Insights into the treatment burden of hereditary angioedema in the evolving treatment landscape

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Hereditary angioedema (HAE) is a rare genetic disease characterized by unpredictable, recurrent, and potentially life-threatening episodes of cutaneous and submucosal swelling in various parts of the body.[1,2] The estimated prevalence of HAE is ~1:50,000.[3,4] HAE is commonly caused by an inherited (~75% of cases) or *de novo* (~25% of cases) alteration in the *SERPING1* gene, which codes for the serine protease inhibitor C1 esterase inhibitor (C1-INH).[1,3,4] Pathogenic mutations in the *SERPING1* gene cause C1-INH quantitative deficiency (type I HAE) or dysfunction (type II HAE), which results in dysregulation of the kallikrein–kinin cascade, causing uncontrolled vascular permeability and subsequent swelling.[1,2]

HAE symptoms typically manifest during childhood or early adolescence, with the development of recurrent episodes of angioedema in the extremities, face, gastrointestinal tract, or upper airway.[5–7] Untreated HAE attacks usually resolve within 2–5 days but can cause localized pain and gastrointestinal discomfort and can carry a risk of life-threatening asphyxiation if the larynx is involved.[5,6] Clinical presentation is highly variable among patients with HAE, with some experiencing swelling episodes multiple times a week and others experiencing swelling attacks less than once per year.[5,6,8] There are some identifiable triggers for HAE attacks (such as physical trauma or stress), but many episodes occur spontaneously, with varying frequency and severity.[5] HAE symptoms can be debilitating if not well controlled and have a substantial impact on patients' quality of life by interfering with their productivity and daily activities.[9,10] In addition, levels of depression and anxiety are elevated in patients with HAE compared with the average population, potentially because of the unpredictable and life-threatening nature of their disease.[7,11,12]

Although there is no cure for HAE, on-demand therapies can be used to reduce the severity and duration of acute attacks, and prophylactic treatments can be used to reduce the severity and frequency of attacks.[2,13] Historically, prophylactic HAE medications were limited by efficacy concerns (antifibrinolytics) or numerous adverse effects (androgens); however, the HAE prophylactic armamentarium has expanded in recent years to include several treatments with improved safety and efficacy.[2,14,15] Current standard-of-care prophylactic treatment options include two self-administered subcutaneous (SC) treatments: a plasma-derived C1-INH concentrate, Haegarda (CSL Behring, King of Prussia, PA) (SC-C1-INH), and a plasma kallikrein inhibitor, Takhzyro (Takeda, Cambridge, MA) (lanadelumab); also, there is a newly approved oral plasma kallikrein inhibitor, Orladeyo (BioCryst, Durham, NC) (berotralstat).[16–19] These therapies have benefited patients greatly; however, patients can experience substantial burdens related to the management of their disease. For example, learning to self-administer an intravenous or SC therapy often requires training, and the self-administration process itself can be cumbersome.[20,21] In addition, repeated injections can be time-consuming and are associated with injection-site pain/reactions and can cause anxiety for patients who are averse to injections.[22–25] Caregivers and family members can also experience tremendous socioeconomic burdens associated with caring for the patient with HAE, including missing work or leisure

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days to help the patient they care for and absorbing the financial costs of chronic disease management (such as long-term treatment and hospitalizations).[26–28]

As the HAE treatment landscape continues to evolve, it is important to understand how modern prophylactic treatments are used and how they affect patients' and caregivers' quality of life. Personal characteristics, lifestyle, and disease course are unique to each patient; therefore, personalized medicine facilitated by shared decision-making should be the goal of HAE management as more therapies become available. We conducted three independent, corresponding surveys to better understand the patient, caregiver, and physician experiences with managing HAE and to identify factors that impact prophylaxis-associated treatment burden, overall well-being of patients and caregivers, and treatment preferences. The three studies provide valuable insights into the patient (Radojicic *et al.*),[29] caregiver (Craig *et al.*),[30] and physician (Riedl *et al.*)[31] perspectives.

The survey questions covered a range of topics, including respondent characteristics and current experience with prophylactic treatments. Fully anchored, 4-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. A table available in the supplementary material (Supplemental Table 1) provides a list of questions and responses included in the reports, although this is not a comprehensive list of all the questions included in the surveys.

Survey-based studies such as those reported in this supplement are commonly conducted to understand various stakeholder perspectives; however, we recognize that studies of this nature have limitations that should be considered. For example, the respondents included in the study were identified in collaboration with an online panel company to which the respondents had provided permission to be contacted for research purposes. This recruitment method may have introduced selection bias to the study results. In addition, the collected data were from self-reported surveys, which may have introduced responder bias.

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