Patient perspectives on the treatment burden of injectable medication for hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare, chronic disease characterized by debilitating swelling episodes in various parts of the body. Patients experience significant burdens related to the symptoms and management of HAE, which can affect their daily lives and reduce their overall quality of life. Prophylactic treatment options have expanded in the past decade to the benefit of patients; however, these therapies require scheduled injections, which can be painful, burdensome, and time consuming. We conducted an online survey of patients with HAE in the USA to better understand their experiences with available prophylactic medications and the associated treatment burdens. Our survey results suggest that most patients are satisfied with their current therapies but desire novel medications with a simpler route of administration and that, although most patients experience significant treatment-related burdens, they learn to cope with these challenges over time.

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Hereditary angioedema (HAE) is a rare disease, caused by genetic mutations, that leads to recurrent severe episodes of edema of the extremities, face, gastrointestinal tract, and upper airway, which can be life-threatening.[1–3] Along with the impact on physical health, HAE has a significant impact on the quality of life (QoL) of patients, which affects work, school, and everyday activities.[4–6] HAE attacks can be managed with on-demand treatment (administered immediately after the onset of swelling) and/or with prophylactic treatment (a long-term approach with the aim of decreasing the number and severity of attacks).[7,8]

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New prophylactic medications have become available in recent years, which benefit patients greatly; however, patients still experience significant burdens related to the treatment and management of their disease. For example, learning to self-administer a subcutaneously (SC) delivered therapy can be time consuming and typically requires training, and the self-administration process can be cumbersome.[9,10] In addition, injectable prophylactic HAE treatments are associated with injection-site pain and reactions.[11–13] To better understand the patient experience with current prophylactic HAE treatments and the burdens associated with them, we conducted a survey of patients with HAE in the USA with the aim of identifying unmet treatment needs. Here, we report the results of the survey and describe patient opinions on the advantages and disadvantages of HAE prophylaxis and its impact on their QoL.

METHODS

Study Design and Participants

The patient survey was conducted as part of a series of three blinded online surveys in 2020 that examined the perceptions of HAE-related burdens and treatment preferences from the patient, caregiver, and physician perspectives. The participants were recruited separately, and the surveys were unique to each patient group; however, some questions were asked in parallel across the three surveys to allow for cross-comparison. The surveys were developed in collaboration with HAE experts (C.R., M.R., T.C., A.B.) and included a combination of validated instruments and additional questions that covered a range of topics with regard to

the management of HAE, experiences with disease- and treatment-related tasks, perceived burdens, and treatment preferences. This article describes the responses obtained from the patients.

Before the administration of the survey, the survey instrument was pilot tested with five patients to evaluate its face validity. Minor wording changes to improve clarity and relevance were made to the survey based on feedback from these patients. Participants were eligible for the study if they met the following inclusion criteria: ≥18 years of age, resident of the United States, diagnosis of type I or type II HAE by a health care professional as reported by the patient, and currently receiving HAE prophylaxis (defined as medication taken on a regular schedule to prevent HAE attacks before they start).

Ethical Approval

This study was reviewed by the Western Institutional Review Board and was found to qualify for exempt status.

Data Collection

Eligible participants were invited, by e-mail, to participate in the online survey by an online panel company to which patients had provided permission to be contacted for research purposes. Information about the purpose and nature of the survey was presented to potential participants; only patients who selected "yes" (from "yes/no" options) to indicate consent to participate in the study could enter the screening portion of the survey. Each participant was offered a nominal honorarium for completing the survey. The median length of time taken to complete the online patient survey was 37 minutes. Patients were blinded to the study sponsor and the study sponsor was blinded to the patients.

Measures

The patient survey included 13 screening items, 49 base items that all patients were asked, and 16 additional items with conditional bases. Survey questions covered a range of topics, including patient characteristics, current experience with prophylactic treatment, and perceived benefits of oral prophylaxis. Fully anchored, four-point Likert scales were used to assess agreement (strongly agree, somewhat agree, somewhat disagree, strongly disagree). Responses of somewhat agree and strongly agree were reported as "agree" unless otherwise noted. Other Likert scales, such as 10-point scales, were used to assess survey responses that measured impact, influence, likelihood, and satisfaction.

