiansen is a member of the US HAEA Medical Advisory Board, and participated in advisory boards for BioCryst, CSL Behring, and KalVista Pharmaceuticals.

Maeve O'Connor is a speaker/consultant/advisor or researcher for AbbVie, AstraZeneca, Blueprint, CSL, Grifols, GSK, KalVista Pharmaceuticals, TEVA, Pharming, and Sanofi; and Chief Medical Officer of the CIIC.

Timothy Craig received research support and was a consultant for Astria, BioCryst, BioMarin, CSL Behring, Intellia, Ionis, KalVista Pharmaceuticals, Pharvaris, and Takeda; received speaker fees from CSL Behring and Takeda; and travel support from BioCryst, CSL Behring, and Takeda.

Cristine Radojicic is a member of advisory boards for CSL, KalVista Pharmaceuticals, and Pharvaris.

H James Wedner receives research funds from Arista, BioCryst, BioMarin, GSK, ImmunoTherapeutics, Ionis, KalVista Pharmaceuticals, Pharvaris, and Takeda. He receives consulting fees from Arista, BioMarin, BluePrint, CSL, Grifols, Ionis, KalVista Pharmaceuticals, Pharvaris, and Takeda. He is a speaker for BioCryst, BluePrint, CSL, GSK, Grifols, and Takeda.

Julie Ulloa received consulting fees from KalVista Pharmaceuticals.

Vibha Desai is an employee of KalVista Pharmaceuticals.

Christopher Utter is an employee of KalVista Pharmaceuticals.

Tomas Andriotti is a former employee of KalVista Pharmaceuticals.

Paul Audhya is an employee of KalVista Pharmaceuticals.

Paula Busse received consulting fees from ADArx, Astria, Behring, BioCryst, CSL, CVS Specialty, KalVista Pharmaceuticals, Pharvaris, and Takeda.

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Key Words: On-demand treatment; HAE; hereditary angioedema; treatment delay; injection therapy; treatment barriers; oral therapy

Abbreviations/Acronyms: C1-INH, C1 esterase inhibitor; FDA, Food and Drug Administration; HAE, Hereditary angioedema; HAEA, Hereditary angioedema Association; HAE-C1INH, hereditary angioedema with C1 inhibitor deficiency; IQR, interquartile range; IV, intravenous; LTP, long-term prophylaxis; N/A, not applicable; OD, on-demand treatment; SC, subcutaneous; SD, standard deviation; US, United States

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Abstract

Background: Hereditary angioedema (HAE) is clinically characterized by recurrent attacks of cutaneous and submucosal swelling.

Objective: To investigate real-world timing, potential barriers, and impact of delaying on-demand treatment (OD) of HAE attacks

Methods: Patients with HAE (type I or II) aged ≥12 years with ≥1 treated (Treated Cohort) or untreated (Untreated Cohort) attack in the past 3 months were recruited by the US HAE Association. Respondents completed a 20-minute, self-reported, online survey about their last HAE attack.

Results: In the Treated Cohort (n = 94), of the 67% who reported treating their attack early, only 26% administered OD in <1 hour. Seventy-nine percent (n=74) reported treatment-related anxiety, which correlated with treatment delay. Time to treatment paralleled changes in attack severity (33% mild attacks treated in <1 hour vs 67% ≥1 hour, progressed to moderate/severe) and mean duration (<1 hour: 0.7 day; >8 hours: 2.7 days). In the Untreated Cohort (n = 20), 50% of respondents describing their last untreated attack as mild experienced progression to moderate or severe, and 25% reported spread to another site including the larynx and face. Untreated attacks lasted a mean of 2.3 days.

Conclusion: The disparity between survey respondents' perception of treating early and actual time to OD administration is striking. Treatment-related anxiety was a common reason for delaying OD. Increased treatment intervals translated into progression of HAE attack severity, duration, and spread to other sites. Suboptimal management of attacks intensifies the HAE disease burden, underscoring the need for improved treatment options, guidance, and removal of OD administration barriers.

INTRODUCTION

Hereditary angioedema (HAE) is clinically characterized by recurrent episodes of swelling involving subcutaneous and submucosal tissues.[1] Individuals affected have significant disease-associated morbidity and risk of mortality. All patients with HAE are at risk for painful, disfiguring, and disabling attacks. Stress, arising from the unpredictability of swelling and specter of asphyxiation, promotes a disproportionate prevalence of anxiety and depression. Before the advent of targeted treatments, patients reported pervasive disruption of their lives, evident in their inability to pursue desired social, educational, and professional goals. The collective disease burden is manifested by meaningful reductions in health-related quality of life scores for people with HAE.[2–5]

Beginning in 2009, the US Food and Drug Administration (FDA) approval of effective medications capable of arresting the progression of attacks has transformed the management of HAE.[6] Currently, 4 on-demand treatments (ODs) are available, each of which has been shown to reduce the severity and duration of swelling.[6] Despite the favorable impact of these therapies, unmet needs remain, including lingering fear of laryngeal attacks, disruption in daily life, side effects, and fear of having children because of their risk of inheriting HAE.[2] All currently FDA-approved ODs require parenteral administration, which imposes a significant treatment burden.[7,8] The high cost of therapy has also been cited as a barrier to access that affects patients' decision to use these medications.[9]

The US Hereditary Angioedema Association (HAEA) guidelines advocate for all attacks to be considered for treatment regardless of location or severity.[10] Recommendations further highlight that OD should be initiated at the onset of an attack to reduce morbidity and prevent mortality. Despite these directives, study findings suggest that some patients elect to forgo or postpone acute treatment.[9,11–13] There is little information that captures the underlying reasons surrounding these choices. Furthermore, the full impact on an array of attack outcomes from withholding or delaying OD is largely unexplored in a real-world setting.

In this study, we investigate OD time to treatment for groups of adults and adolescents with HAE. The disparities between patients' perception of early OD and

their reported time to treatment are examined. We describe the barriers to early OD administration and explore the association between treatment anxiety and delay. The relationship between time to treatment and morbidity outcomes, including attack severity, duration, and additional site involvement, are analyzed.

METHODS

Study design

Using the not-for-profit patient advocacy organization, the US HAEA, membership database, patients were identified who were aged ≥12 years and reported a physician's diagnosis of HAE type I or type II. After institutional review board approval on December 14, 2022 (Advarra, Columbia, MD, USA), patients meeting criteria were recruited from April to June 2023 and were invited to participate in a 20-minute, online survey via an email from the US HAEA. Respondents provided consent for their data to be used anonymously or in aggregate and survey participants were offered compensation for the time required to complete the survey.

The survey included questions on demographics, comorbidities, attack frequency, and location in the past 12 months, last attack characteristics, and experiences. Survey participants were asked to identify their OD and, if relevant, their long-term prophylaxis (LTP) treatment at the time of their last attack.

Survey development and administration

Pretest revision

Surveys were pretested by a representative adolescent and adult patient to evaluate the comprehension level and accuracy of the survey questions. During the pretest, respondents completed an anonymized survey via electronic link followed by a 45-minute conversation conducted by videotelephony software (Zoom Video Communications, Qumu Corporation, Minneapolis, MN, USA) with survey developers at Outcomes Insights, Inc (Calabasas, CA, USA). During the unstructured call, respondents were asked to provide feedback on their survey experience. Questions were revised on the basis of the pretest responses to optimize comprehension, clarity, and quality. US HAEA shared the finalized surveys with its members via email in the form of an anonymized electronic link. The full survey is included in the online supplement**.**

Screening

Patients with HAE were asked if they had been diagnosed by a physician and with which type of HAE. Patients meeting all the inclusion criteria (aged ≥12 years; HAE with low functional levels of C1 inhibitor, [HAE-C1INH], type I or II; available approved OD; if taking LTP, a nonandrogen approved drug; experiencing ≥1 attack within the last 3 months) were then allowed to enter the survey.

