WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

A narrative review of recent literature of the quality of life in hereditary angioedema patients

Herberto José Chong-Neto

ABSTRACT

Hereditary angioedema (HAE) is a rare disorder that causes unpredictable and debilitating cutaneous and submucosal edema and can lead to death. HAE can impair patients' ability to perform daily activities, proportional to pain severity, with patients reporting lower productivity, missed time from work or school and potentially resulting in missed career and educational opportunities. Many patients with HAE experience a significant psychological burden, including anxiety and depression. Available treatment aims to prevent and/or treat HAE attacks as they occur, to reduce morbidity and mortality and, finally, to improve health-related quality of life. Two different validated specific angioedema instruments are available to assess patients' quality of life. The Angioedema Quality of Life Questionnaire (AE-QoL) examines diagnosed patients' quality of life but is not specific for HAE. The disease-specific questionnaire is the Hereditary Angioedema Quality of Life (HAE-QoL), and the first used for hereditary angioedema with C1 inhibitors (C1-INH) deficiency. These quality-of-life instruments are helpful to the HAE patients' assessment and to the development of better therapeutic strategies as clinical tools, as defined by international guidelines. Considering this context, this review was conducted to compare the effects of acute vs. long-term prophylaxis on HAE patients' health-related quality of life. In addition, the prevalence of anxiety and depression among these individuals was also reviewed.

Keywords: Angioedema, Hereditary, Health-related quality of life, Patient reported outcome measures, Questionnaire, Preventive therapy

INTRODUCTION

Hereditary angioedema (HAE) is a rare, potentially fatal disorder, that causes recurrent swelling of the skin and submucosa.[1,2] The contact activation system mediates the bradykinin release that causes increase in vascular permeability and vasodilation, leading to angioedema. This system is regulated by C1 inhibitors (C1-INH). C1-INH inhibits the activated factor XII (FXIIa) and kallikrein. The production of bradykinin is increased when plasma levels of functional C1-INH are insufficient leading to a sustained activation of FXIIa and kallikrein.[3] HAE has a prevalence estimated at approximately 1:40,000, with literature estimates ranging from 1:10,000 to 1:50,000.[4-6]

There are 2 different HAE types generated by functional C1-INH (HAE-C1-INH) deficiency: 85% of cases are HAE-C1-INH type I, caused by low C1-INH plasma levels, and 15% of cases are type II,

Division of Allergy and Immunology, Complexo Hospital de Clínicas, Federal University of Paraná, Curitiba, Paraná, Brazil; E-mail: hchong@ufpr.br.
Full list of author information is available at the end of the article

which presents with low functional C1-INH activity despite normal plasma levels of this inhibitor.[3]

HAE with C1-INH normal plasma levels (nC1-INH) or with C1-INH deficiency have similar clinical symptoms. Increased blood estrogen levels, as caused by pregnancy or exogenous injection, and gene alterations have been linked to HAE with nC1-INH.[7,8] Five different mutations were identified in HAE-nC1-INH families: four in F12 gene, responsible for protein variations of the coagulation factor XII proline-rich region (HAE–FXII); in the *PLG* gene that encodes plasminogen; in the *ANGPT1* gene that encodes angiopoietin-1; in the *KNG1* gene that encodes kininogen 1; in the *MYOF* gene that encodes for myoferlin and in *HS3ST6* gene that leads to a sulfation functional change of heparan sulfate.[5] However, the genetic defect is unknown in most cases.[7]

The beginning of HAE symptoms usually occurs in patients' childhood or adolescence, increases in puberty, and lasts throughout their lifetime.[9] HAE involves skin, gastrointestinal and respiratory systems. Urticaria or pruritus are not HAE symptoms, but it is possible to occur nonpruritic macular rash that might be mistaken for urticaria.[7] Although resolution of HAE symptoms typically occurs within 3–5 days, if untreated they cause considerable morbidity and mortality.[10]

HAE can affect almost every aspect of a patient's life because it is a chronic, incapacitating, and disfiguring disorder. Before receiving a diagnosis, people with HAE may experience poor treatment and unnecessary medical procedures. Diagnosis is still delayed and about one third of the cases can take more than 10 years.[11,12] HAE attacks are painful, unpredictable, incapacitating, and typically demand immediate medical intervention. Face involvement leads to disfiguration and promotes social stigmatization, isolation, and depression.