Two validated questionnaires were included in the survey: The Treatment Burden Questionnaire (TBQ); (Mapi Research Trust, Lyon, France) and the World Health Organization–Five Well-Being Index (WHO-5); (World Health Organisation, Geneva, Switzerland). The TBQ was originally developed to describe the personal treatment burden among patients with various chronic conditions. The questionnaire is composed of 15 general treatment-related items rated on a Likert scale that ranges from 0 (not a problem) to 10 (a large problem), with the scores for each item totaled to range from 0 (no treatment burden) to 150 (maximum treatment burden).[14,15] The WHO-5 is used to assess patients' personal psychological well-being. This questionnaire is composed of five general items that describe personal well-being, rated on a Likert scale from 0 (at no time) to 5 (all of the time).[16] The raw scores for all five items are totaled and then multiplied by 4 to give a final score between 0 (minimum well-being) and 100 (maximum well-being), with a score < 50 considered to represent poor personal well-being.[16]

Data Analysis

All data were anonymized and analyzed in aggregate, and a descriptive statistical analysis of the data was performed. Student's *t*-tests and z-tests were used to assess statistical significance between means and percentages, respectively. Statistics were unweighted and did not take into account demographic variation. Percentile values were rounded to the nearest whole number.

RESULTS

Patient Characteristics

Seventy-five patients completed the survey between May 20 and June 10, 2020. The average age was 44.1 years, 80% of the patients were women, 77% had type I HAE, 85% were treated for their HAE primarily by allergy/immunology health care professionals, and 39% had a caregiver to help them manage their disease. The mean time since the diagnosis of HAE was 24.6 years and the mean duration of HAE treatment was 15.1 years. The patients reported experiencing an average of approximately one attack per month in the 6 months before completing the survey. Patient characteristics are presented in Table 1.

Current and Past Prophylaxis Use

Eighty-four percent of the patients reported currently using SC-administered prophylaxis (n = 63), including 53% who were using lanadelumab and 25% who were using SC-C1-INH (Haegarda; CSL Behring, King of Prussia, PA) (Fig. 1). In addition, 8% reported using IV-administered C1-INH (IV-C1-INH; Cinryze; Takeda, Cambridge, MA) and 4% reported using oral androgens (Fig. 1). Sixty-eight percent of the patients who used lanadelumab and 37% of those who used

Table 1 **Patient characteristics (*N* = 75)**

Characteristic	Result
Age, mean, y	44.1
Sex, *n* (%)	
Women	60 (80)
Men	15 (20)
U.S. region, *n* (%)	
South	32 (43)
Midwest	14 (19)
Northeast	17 (23)
West	12 (16)
Time since diagnosis, mean, y	24.6
HAE type, *n* (%)	
I	58 (77)
II	17 (23)
No. HAE attacks, mean ± SD	
In the past mo	1.0 ± 1.2
In the past 3 mo	3.2 ± 3.5
In the past 6 mo	6.1 ± 6.3
Duration of treatment for HAE, mean ± SD, y	15.1 ± 12.0
Primary health care professional for HAE treatment, *n* (%)	
Allergy/immunology	64 (85)
Internal medicine	5 (7)
Primary care, general, family practice	3 (4)
Pulmonology	1 (1)
Rheumatology	1 (1)
Other	1 (1)

HAE = hereditary angioedema; SD = standard deviation.

SC-C1-INH had received their current prophylactic treatment for at least 1 year before completing the survey. Most of the patients reported using IV-C1-INH (64%), lanadelumab (61%), or androgens (56%) as prophylactic medication at least once in the past.