Survey respondents were categorized into 2 groups. The Treated Cohort included patients who treated ≥1 HAE attack with an approved OD in the last 3 months. The target sample size for the Treated Cohort comprised 100 patients (minimum, n = 50 for OD only at time of last treated attack; maximum, n = 50 for nonandrogen LTP at time

of last treated attack; n = 20 adolescents, n = 80 adults). The Untreated Cohort included adult patients who had an attack in the past 3 months that was not treated with an OD. The target sample size for the Untreated Cohort was 20 patients (minimum, n = 10 for OD only at the time of last untreated attack; maximum, n = 10 for nonandrogen LTP at the time of untreated attack).

Data collection, end points, and analysis

The primary end points were time to OD administration, attack severity, change in attack severity, and attack duration (from attack onset to resolution). The secondary end points were spreading of attacks, barriers to treating early or reasons for not treating, treatment-related anxiety (assessed on a visual analog score scale of 0–10 [not anxious, 0; mildly anxious, 1–3; moderately anxious, 4–6; extremely anxious, 7–10]), and injection-site side effects.

Statistical methods

For the Treated Cohort, data were analyzed overall and separately for adult and adolescent respondents and by treatment group at the time of last attack (OD only and OD plus LTP). For the Untreated Cohort, data were analyzed overall (adult respondents only) and by treatment group at the time of last attack (OD only and OD plus LTP). Means (standard deviation [SD]) and medians (interquartile range [IQR]) were calculated for continuous variables and by number and percentage for categorical variables.

RESULTS

Patient selection

Two-hundred-eighty-five patients aged ≥12 years entered the survey, of which 251 reported HAE type I or type II (Figure 1). One-third of those identified with ≥1 attack in the past 3 months did not treat their last attack (n = 56). Ninety-four eligible patients were retained in the Treated Cohort. Of the patients eligible, 20 were retained for the Untreated Cohort.

Results for the Treated Cohort

General characteristics

The Treated Cohort comprised 80 adults (predominantly female [78.8%], with a mean age of 43.8 years) and 14 adolescents (predominantly male [64.3%], with a mean age of 14.1 years; Table 1A). Fifty-four percent of respondents (n = 51) were receiving nonandrogen LTP at the time of their last attack (median duration of current LTP was 11 months, IQR 4–10). Of note, 28.8% of adults reported a comorbid physician diagnosis of anxiety, and 25.5% reported depression. For adolescents, 35.7% reported anxiety, and 14.3% reported depression.

Characterization of attacks over the past 12 months

Respondents receiving OD only at the time of last treated attack (n = 43) reported a median of 6 attacks (IQR 3–15 attacks) in the 12 months before the survey. Those who were receiving LTP at the time of last treated attack (n = 51) reported a median of 6 attacks (IQR 3–14 attacks) in the prior 12 months. Of all respondents, 57.4% (54 of 94) had ≥6 attacks, and 22.3% (21 of 94) required emergency services or hospitalization for their attacks at least once in the prior year. Of adolescent respondents, 57.1% (8 of 14) required emergency services or hospitalization at least once (Table 1B). Most patients (87.2%) reported self-administering OD. A lower proportion of adolescents (64.3%) self-administered OD.

OD and LTP medications at the time of the last treated attack

Sixty-three participants (67.0%) treated their last attack with subcutaneous OD and 31 (32.9%) with intravenous treatment. Most adults (76.3%) used icatibant for OD (eTable 1A). For adults receiving LTP, the majority were receiving lanadelumab (62.8%) (eTable 1B). For adolescents, OD comprised plasma-derived (50.0%) and recombinant (50.0%) C1 inhibitor; berotralstat (37.5%) was the most common LTP.

Characteristics of the last treated attack

The median time since the last treated attack was 14 days (IQR, 7–28 days). Of respondents, 55.3% rated the attack as moderate in severity, with 16.0% rating the attack as severe or very severe at the time of treatment (Table 2). Attack locations included 59.6% abdominal, 21.3% peripheral, 7.4% face, and 6.4% throat.

Time to treatment

Overall, the mean time to treatment for the last attack was 3.8 hours (SD, 6.3 hours). Only 21.3% of adults (17 of 80) and 7.1% of adolescents (1 of 14) treated in <1 hour, with a mean time to treatment of 3.2 hours (SD, 4.0 hours) and 7.7 hours (SD, 13.0 hours), respectively (Figure 2A). The shortest time to treatment was recorded for attacks affecting the face (mean, 1.4 hours); in contrast, those affecting the abdomen had the longest time to treatment (mean, 4.7 hours; Figure 2B).

Patient perception for attack treatment (early vs not early) and time to treatment

Most respondents (n = 63; 67.0%) believed they had treated their attack early, despite only 25.4% of these treating in <1 hour (Figure 3A). The mean time to treatment for these patients was 2.9 hours (SD, 4.5 hours). Thirty-one respondents (32.9%) reported not treating their attack early, with 90.3% waiting ≥2 hours to treat their attack. The mean time to treatment for these patients was 5.7 hours (SD, 8.8 hours).

Barriers reported for OD administration

Respondents were asked "What prevented you from treating this HAE attack sooner with on-demand treatment?" Those who selected the option "I treated my attack immediately," regardless of actual time to treatment, were excluded from the analysis of respondents reporting barriers to early treatment. The 85 remaining respondents (90.4%) reported their top 5 barriers to treating attacks early (Figure 3B). The most common barriers noted by respondents included uncertainty whether the attack was real (52.9%), belief the attack was going to be mild (38.8%), desire to save OD for a severe attack (31.8%), not having OD with them (20.0%), and desire to avoid injection pain/stinging/burning (18.8%). A higher percentage of those treating later reported

treatment-administration–related barriers, with 22.2% of those treating in <1 hour versus 38.9%–56.8% of those treating between 1 and <8 hours, respectively (eTable 2).

Impact of time to treatment on attack duration

Overall, the mean attack duration was 1.7 days for adults and 1.9 days for adolescents. Across subgroups of OD only and OD plus LTP for adults and adolescents, the mean ranged from 1.6 to 1.9 days (eFigure 1A). As time to treatment increased, the mean attack duration increased from 0.7 days for those who treated in <1 hour to 2.7 days for those who treated in ≥8 hours (eFigure 1B).

Relationship between time to treatment and attack severity

There was a parallel relationship between attack severity at the time of treatment and the interval length of time to treatment. For those treating at <1 hour, 50.0% had a mild attack at the time of treatment, whereas only 11.1% had a mild attack at the time of treatment for those treating ≥5 but <8 hours (Figure 4A). This is in keeping with the finding that 44.6% of patients' attacks progressed in severity after treatment. For attacks that were mild at outset, there was escalation to moderate in 44.4% of cases and to severe in 11.1% of cases (Figure 4B). For moderate attacks, there was a similar pattern, with 40.4% progressing to severe and 7.7% to very severe, and for attacks that were severe at the outset, 16.7% progressed to very severe.

In general, a lower percentage of patients who treated within an hour had their attack severity increase over time than those treating in ≥1 hour (Figure 4C). For those with mild attacks at treatment, 33.3% vs 66.6% treating in <1 versus ≥1 hour, respectively, had their attack increase in severity. For those with moderate attack at

treatment, 28.5% versus 51.1% treating in <1 versus ≥1 hour, respectively, had their attack increase in severity.

Spread in attack location

The attacks spread from the initial site to another site for 27.5% of adults (22 of 80) and 42.8% of adolescents (6 of 14). For these patients, sites of spread included the throat (16.7% in the OD only subgroup for adults [n = 12] and for adolescents [n = 6]; eFigure 2). Attack spreading occurred in 27.8% of those who treated <1 hour and 30.2% of those who treated ≥1 hour.

Treatment-related anxiety and time to treatment

Fifty percent of adolescents (7 of 14) and 32.5% of adults (26 of 80) reported being extremely anxious about the use of OD for their HAE attack (Figure 5A). There appeared to be a direct relationship between the level of anxiety and time to treatment, with 30.0% of those reporting no anxiety treating in <1 hour versus 12.1% identifying as extremely anxious treating in <1 hour (Figure 5B). The mean time to treatment for respondents who were not anxious was 2.4 hours (SD, 2.4 hours) and 5.4 hours (SD, 9.4 hours) for those who were extremely anxious.