HAE can impair the patient's quality of life (QoL) not only due to impact on functional abilities caused by edema, but also due to pain and other frequent attack symptoms including fatigue, nausea, vomiting. The HAE patient's health-related quality of life (HRQoL) is equivalent to other chronic conditions as severe asthma and Crohn's disease.[13] A study conducted in Sweden using

different instruments reported that most affected HRQoL dimensions are pain/discomfort, anxiety/depression, energy/fatigue, general health, fears/shame, and fatigue/mood.[14] In addition, the higher the number of attacks, the higher the impact on patients' HRQoL, highlighting the importance of proper disease management.[15,16]

As HAE is a genetic disease, there is still no treatment directed at the cause of this condition. Thus, therapeutic approach aims to prevent or treat HAE attacks as they occur, to reduce morbidity and mortality and finally to improve HRQoL.[3] The disease management may be composed by on-demand treatment of attacks and prophylactic treatment, depending on different aspects.[10] Despite clinical benefits of the treatment, Nordenfelt et al (2017) found no significant differences in terms of HRQoL among patients receiving or not prophylactic medication.[14] In addition, Bork et al (2021) published a consensus report providing guidelines about the assessment of disease burden and the impact on QoL.[17] This review was conducted to compare the effects of acute vs long-term prophylaxis on HAE patients' health-related quality of life. In addition, the prevalence of anxiety and depression among these individuals was also reviewed.

Methods

A search was conducted using Mesh terms "Quality of Life", "Hereditary Angioedema" in the PUBMED database in December 2021 and recent articles published in English between 2011 and 2021 were selected according to the subjects of interest. An additional search with the objective to identify publications reporting QoL with treatments for acute attacks and long-term prophylaxis was also performed. The studies that evaluated the HRQoL effect of HAE specific treatments were eligible. The long-term prophylaxis treatments of interest were restricted to the kallikrein inhibitors were restricted to berotralstat and lanadelumab. The following sources of information were not included abstracts, conference posters, and secondary sources. In Table 1 and Table 2 general characteristics of these 14 key studies included are shown.

Author, Year	Country	Type of study	Treatment	Follow up	QoL instrument	Results summary

Nunes et al. (2021)[24]	Brazil	NR	Systematic intervention	14 months	HAE-QoL	Mean total HAE-QoL scores differences between baseline and further visits:
						    Increase of 15.2 (95% CrI: 1.23–29.77) at 8 months.
						    Increase of 26 (95% CrI: 14.56–39.02) at 14 months.

Zanichelli et al. (2018)[40]	Italy	Observational	Plasma-derived C1-INH-nf	12 months	HAE-QoL, 6 months recall Italian version, TSQM	Baseline median total HAE-QoL score: 86 (IQR: 76–103).
						HAE-QoL differences between screening/enrollment (visit 1), 3 months (visit 2), 6 months (visit 3), and 12 months (visit 4, end of study):
						    Total: visit 3 vs 1 (6.4 ± 13.5; $p = 0.49$); visit 4 vs 1 (5.4 ± 21.4; $p = 0.59$); visit 4 vs 3 (-1.1 ± 13.4; $p = 0.91$).
						    Physical functioning and health: visit 3 vs 1 (0.7 ± 2.8; $p = 0.67$); visit 4 vs 1 (0.9 ± 3; $p = 0.55$); visit 4 vs 3 (0.2 ± 2.2; $p = 0.90$).
						    Disease related stigma: visit 3 vs 1 (0 ± 2.3); visit 4 vs 1 (0 ± 2.8; $p = 1$); visit 4 vs 3 (0 ± 1.4).
						    Emotional role and social functioning: visit 3 vs 1 (0.1 ± 2.7; $p = 0.71$); visit 4 vs 1 (0.5 ± 2.7; $p = 0.36$);