Opinions with Regard to Current Prophylaxis

Generally, patients with HAE reported that their current prophylactic treatment had a positive impact on their lives. For example, the patients described decreased attack frequency (53%), improved QoL (37%), and improved mental health (29%) as positive effects associated with their current prophylaxis use. Fifty-four percent of the patients who self-administered prophylactic SC medication reported being satisfied with their current route of administration (as indicated by a rating of ≥8 on a scale from 1 to 10, where 0 indicated "not at all satisfied" and 10 indicated "extremely satisfied"). Patients reported feeling in control (47%), grateful (46%), confident (43%), and relieved (29%) when asked how they felt about their current prophylactic therapy.

Treatment Burden: Impact on Daily Life

Despite most of the patients perceiving a positive impact of HAE prophylaxis, they reported a significant treatment burden with current prophylactic therapies, with the average patient-reported TBQ score being 44.5. The mean patient-reported TBQ score was higher for the patients who received SC-C1-INH prophylaxis (59.9 [*n* = 19]) and patients who received IV-C1-INH prophylaxis (59.5 [*n* = 6]) compared with the patients who received lanadelumab prophylaxis (34.6 [*n* = 40]) (Fig. 2). Forty-four percent of the patients (which included 78% of those who received IV prophylaxis and 39% of those who received SC prophylaxis) reported that HAE treatment had impaired their everyday work and activities at least a little bit. In addition, 23% of the patients (which included 33% of those who received IV prophylaxis and 23% of those who received SC prophylaxis) indicated that they needed to schedule personal and professional obligations around taking their medication.

Treatment Burden: Challenges with Administration of Prophylaxis

The patients reported several challenges associated with storing, preparing, and administering their HAE medication. The patients reported preparation and administration times of ~14 minutes for lanadelumab and 30 minutes for SC-C1-INH has 20% of the patients reported that the administration time of their current prophylactic treatment has a negative impact on their lives. Eighty-four percent of the patients agreed that they would prefer to be able to administer their medication when and where needed, and 43% agreed that it was inconvenient to store or prepare their medication (Fig. 3). Moreover, 19% of the patients reported skipping their medication because their injections or infusions were inconvenient.

The patients also found needles (73%) and injections or infusions (68%) to be unpleasant, and many reported that they are tired of their injections or infusions (58%) or that their veins are bad, which make injections or infusions difficult (54%) (Fig. 3). In addition, more than half of the patients (51%) reported experiencing injection-site reactions or discomfort from administering medication, with a fourth of the patients reporting that the adverse effects of their medication interfered with their QoL. Sixty-one percent of the patients reported discussing challenges of prophylaxis administration with their physician; most of these (59%) found this conversation extremely helpful.