Reasons for treatment-related anxiety

For adults (n = 62), the prevailing top 3 ranked reasons for anxiety were related to availability/cost (69.4%), with 41.9% citing “running out of medication if I needed it later,” 43.5% “desiring not to waste an OD if the attack was less severe,” and 22.6% noting “the cost of the OD” (Table 3). Efficacy concerns followed in prevalence (59.7%), with 27.4% citing “uncertainty with how long the treatment would take to begin working,” and

24.2% “uncertainty over whether the treatment would work.” “Anticipating burning or pain with the injection” was noted by 19.4% of adult respondents.

For adolescents (n = 12), the dominant reason for anxiety was related to drug delivery, with 58.3% citing “finding a vein for administration.” This was followed by efficacy, with 50.0% identifying “uncertainty over whether the treatment would work” followed by 25.0% citing “anticipating burning or pain with the injection” and 25.0% “anticipating side effects with the injection.” Twenty-five percent of adolescents and 16.1% of adults reported being anxious over “uncertainty if the attack would become severe enough to treat.”

Side effects with OD

For the 77 respondents reporting side effects associated with their last treated attack, 44.2% reported “burning or pain while injecting the medication” as the most severe side effect, with a mean duration of 23.1 minutes (SD, 36.9 minutes) and median of 10.0 minutes (IQR, 5.0–20.0 minutes; eTable 3A and 3B). Of those 77 respondents, 19.5% reported “pain with the needle” as the most severe side effect, with a mean duration of 52.1 minutes (SD, 100.0 minutes) and median of 10.0 minutes (1Q, 1.0 minute; 3Q, 60.0 minutes).

Results for the Untreated Cohort

General characteristics

The Untreated Cohort consisted of 20 adult respondents, with a mean age of 38.5 years and 80.0% with HAE type I (Table 1A). Similar to the Untreated Cohort, most respondents were female (75.0%), and 30.0% were diagnosed with anxiety and 10.0% with depression.

Characterization of attacks over the past 12 months

In the 12 months before the survey, respondents receiving OD only (n = 9) reported a median of 6 attacks (IQR, 3–14 attacks), and LTP users (n = 11) reported a median of 3.0 attacks IQR, 2–10 attacks). Of the untreated respondents, 45.0% (9 of 20) had ≥6 attacks, and 15.0% (3 of 20) required emergency services or hospitalization for their attack at least once. Slightly more than half reported self-administering their OD (Table 1B).

OD and LTP medications at the time of the untreated attack

Icatibant was the most commonly prescribed OD (75.0%). Among the 11 patients receiving LTP at the time of their last attack, berotralstat (45.5%) was the most commonly used LTP.

Characteristics of the last untreated attack

The median time since the last untreated attack was 25 days (IQR, 7–45 days; Table 2); 70.0% rated their last attack as mild, 20.0% as moderate, and 5.0% as severe. Fifty-five percent of attacks were reported as peripheral, 20.0% abdominal, and 15.0% facial. Untreated HAE attacks lasted an average of 2.3 days (SD, 1.9 days) and a median of 2 days (IQR, 1–3 days). Patients taking LTP had somewhat longer attacks (mean 2.6

days [SD, 2.2 days]; median, 2 days [IQR, 1–3 days]) than those receiving OD only (mean, 1.9 days [SD, 1.4 days]; median, 2 days [IQR, 1–2 days]).

Untreated attack severity and progression

Of respondents who described their last untreated attack as mild, 50.0% had their attack progress to moderate or severe (eFigure 3). Overall, severity progressed in 45.0% (9 of 20) of the untreated attacks. Five attacks (25.0%) spread to other locations, including 1 to the larynx and 1 to the face.

Reasons for nontreatment

When respondents were asked their reasons for not treating their last attack, the top-ranked reasons were wanting to save OD for a severe attack (25.0%), presumption the attack would stay mild (20.0%), and uncertainty of whether the attack was real (20.0%) (eFigure 4).

DISCUSSION

There is broad consensus that on-demand treatment of HAE should be considered for all attacks of angioedema.[10,14,15] Despite this established recommendation, our survey found that one-third of HAE respondents failed to treat their last attack (Figure 1). Among those patients enrolled in the Untreated Cohort, the primary reason for omitting OD administration was uncertainty whether the attack was real followed by the belief that the attack would remain mild. In contrast to patient expectations, however, our survey data indicated that attacks often evolve. Half of the untreated respondents who initially rated their attacks as mild experienced a progression in severity. Further, 25% of

the untreated attacks spread to involve additional sites including the larynx and face. The mean untreated attack duration was 2.3 days, as opposed to 0.7 days for individuals who administered OD in <1 hour. Taken together, electing to withhold OD may prolong attack duration, augment morbidity, and potentially, increase the risk of mortality for patients with HAE.

Global guidelines uniformly emphasize the importance of early treatment for HAE attacks.[10,14,15] In our study, 67.0% of the Treatment Cohort reported their last attack was treated early. Despite this perception, only 25.4% used OD <1 hour (Figure 3A). The mean time to treatment was 3.2 hours for adults and 7.7 hours for adolescents. Time to OD intervals were positively correlated with the duration of attacks. Individuals treating within <1 hour reported a mean of 0.7 days, whereas those treating in ≥8 hours required 2.7 days for attack resolution (eFigure 1B). Progression in attack severity also paralleled the length of treatment delay (Figure 4A). Overall, the consequences of lengthened time to treatment include increased severity and duration of attacks.

Treatment-related anxiety was characterized as extreme for half of the adolescents and nearly a third of participating adults. The presence and degree of anxiety had a significant influence on treatment delay, with 30.0% of patients identifying as not anxious administering OD in <1 hour versus only 12.1% of patients identifying as extremely anxious falling within this time frame (Figure 5B). The underlying reasons highlight substantial remaining unmet needs for OD. For adolescents, fear that they would be unable to find a vein; lack of confidence that the therapy would work; and the anticipation of burning, pain, or side effects with the injection were the most common concerns. For adults, the basis differed, with treatment anxiety centered on availability

issues as reflected by fear of running out of or wasting their OD on a “mild” or “not real” attack. Efficacy concerns were also prominent for adults, with uncertainty surrounding how long the treatment would take to begin working and whether the treatment would work at all. As was the case with 25.0% of adolescents, the anticipation of burning or pain with the injection was a source of anxiety for 19.4% of adults (Table 3). The finding that burning or pain with injection was the most common severe side effect (44.2% of the study patients) provides support for the validity of patient injection-related treatment anxiety (eTable 3).

Outcomes from our study reveal that the real-world management of HAE attacks remains suboptimal. Inadequate adherence to OD expert recommendations is evident in patient-recorded treatment patterns. Despite most HAE respondents reporting early treatment of attacks, their perception appeared inaccurate in more than 70% of cases. This disparity raises questions about whether physician communication or patient comprehension of the treatment guidelines are satisfactory. The elapsed recorded time until OD administration averaged several hours for both adults and adolescents. Consequences of expanded time to treatment intervals beyond 1 hour included enhanced morbidity with progression in severity, additional site involvement, and duration of attacks. Availability, efficacy, administration, and side-effect concerns presented significant treatment barriers contributing to delay for most patients. This was particularly striking within the adolescent cohort for whom the mean time to treatment was more than 7 hours. Fifty-eight percent of adolescents were fearful that they would be unable to find a vein to administer their OD, and half expressed uncertainty that the drug would work. These results emphasize the inadequacy of our current HAE

treatment landscape in which the only approved ODs for adolescents and children require intravenous administration.

Strengths of our study include capturing real-world utilization data for OD, influence of the timing of treatment on attack morbidity, and barriers to administration for patients with HAE. Weaknesses include the retrospective design, potential recall bias, and small sample size for the Untreated Cohort.