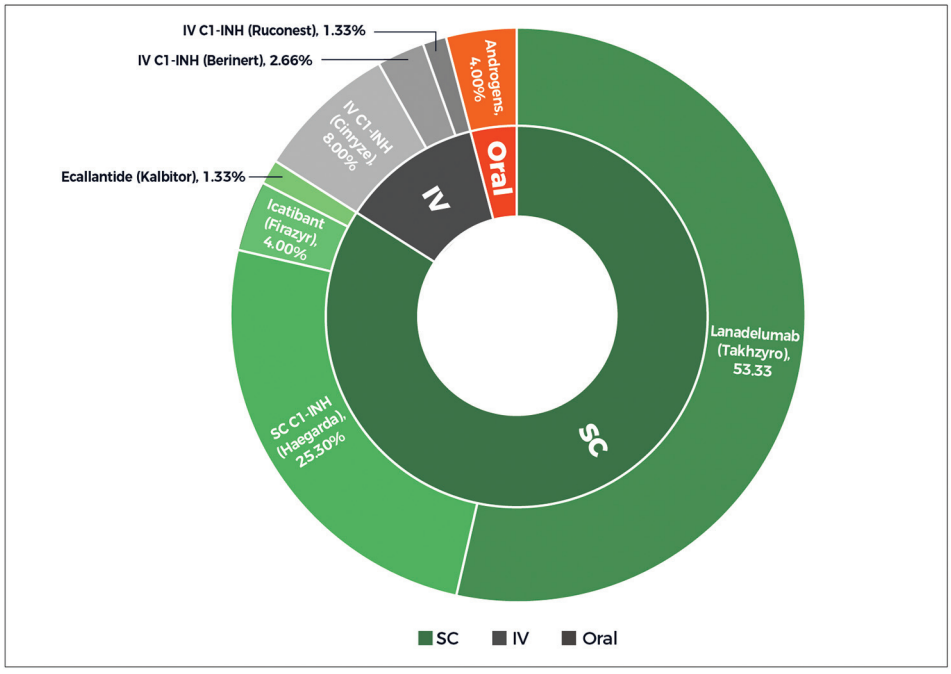

Figure 1. *Patient-reported prophylaxis use (N = 75). Therapies were categorized by route of administration: SC, IV, or oral. Some patients received more than one prophylactic medication. Not all medications listed here are approved by the FDA for HAE prophylaxis. SC = subcutaneous; IV = intravenous; FDA = U.S. Food and Drug Administration; HAE = hereditary angioedema; C1-INH = C1 esterase inhibitor.*

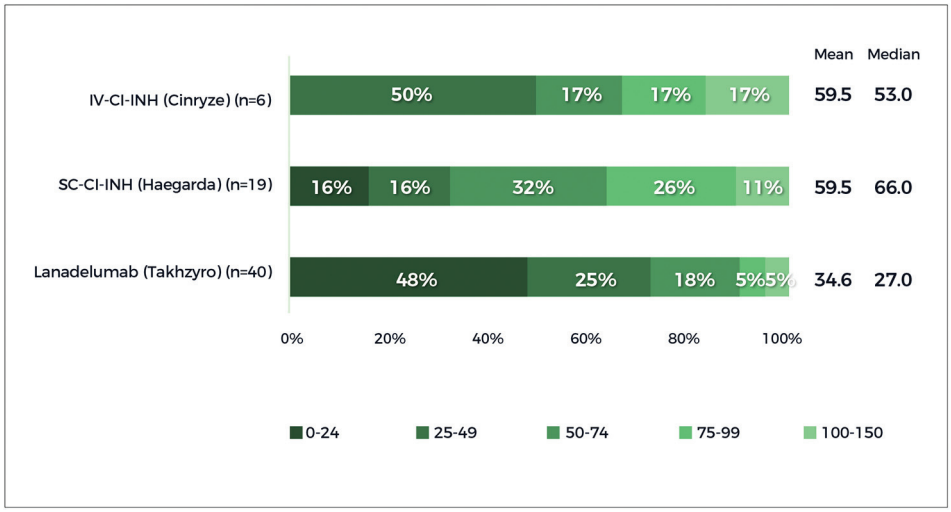

Figure 2. *Patient-reported treatment burden as assessed by the TBQ. TBQ scores reported here are only for the patients who received currently approved therapies for HAE prophylaxis. Due to rounding, the sum of percentages may not equal 100. A score of 0 indicates no treatment burden and 150 indicates maximum treatment burden. TBQ = Treatment Burden Questionnaire; HAE = hereditary angioedema; C1-INH = C1 esterase inhibitor; IV = intravenous; SC = subcutaneous.*

Treatment Burden: Impact on Mental Health

Analysis of additional survey data indicates that the treatment burden associated with prophylaxis may have a negative emotional impact on the patients, particularly when they initiate a new prophylactic medication. The patients reported feeling nervous (47%), overwhelmed (33%), stressed (31%), and intimidated (26%) when starting a new prophylactic medication. Additional responses suggest patients learn to cope with the difficult aspects of their treatment over time. For example, 71% of patients who started their current prophylactic treatment in the past 6 months and only 42% of those who started their medication ≥ 7 months ago reported ongoing anxiety about taking their HAE medication (Fig. 4).

Ninety-four percent of patients who had initiated their current prophylactic treatment in the past 6 months and 71% of those who had initiated their medication ≥ 7 months ago said they tried not to think about the demanding nature of their HAE treatment. Sixty-nine percent of patients who had initiated their current prophylactic treatment in the past 6 months and 55% of those who had initiated their medication ≥ 7 months ago reported tiring of injections or infusions. In addition, most patients (including 65% who had started their current treatment in the past 6 months and 96% who

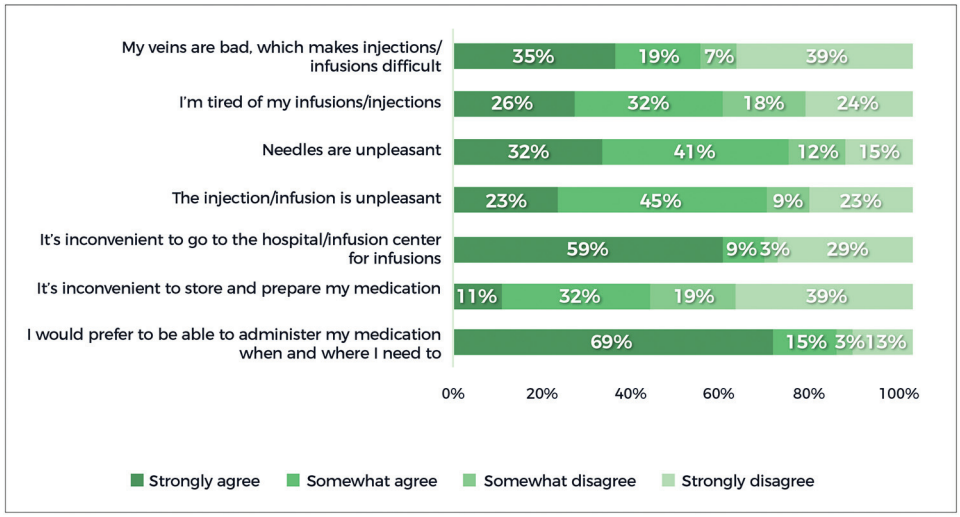

Figure 3. *Patient-reported challenges with prophylaxis. Base values vary; responses of "not applicable" and "not sure" have been excluded.*

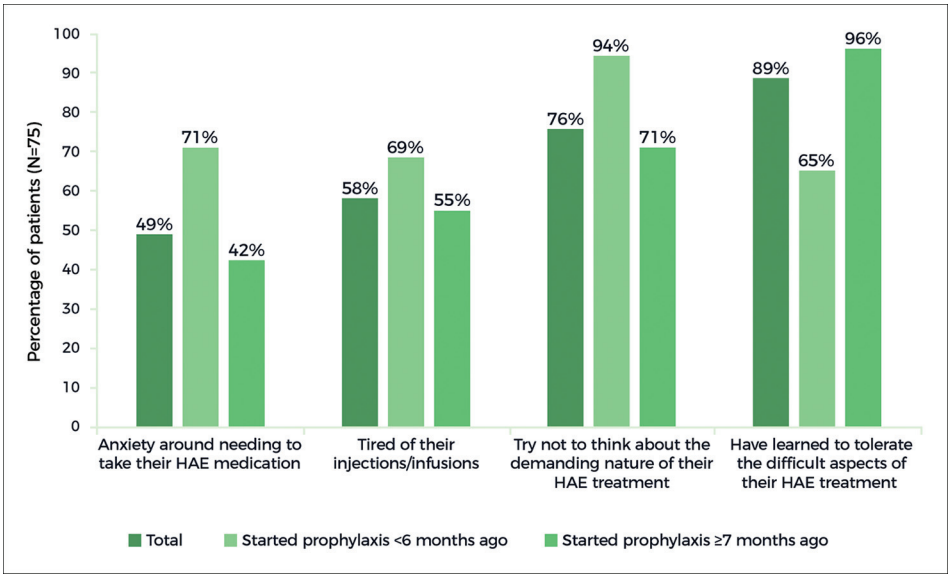

Figure 4. *Psychological impact of treatment burden on the patients with HAE. Base values vary; responses of "not applicable" and "not sure" have been excluded. HAE = hereditary angioedema.*

had started their medication ≥ 7 months ago) agreed that they had learned to tolerate the difficult aspects of their HAE treatment.