Conclusion

There is a significant disparity between patient perception of early treatment and the reported time to treatment. Treatment-related anxiety, a factor influencing nearly half of the patients, was directly related to treatment delay. Identified barriers surrounding OD included availability, efficacy, drug delivery, and side-effect concerns. The consequences of lengthening time to treatment intervals included increased attack severity and duration. Our findings suggest that OD management of attacks remains suboptimal thereby adding to the burden of disease for individuals with HAE.

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FIGURE LEGENDS

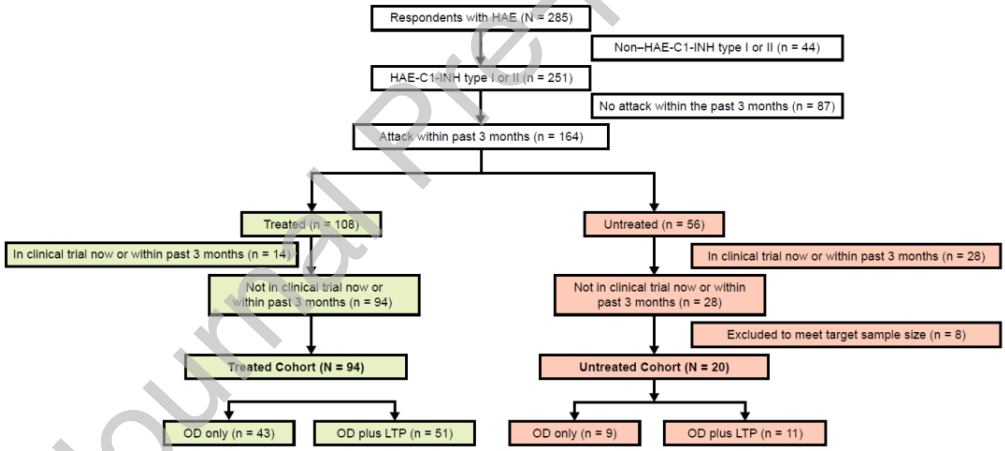
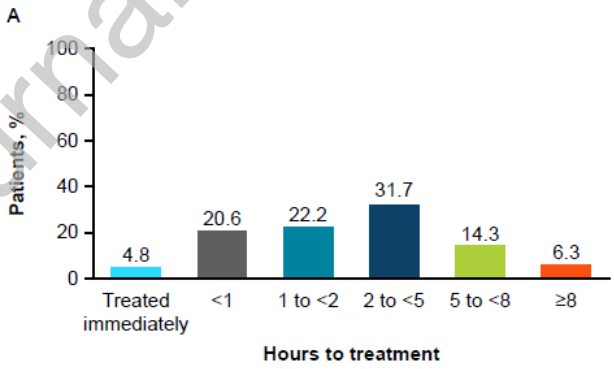


Figure 1. Patient flow diagram. Abbreviations: HAE, hereditary angioedema; HAE–C1-INH, hereditary angioedema C1 inhibitor; LTP, long-term prophylaxis; OD, on-demand treatment.

Figure 2. (A) Time to treatment and (B) time to treatment by attack location.

Note: Values <5% are not labeled. Abbreviations: IQR, interquartile range; LTP, long-term prophylaxis; max, maximum; min, minimum; OD, on-demand treatment.



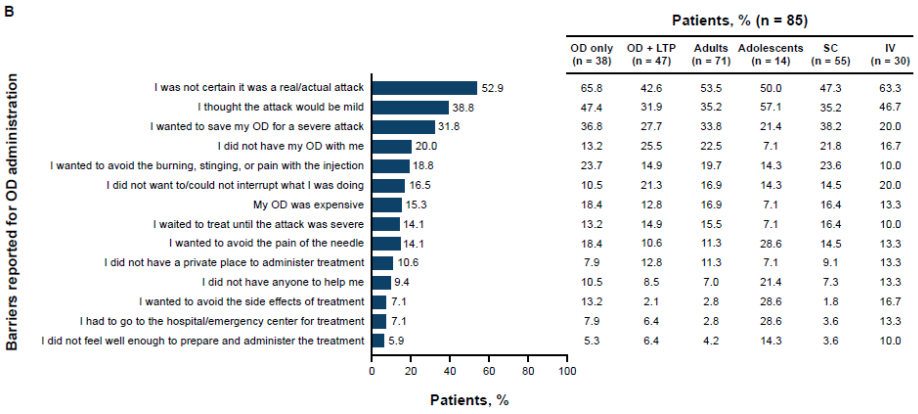
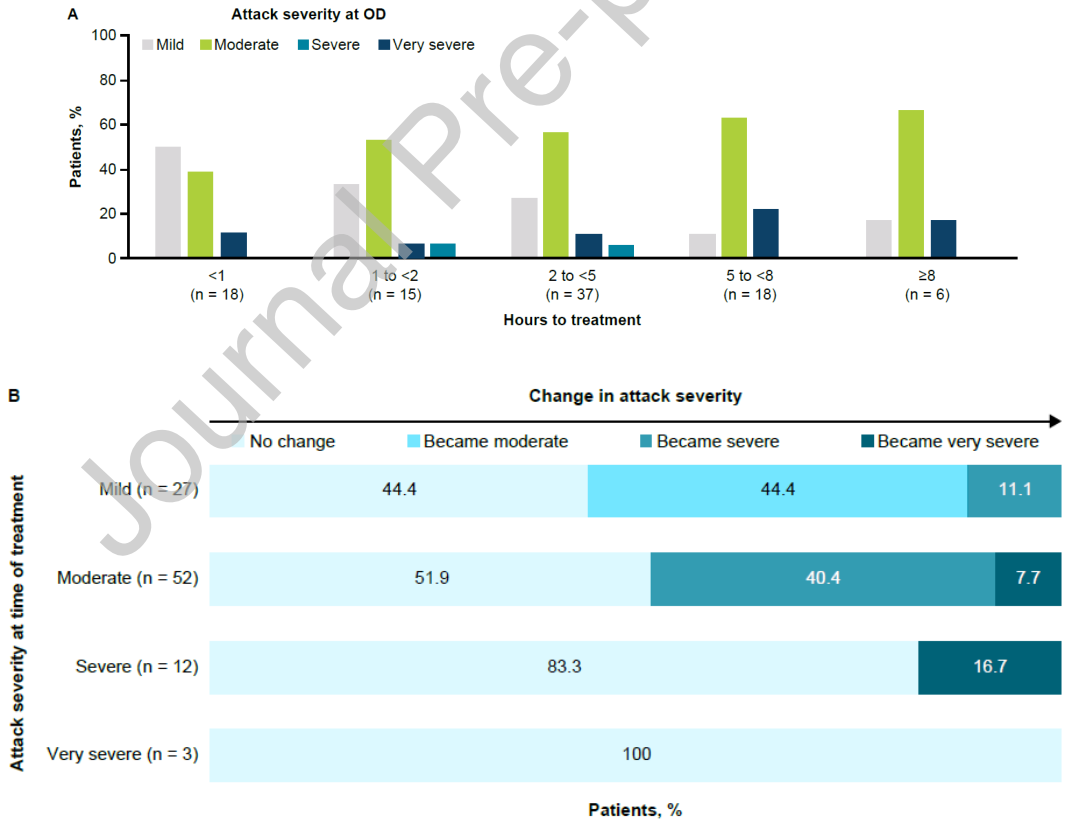


Figure 3. (A) Time to treatment for patients who perceived they treated their attack early (n = 63) and (B) barriers reported for OD administration (n = 85). Abbreviations: IV, intravenous; LTP, long-term prophylaxis; OD, on-demand treatment; SC, subcutaneous.