Unmet Needs

Although most patients reported being satisfied with their current prophylactic treatment and learned to cope with its challenges, many agreed that there is a need for new HAE treatments. Specifically, 86% of the patients reported that they were satisfied with their current treatment but would still be interested in a medication that is easier to administer and 61% wished they could treat their HAE more discreetly.

DISCUSSION

Most patients in this survey reported being satisfied with their current HAE treatment, citing decreased attack frequency, improved QoL, and improved mental health as the main positive impacts that prophylaxis has had on their lives. This concurs with a 2015 survey of 143 patients with HAE, in which 39% of the patients reported being "very satisfied" and 22% of the patients reported being "moderately satisfied" with current prophylactic treatments.[17] Despite the high level of treatment satisfaction identified in our study, most patients surveyed would have prefered a treatment that is more discreet and easier to administer. These preferences were also reported in another patient survey study published in 2018, which found that, of 38 patients with type I or type II HAE, 50% reported that they would prefer a non-invasive method of administration, with 24% stating a preference for an oral treatment.[18]

Although prophylaxis has reduced the HAE disease burden, the survey data from patients with HAE

reported here demonstrate a substantial burden of treatment, with the average patient-reported TBQ score being 44.5. To put this score into context, a U.S.-based study found that older adults with chronic multi-morbidities who received post-acute care and transitioning from skilled nursing facilities to a home setting reported an average score of 37 on the TBQ.[19] The mean TBQ score for patients who received SC-C1-INH and patients who received IV-C1-INH was > 59, which may be an indication that these patients are at risk of becoming overwhelmed by their medical care.[20]

Patient-reported challenges of prophylactic treatment included the inconvenient and time-consuming nature of medication storage, and the preparation and administration of treatment, which interfered with work and other daily activities. This is consistent with a 2017 survey in the United States of 445 patients with HAE (most of whom had received or were receiving long-term prophylaxis), in which interference in work activities was identified: mean ± standard deviation percentage impairments were 5.9% ± 14.1% for absenteeism, 23.0% ± 25.8% for presenteeism, 25.4% ± 28.1% for work productivity loss, and 31.8% ± 29.7% for activity impairment.[1]

Injection- or infusion-related difficulties were also reported as being a significant challenge by the patients, with the majority finding needles and infusions unpleasant, and more than half reporting that they were tired of their injections or infusions or that their veins were bad. These findings are similar to results from a 2015 survey of 50 patients with HAE who received acute or prophylactic IV treatment, in which 62% of the patients who used a peripheral vein to administer treatment reported having difficulty finding a usable vein or getting the infusion to work properly at least some of the time.[11] Furthermore, injection-site reactions are the most common adverse event associated with SC HAE prophylaxis medications lanadelumab and SC-C1-INH.[16,17]

Our findings also suggest that the treatment burden associated with both IV and SC prophylaxis has an adverse emotional impact on patients, who report both feeling overwhelmed when starting prophylaxis and experiencing ongoing anxiety about taking their medication. The aforementioned 2017 survey of 445 patients with HAE found that 49.9% of the patients experienced anxiety and 24.0% had depression, as per the Hospital Anxiety and Depression Scale.[1] These findings may reflect the impact of HAE as a chronic, unpredictable, and life-threatening condition.

Our findings suggest that patients with HAE are often resilient and may learn to cope with the demanding nature of their HAE treatment, likely because of the positive impact that prophylactic medication has had on their lives. Although many patients discussed the challenges of their treatment with their physician, only slightly more than half of them found this conversation helpful. Most patients reported seeing an allergy/immunology specialist for their HAE medical care; however, experience in managing HAE is highly variable among specialists, which may lead to substantial inter-patient differences in treatment discussions.[21] These findings suggest that improvements in patient–physician dialog may be necessary to promote shared decision-making in HAE management. The development and utilization of HAE shared decision-making aids that describe treatment choices may facilitate these discussions, promoting patient knowledge and empowerment, which can translate to improved adherence.[22,23]

Study Limitations

Limitations common across patient, caregiver, and physician surveys are reported in Banerji *et al*.[24] In addition to those limitations, patient patients were predominantly women, despite HAE being an autosomal dominant condition that affects females and males in approximately equal numbers. The sample size of the patients who responded to the survey was small (N = 75), particularly for the subpopulations (SC [n = 63], IV [n = 9], and oral [n = 3] prophylaxis), which resulted in a lack of statistically significant outcomes.