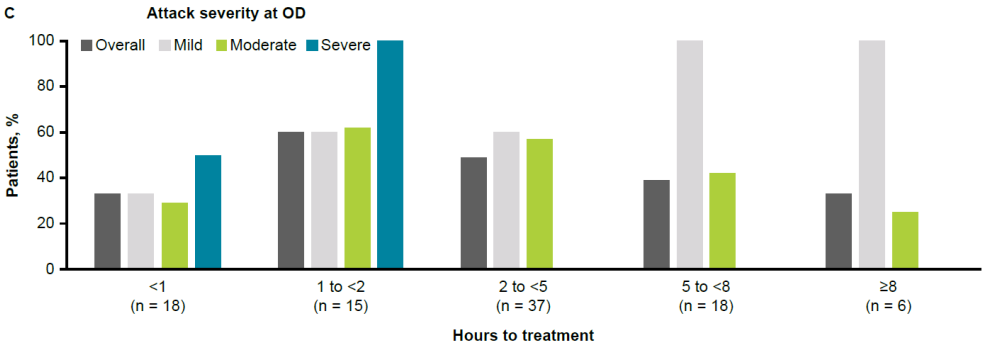


Figure 4. (A) Relationship between time to treatment and attack severity, (B) change in attack severity and progression after treatment, and (C) change in attack severity by time to treatment. Note: Values less <5% are not labeled. Abbreviations: OD, on-demand treatment.

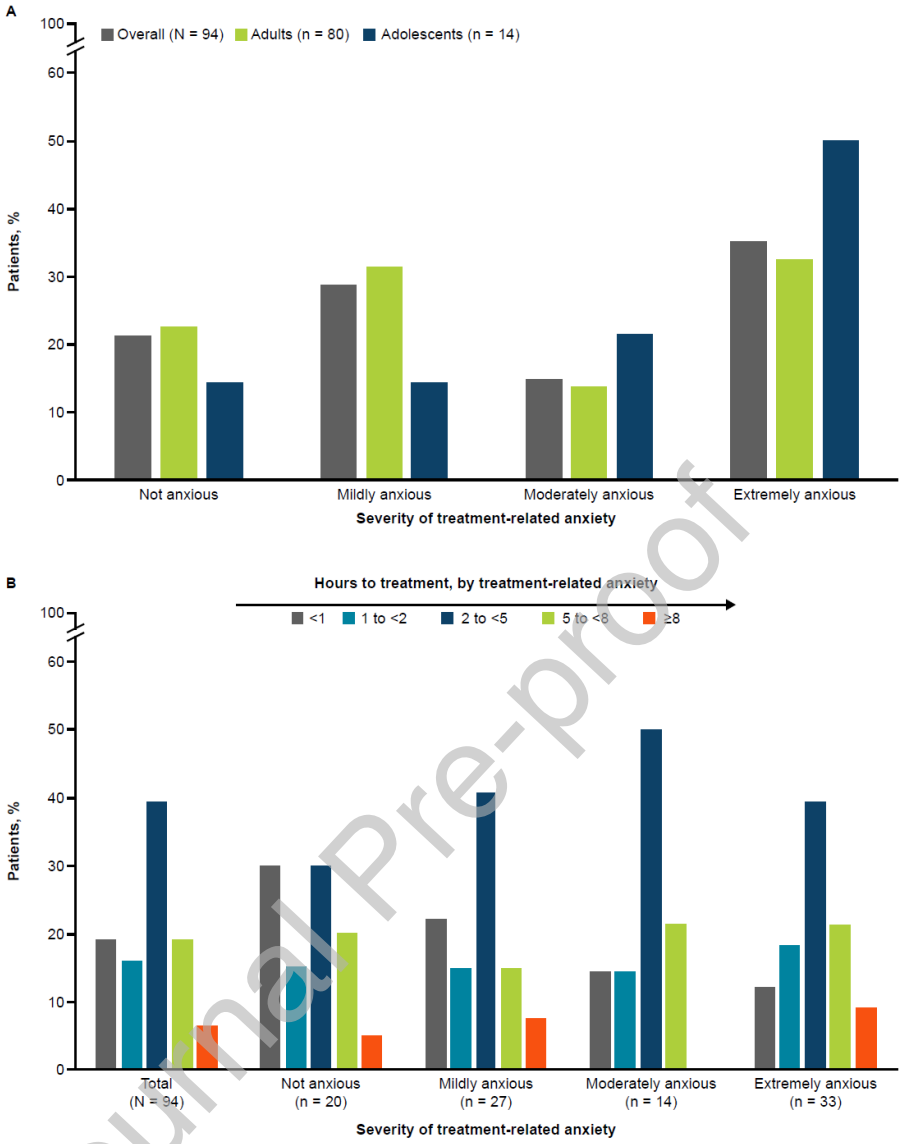


Figure 5. (A) Treatment-related anxiety among adults and adolescents and (B) relationship between treatment-related anxiety and time to treatment.

Table 1. (A) Respondent characteristics and (B) characterization of attacks over the past 12 months.

A.

Respondent characteristics	Treated Cohort					Untreated Cohort		
	Total (N = 94)	**OD only (n = 43; 46%)**	**OD + LTP (n = 51; 54%)**	**Adults (n = 80; 85%)**	**Adolescents (n = 14; 15%)**	**Total (N = 20)**	**OD only (n = 9; 45%)**	**OD + LTP (n = 11; 55%)**
Current age, mean (SD), y	39.4 (17.4)	42.6 (18.7)	36.7 (15.8)	43.8 (15.0)	14.4 (1.5)	38.5 (14.6)	45.1 (14.2)	33.1 (13.1)
Age at diagnosis, mean (SD), y	18.0 (12.6)	19.0 (12.7)	17.2 (12.5)	20.0 (12.5)	6.4 (4.1)	19.5 (14.1)	23.6 (18.1)	16.1 (9.4)
Sex, n (%)								
Male	26 (27.7)	10 (23.3)	16 (31.4)	17 (21.3)	9 (64.3)	5 (25.0)	3 (33.3)	2 (18.2)
Female	68 (72.3)	33 (76.7)	35 (68.6)	63 (78.8)	5 (35.7)	15 (75.0)	6 (66.7)	9 (81.8)
Race/ethnicity, n (%)								
White	82 (87.2)	39 (90.7)	43 (84.3)	71 (88.8)	11 (78.6)	18 (90.0)	8 (88.9)	10 (90.9)
Hispanic or Latino	8 (8.5)	1 (2.3)	7 (13.7)	6 (7.5)	2 (14.3)	1 (5.0)	1 (11.1)	—
Black/African American	3 (3.2)	1 (2.3)	2 (3.9)	2 (2.5)	1 (7.1)	1 (5.0)	—	1 (9.1)
American Indian or Alaskan Native	2 (2.1)	1 (2.3)	1 (2.0)	—	2 (14.3)	2 (10.0)	1 (11.1)	1 (9.1)
Asian	3 (3.2)	2 (4.7)	1 (2.0)	3 (3.8)	—	1 (5.0)	—	1 (9.1)
Other	6 (1.1)	—	1 (2.0)	1 (1.3)	—	—	—	—
HAE type, n (%)								
Type I	76 (80.9)	34 (79.1)	42 (82.4)	65 (81.3)	11 (78.6)	16 (80.0)	8 (88.9)	8 (72.7)
Type II	18 (19.1)	9 (20.9)	9 (17.6)	15 (18.8)	3 (21.4)	4 (20.0)	1 (11.1)	3 (27.3)
Comorbidities, n (%)								
Anxiety	28 (29.8)	11 (25.6)	17 (33.3)	23 (28.8)	5 (35.7)	6 (30.0)	2 (22.2)	4 (36.4)

Depression	23 (24.7)	10 (23.3)	13 (25.5)	21 (26.3)	2 (14.3)	2 (10.0)	1 (11.1)	1 (9.1)
Asthma	16 (17.0)	9 (20.9)	7 (13.7)	12 (15.0)	4 (28.6)	3 (15.0)	1 (11.1)	2 (18.2)
Arthritis	16 (17.0)	6 (14.0)	10 (19.6)	16 (20.0)	—	3 (15.0)	1 (11.1)	2 (18.2)
Obesity	15 (16.0)	5 (11.6)	10 (19.6)	15 (18.8)	—	6 (30.0)	5 (33.3)	3 (27.3)

B.