CONCLUSION

These survey results highlight the unmet need for HAE therapies that are easier to administer than current treatments and the importance of understanding the treatment burden as perceived by the patient to better manage a chronic, lifelong disease such as HAE. As new therapies become available for patients, the burden of treatment associated with each medication, along with efficacy, safety, and tolerability, should be considered when choosing a therapy. Shared decision-making and an individualized approach to HAE management should be promoted by addressing the risks and benefits of different treatments for each patient to improve his or her overall health and QoL.

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REFERENCES

1. Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol. 2020; 124:600–607.
2. Johnston DT. Diagnosis and management of hereditary angioedema. J Am Osteopath Assoc. 2011; 111:28–36.
3. Bork K, Meng G, Staubach P, et al. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006; 119:267–274.
4. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality

of life, productivity, and depression. Allergy Asthma Proc. 2010; 31:407–414.
5. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. Patient Prefer Adherence. 2016; 10:1699–1707.
6. Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. Acta Derm Venereol. 2015; 95:706–710.
7. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021; 9:132–150.e3.
8. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. Br J Hosp Med (Lond). 2019; 80:391–398.
9. Caballero T, Sala-Cunill A, Cancian M, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. Int Arch Allergy Immunol. 2013; 161:10–16.
10. Murphy E, Donahue C, Omert L, et al. Training patients for self-administration of a new subcutaneous C1-inhibitor concentrate for hereditary angioedema. Nurs Open. 2018; 6:126–135.
11. Riedl MA, Banerji A, Busse PJ, et al. Patient satisfaction and experience with intravenously administered C1-inhibitor concentrates in the United States. Ann Allergy Asthma Immunol. 2017; 119:59–64.
12. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA. 2018; 320:2108–2121.
13. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. N Engl J Med. 2017; 376:1131–1140.
14. Tran V-T, Montori VM, Eton DT, et al. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. BMC Med. 2012; 10:68.
15. Tran V-T, Harrington M, Montori VM, et al. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. BMC Med. 2014; 12:109.
16. Topp CW, Østergaard SD, Søndergaard S, et al. The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom. 2015; 84:167–176.
17. Banerji A, Li Y, Busse P, et al. Hereditary angioedema from the patient's perspective: a follow-up patient survey. Allergy Asthma Proc. 2018; 39:212–223.
18. Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: implications for future therapies. Allergy Asthma Proc. 2018; 39:74–80.
19. Schreiner N, Schreiner S, Daly B. The association between chronic condition symptoms and treatment burden in a skilled nursing population. J Gerontol Nurs. 2018; 44:45–52.
20. Tran V-T, Montori VM, Ravaud P. Is my patient overwhelmed?: determining thresholds for acceptable burden of treatment using data from the ComPaRe e-cohort. Mayo Clin Proc. 2020; 95:504–512.
21. Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: follow-up survey of US physicians. Ann Allergy Asthma Immunol. 2020; 126:264–272.
22. Gagné ME, Légaré F, Moisan J, et al. Impact of adding a decision aid to patient education in adults with asthma: a randomized clinical trial. PLoS One. 2017; 12:e0170055.
23. Settipane RA, Bukstein DA, Riedl MA. Hereditary angioedema and shared decision making. Allergy Asthma Proc. 2020; 41 (Suppl 1):S55–S60.
24. Banerji A, Riedl MA, Craig TJ, et al. Insights into the treatment burden of hereditary angioedema in the evolving treatment landscape. Allergy Asthma Proc. 2021; 42(Suppl 1):S1–S3. □