Characterization of attacks over the past 12 months	**Treated Cohort**					**Untreated Cohort**		
	Total (N = 94)	**OD only (n = 43; 46%)**	**OD + LTP (n = 51; 54%)**	**Adults (n = 80; 85%)**	**Adolescents (n = 14; 15%)**	**Total (N = 20)**	**OD only (n = 9; 45%)**	**OD + LTP (n = 11; 55%)**
Attack frequency, n (%)								
1–5	40 (42.5)	17 (39.5)	23 (45.1)	32 (40.0)	8 (57.1)	11 (55.0)	4(44.4)	7 (63.6)
6–10	22 (23.4)	12 (27.9)	10 (19.6)	19 (23.8)	3 (21.4)	4 (20.0)	2 (22.2)	2 (18.2)
11–15	15 (15.9)	6 (14.0)	9 (17.6)	13 (16.3)	2 (14.3)	2 (10.0)	1 (11.1)	1 (9.1)
16–20	6 (6.3)	3 (7.0)	3 (5.9)	5 (6.3)	1 (7.1)	1 (5.0)	1 (11.1)	—
≥21	11 (11.7)	5 (11.6)	6 (11.8)	11 (13.8)	—	2 (10.0)	1 (11.1)	1 (9.1)
Use of emergency services or hospitalizations for attacks over the past 12 mo, n (%)	21 (22.3)	9 (20.9)	12 (23.5)	13 (16.3)	8 (57.1)	3 (15.0)	1 (11.1)	2 (18.2)
Self-administration of OD, n (%)	82 (87.2)	37 (86.0)	45 (88.2)	73 (91.3)	9 (64.3)	11 (55.0)	3 (33.3)	8 (72.7)

Abbreviations: LTP, long-term prophylaxis; OD, on-demand treatment; SD, standard deviation.

Table 2: Characteristics of last attack

Last attack characteristics	Treated Cohort					Untreated Cohort		
	Total (N = 94)	**OD only (n = 43; 46%)**	**OD + LTP (n = 51; 54%)**	**Adults (n = 80; 85%)**	**Adolescents (n = 14; 15%)**	**Total (N = 20)**	**OD only (n = 9; 45%)**	**OD + LTP (n = 11; 55%)**
Days since last attack								
Mean (SD)	21.1 (18.6)	21.5 (21.1)	20.8 (16.5)	20.7 (18.3)	23.4 (20.8)	29.4 (24.1)	18.6 (17.4)	38.3 (25.9)
Median (IQR)	14.0 (7.0–28.0)	14 .0 (7.0–28.0)	21.0 (7.0–28.0)	14.0 (7.0–28.0)	17.5 (14.0–28.0)	25.0 (7.0–45.0)	14.0 (7.0–21.0)	21.0 (7.0–45.0)
Days since last attack, n (%)								
≤ 30	86 (91.5)	38 (88.4)	48 (94.1)	73 (91.3)	13 (92.9)	15 (75.0)	8 (88.9)	7 (63.6)
31–60	5 (5.3)	3 (7.0)	2 (3.9)	5 (6.3)	—	4 (20.0)	1 (11.1)	3 (27.3)
61–90	3 (3.2)	2 (4.7)	1 (2.0)	2 (2.5)	1 (7.1)	1 (5.0)	—	1 (9.1)
Initial attack site, n (%)								
Abdominal/stomach	56 (59.6)	27 (62.8)	29 (56.9)	46 (57.5)	10 (71.4)	4 (20.0)	1 (11.1)	3 (27.3)
Peripheral (eg, hands, legs, feet, etc.)	20 (21.3)	9 (20.9)	11 (21.6)	18 (22.5)	2 (14.3)	11 (55.0)	7 (77.8)	4 (36.4)
Face	7 (7.4)	3 (7.0)	4 (7.8)	6 (7.5)	1 (7.1)	3 (15.0)	1 (11.1)	2 (18.2)
Throat	6 (6.4)	3 (7.0)	3 (5.9)	5 (6.3)	1 (7.1)	1 (5.0)	—	1 (9.1)
Genitals	3 (3.2)	—	3 (5.9)	3 (3.8)	—	—	—	—
Tongue	2 (2.1)	1 (2.3)	1 (2.0)	2 (2.5)	—	—	—	—
Other	—	—	—	—	—	1 (5.0)	—	1 (9.1)
Attack severity, n (%)	**At time of treatment**					**At attack onset**		
Mild	27 (28.7)	12 (27.9)	15 (29.4)	26 (32.5)	1 (7.1)	14 (70.0)	7 (77.8)	7 (63.6)
Moderate	52 (55.3)	27 (62.8)	25 (49.0)	45 (56.3)	7 (50.1)	5 (25.0)	1 (11.1)	4 (36.4)
Severe	12 (12.8)	3 (7.0)	9 (17.6)	7 (8.8)	5 (35.7)	1 (5.0)	1 (11.1)	—
Very severe	3 (3.2)	1 (2.3)	2 (3.9)	2 (2.5)	1 (7.1)	—	—	—
Emergency visit/hospitalization for last treated attack, n (%)	8 (8.5)	4 (9.3)	4 (7.8)	4 (5.0)	4 (28.6)	N/A	N/A	N/A

Abbreviations: IQR, interquartile range; LTP, long-term prophylaxis; N/A, not applicable; OD, on-demand treatment; SD, standard deviation.

Table 3: Reasons for treatment related anxiety (by category)

Patients, %	Overall (N = 74)	Adults (n = 62)	Adolescents (n = 12)	OD SC (n = 47)	OD IV (n = 27)
Treatment: Efficacy related	59.5	59.7	58.3	66.0	48.1
Uncertainty about whether the treatment would work	28.4	24.2	50.0	27.7	29.6
Uncertainty about how long the treatment would take to begin working	23.0	27.4	—	29.8	11.1
Worry about a rebound attack after the first treatment	12.2	14.5	—	17.0	3.7
The need to use a second dose for the same attack	14.9	12.9	25.0	17.0	11.1
Side-effect related	12.2	9.7	25.0	10.6	14.8
Anticipating side effects from the injection	12.2	9.7	25.0	10.6	14.8
Needle/injection	24.3	22.6	33.3	29.8	14.8
I am afraid of needles	5.4	4.8	8.3	6.4	3.7
Anticipating burning or pain with the injection	20.3	19.4	25.0	25.5	11.1
Treatment administration	36.5	27.4	83.3	8.5	85.2
Finding the vein to start the intravenous infusion	17.6	9.7	58.3	2.1	44.4
Finding a private area to administer the treatment	4.1	4.8	—	2.1	7.4
Finding someone to help me administer the treatment	9.5	9.7	8.3	2.1	20.2
The process of preparing my treatment	8.1	6.5	16.7	2.1	18.5
Cost	60.8	69.4	16.7	74.5	37.0
The cost of the OD	18.9	22.6	—	23.4	11.1
Running out of OD if I needed it later	36.5	41.9	8.3	46.8	18.5

Desire not to 'waste' an OD if the attack was less severe than I thought	37.8	43.5	8.3	46.8	22.2
Attack related	17.6	16.1	25.0	17.0	18.5
Uncertainty if the attack would become severe enough to treat	17.6	16.1	25.0	17.0	18.5

Abbreviations: IV, intravenous; OD, on-demand treatment; SC, subcutaneous.

eSUPPLEMENTARY TABLES AND FIGURES

eTable 1. (A) OD and (B) LTP at the time of the last treated attack.

A.

OD	Patients, %				
	Total (N = 94)	**OD only (n = 43)**	**OD + LTP (n = 51)**	**Adults (n = 80)**	**Adolescents (n = 14)**
Icatibant	64.9	62.8	66.7	76.3	N/A[a]
Recombinant C1-INH	18.1	20.9	15.7	12.5	50.0
Plasma derived C1-INH	14.9	14.0	15.7	8.8	50.0
Ecallantide	2.1	2.3	2.0	2.5	0

B.

LTP	Patients, %		
	Total (N = 51)	**Adults (n = 43)**	**Adolescents (n = 8)**
Lanadelumab	56.9	62.8	25.0
SC human C1-INH	23.5	25.6	12.5
Berotralstat	13.7	9.3	37.5
IV human C1-INH	5.9	2.3	25.0

Abbreviations: C1-INH, C1 inhibitor; IV, intravenous; LTP, long-term prophylaxis; N/A, not applicable; OD, on-demand treatment; SC, subcutaneous.

[a]Icatibant is not approved for patients aged <18 years.

eTable 2. Barriers to OD by time to treatment.

Barrier to OD, %	Total (N = 94)	Time to treatment, h				
		<1 (n = 18)	1 to <2 (n = 15)	2 to <5 (n = 37)	5 to <8 (n = 18)	≥8 (n = 6)
Needle/injection pain related	21.3	16.7	6.7	24.3	22.2	50.0
I wanted to avoid the pain of the needle	12.8	11.1	6.7	16.2	5.6	33.3
I wanted to avoid the burning, stinging, or pain with the injection	17.0	16.7	6.7	18.9	22.2	16.7
Side effect related	6.4	—	—	8.1	16.7	—
I wanted to avoid the side effects of treatment	6.4	—	—	8.1	16.7	—
Treatment administration related	41.5	22.2	40.0	56.8	38.9	16.7
I did not have a private place to administer treatment	9.6	—	6.7	13.5	16.7	—
I did not feel well enough to prepare and administer the treatment	5.3	—	6.7	10.8	—	—
I did not have anyone to help me	8.5	5.6	6.7	10.8	5.60	16.7
I did not want to/could not interrupt what I was doing	14.9	11.1	—	18.9	22.2	16.7
I did not have my OD with me	18.1	11.1	26.7	21.6	16.7	—
Attack related	70.2	44.4	66.7	78.4	83.3	66.7
I was not certain it was a real/actual attack	47.9	33.3	60.0	56.8	33.3	50.0
I thought the attack would be mild	35.1	22.2	26.7	37.8	50.0	33.3

I waited to treat until the attack was severe	12.8	5.6	—	21.6	16.7	—
Cost/access related	31.9	11.1	33.3	43.2	33.3	16.7
My OD was expensive	13.8	5.6	26.7	18.9	5.6	—
I wanted to save my OD for a severe attack	28.7	11.1	26.7	37.8	33.3	16.7
Hospital/emergency center related	6.4	—	6.7	5.4	11.1	16.7
I had to go to the hospital /emergency center for treatment	6.4	—	6.7	5.4	11.1	16.7
I had run out of OD to use	—	—	—	—	—	—
Other	10.6	22.2	6.7	5.4	5.6	33.3
I treated this attack immediately at the start of it	9.6	27.8	26.7	—	—	—

Abbreviations: OD, on-demand treatment.

eTable 3. Most severe injection-site side effects among patients who were treated with OD and experienced side effects at the injection site by (A) type of OD and (B) duration of side effect.

A.

Injection-site side effect	Type of OD, %				
	Total (N = 77)	**Icatibant (Firazyr + generic) (n = 57)**	**Plasma-derivedC1-INH (Berinert) (n = 8)**	**Recombinant C1-INH (Ruconest) (n = 10)**	**Ecallantide (Kalbitor) (n = 2)**
Burning, stinging, or pain while injecting the medicine	44.2	50.9	12.5	20.0	100.0
Pain from the needle	19.5	12.3	62.5	30.0	–
Redness	10.4	12.3	12.5	–	–
Itching	10.4	14.0	–	–	–
Bruising	6.5	–	12.5	40.0	–
Swelling	3.9	5.3	–	–	–
Hives	2.6	1.8	–	10.0	–
Hemorrhage	1.3	2	–	–	–
Rash	0	–	–	–	–
Infection	0	–	–	–	–
Other	1.3	1.8	–	–	–

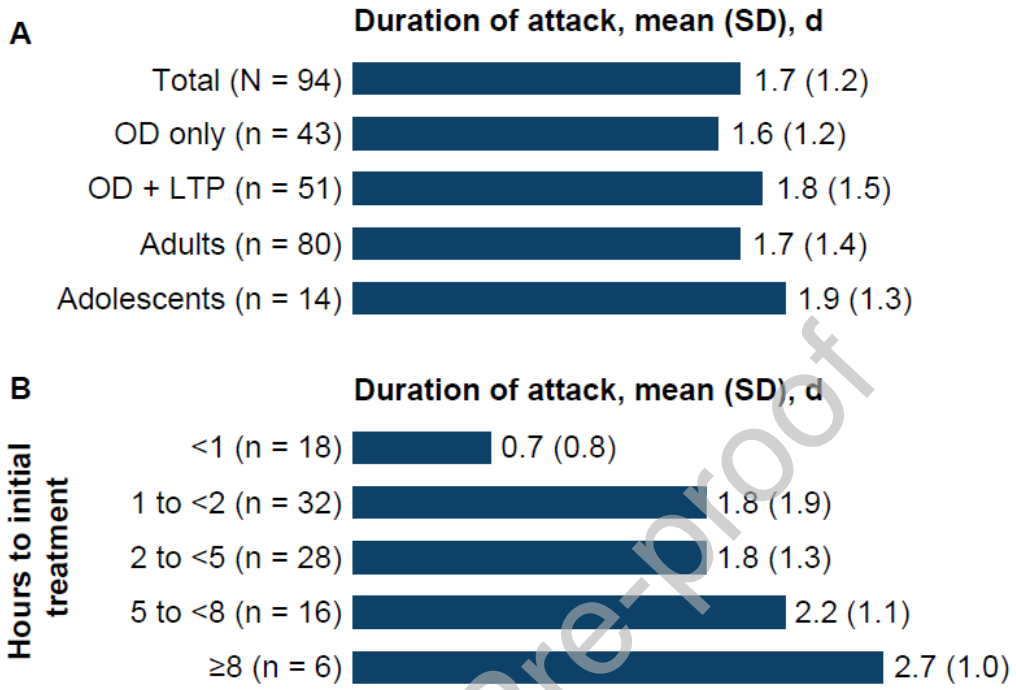
Abbreviations: C1-INH, C1 inhibitor; OD, on-demand treatment.

B.

Injection-site side effect	Patients taking OD, n (%) (N = 77)	Duration of side effect		
		Mean (SD)	Median (IQR)	Minimum, maximum
Burning, stinging or pain while injecting the medicine	34 (44.2)	23.1 (36.9) min	10.0 min (5.0–20.0)	1–180 min
Pain from the needle	15 (19.5)	52.1 (100.0) min	10.0 min (1.0–60.0)	1–360 min
Redness	8 (10.4)	5.4 (7.9) h	2.5 h (1.0–6.0)	0–24 h
Itching	8 (10.4)	4.2 (8.3) h	0.6 h (0.1–4.0)	0–24 h
Bruising	5 (6.5)	2.2 (1.4) d	2.0 d (2.0–3.0)	0–4 d
Swelling	3 (3.9)	17.0 (26.9) h	2.0 h (1.0–48.0)	1–48 h
Hives	2 (2.6)	6.5 (4.9) d	6.5 d (3.0–10.0)	3–10 d
Hemorrhage	1 (1.3)	8.0 (0.0) h	8.0 h (8.0–8.0)	8–8 h
Rash	0	N/A	N/A	N/A
Infection	0	N/A	N/A	N/A
Other	1 (1.3)	4.0 (0.0) h	4.0 h (4.0–4.0)	4–4 h

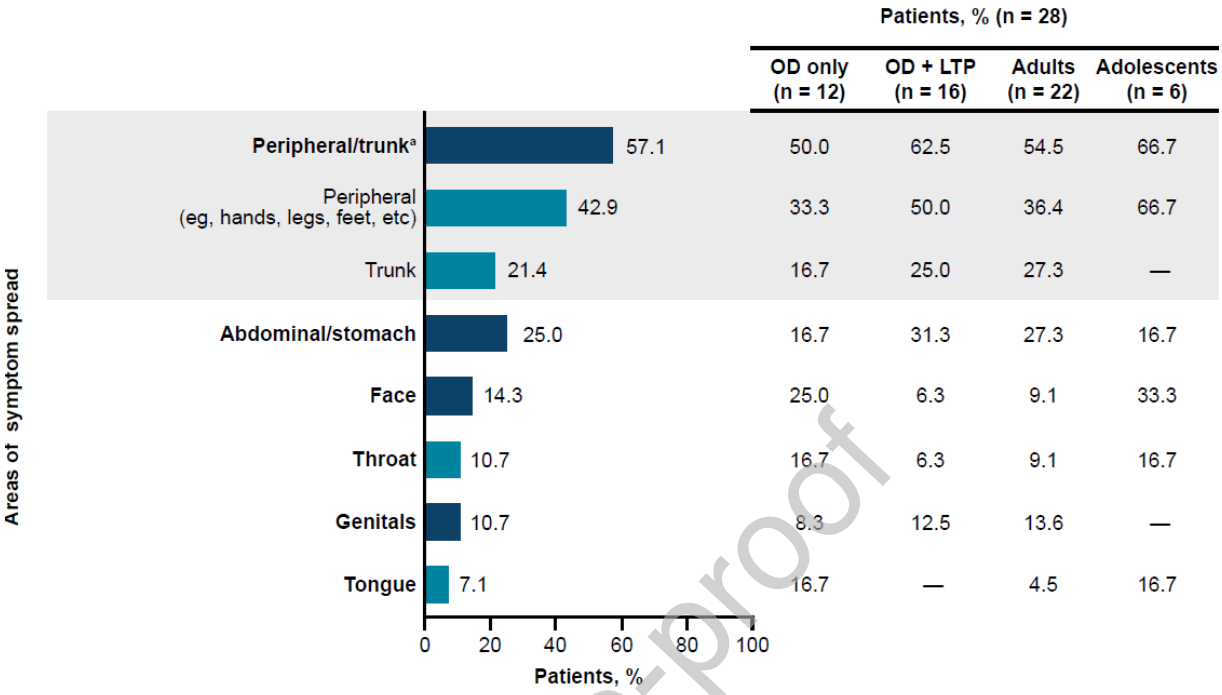
Abbreviations: IQR, interquartile range; N/A, not applicable; OD, on-demand treatment.

eFigure 1. (A) Mean duration of last attack and (B) mean duration of attack by time to treatment.



Abbreviations: LTP, long-term prophylaxis; OD, on-demand treatment.

eFigure 2. Symptom spread for treated attacks. Respondents selected all that apply.

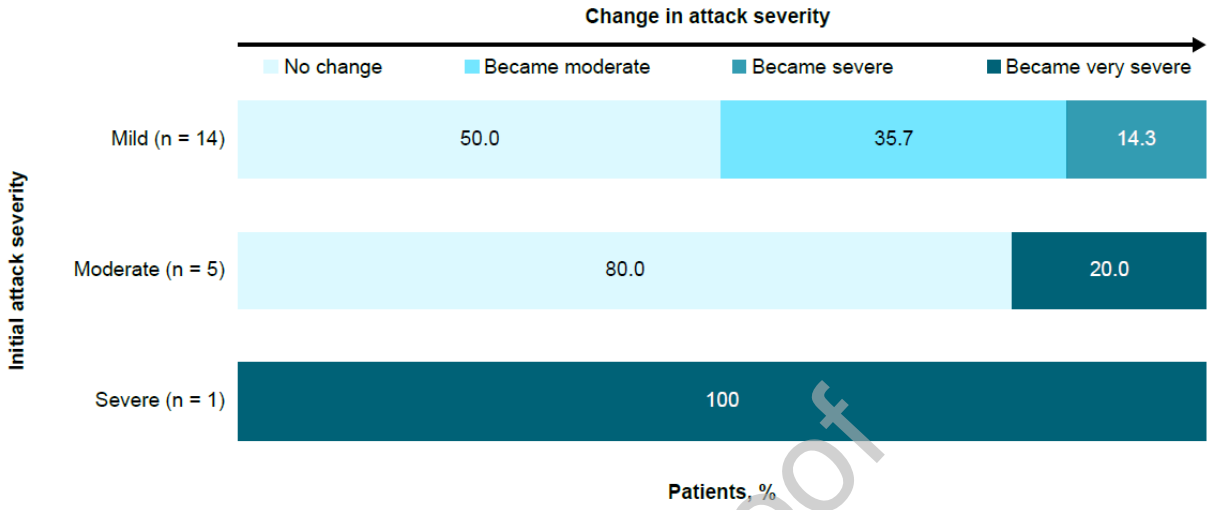


	Patients, % (n = 28)			
	OD only (n = 12)	OD + LTP (n = 16)	Adults (n = 22)	Adolescents (n = 6)
Peripheral/trunk[a]	50.0	62.5	54.5	66.7
Peripheral (eg, hands, legs, feet, etc)	33.3	50.0	36.4	66.7
Trunk	16.7	25.0	27.3	—
Abdominal/stomach	16.7	31.3	27.3	16.7
Face	25.0	6.3	9.1	33.3
Throat	16.7	6.3	9.1	16.7
Genitals	8.3	12.5	13.6	—
Tongue	16.7	—	4.5	16.7

Abbreviations: LTP, long-term prophylaxis; OD, on-demand treatment.

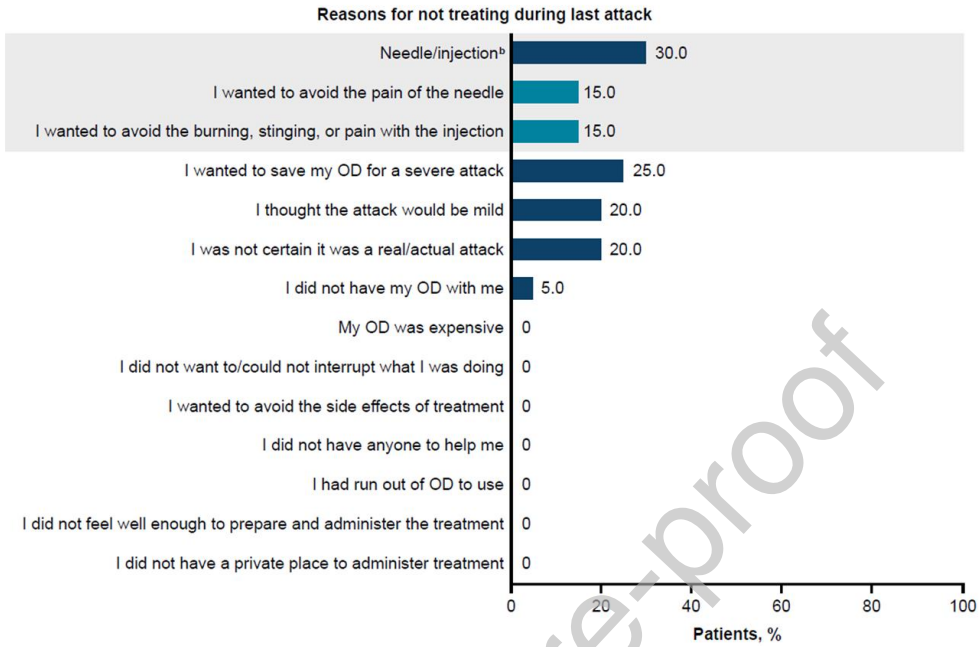
[a]Includes peripheral, trunk, or both.

eFigure 3. Untreated attack severity and progression (n = 20[a]).



[a]Because of small sample size, data should be interpreted with caution.

eFigure 4. Reasons for nontreatment (N = 20[a]).



Abbreviations: OD, on-demand treatment.

[a]Because of small sample size, data should be interpreted with caution.

[b]Combined responses for "I wanted to avoid the pain of the needle" and "I wanted to avoid the burning, stinging, or pain with injection."