Author, Year	Country	Type of study	Treatment	Follow up	QoL instrument	Results summary
						visit 4 vs 3 (0.4 ± 1.6; p = 0.69). Concern about offspring: visit 3 vs 1 (1.4 ± 2.3; p = 0.20); visit 4 vs 1 (0.9 ± 3.1; p = 0.59); visit 4 vs 3 (−0.5 ± 2; p = 0.87). Perceived control over illness: visit 3 vs 1 (1.5 ± 2,9; p = 0.32); visit 4 vs 1 (1.9 ± 3.9; p = 0.24); visit 4 vs 3 (0.4 ± 2.9; p = 0.82). Mental health: visit 3 vs 1 (1.8 ± 3.9; p = 0.41); visit 4 vs 1 (0.5 ± 4.7; p = 0.80); visit 4 vs 3 (−1.3 ± 4.4; p = 0.54). Treatment difficulties: visit 3 vs 1 (0.9 ± 4; p = 0.55); visit 4 vs 1 (0.6 ± 5.8; p = 0.75); visit 4 vs 3 (−0.3 ± 4.6; p = 0.89).
Bewtra et al. (2012)[41]	United States	NR	Single injection of C1-INH	29 months	SF-12	Mean SF-12 scores range: 44.8 to 93.2. Mean SF-12 scores range for patients with the greatest number of treated attacks (47–106 attacks per subject): 70.6 to 82.7. Mean (range) SF-12 component scores for 10 quarters: Physical functioning: 51.1 (45.4–53.6). Role physical: 47.1 (41.4–52.6).

Bodily pain: 45.5 (39.6–50.2).
General health: 52.8 (47.4–59.8).
Vitality: 51.2 (46.1–54.5).
Social functioning: 45.5 (39.3–53.2).
Role emotional: 49.8 (44.9–52.9).
Mental health summary score: 49.6 (44.6–54.5).
Physical health: 48.8 (42.7–52.5).

Table 1. Summary of studies assessing the impact of on-demand treatment of attacks on quality of life in HAE patients. C1-INH-nf: nanofiltered C1-INH; CrI: credible interval; HAE-QoL: Hereditary Angioedema Quality of Life; NR: Not reported; QoL: Quality of Life; SF-12: twelve-item short form; TSQM: Treatment Satisfaction Questionnaire for Medication.

Impact on quality of life

Patients with HAE experience a significant physical and psychological burden that impairs health related quality of life. The HAE burden affects not only healthcare services but also the patient's relationships, education, and work.[9,18,19] To provide a proper understanding of such impact and the effects of treatment on health-related quality of life, disease burden is initially reported in this review.

HAE is a disease characterized by unpredictable acute attacks. The impact on QoL comprises psychiatric aspects, social activities, travel, work/school, and hospitalization. The unpredictable character of attacks leads to difficulties for patients, their families, and employers. The number of attacks experienced by a patient over a period correlates with worse scores in several domains of different instruments, such as functioning, fatigue/mood, fears/shame, nutrition, anxiety/depression, and also productivity.[15,16]

Productivity

HAE can lead to a reduction in workplace productivity.[20] Time missed from both work and school is common for patients with HAE and can result in missed opportunities for career and educational advancement and has a major negative economic impact due to productivity lost. Therefore, the condition causes delay in education and increase in stress during and between attacks.[21] The socioeconomic burden overwhelms patients, parents, and caregivers; on average, 20 work or school days are lost per year.[22]

Even with acute treatment available in hospitals in Japan, 21.2% of HAE patients were admitted overnight with a need of hospitalization of at least one day, and 28.7% had been away from work or school in a survey carried out in March–May 2014.[23] A Sweden study showed that 44% of patients were absent from work during an HAE attack, and 81% of severe attacks resulted in absenteeism. Furthermore, 57% of patients suffered attacks at least once a month and HAE had impeded their advance in workplace or school.[14] According to a European Union report considering data from May–December 2011 and a 6-month recall period, 42% of HAE patients have

Author, Year	Country	Type of study	Treatment	Follow up	QoL instrument	Results summary
Buttgereit et al. (2021)[43]	Germany	NR	Lanadelumab, every other week	Median period of 29.9 weeks	AECT and AE-QoL	AE-QoL – before and during treatment mean change (95% CI; p-value): Total score: 32 (22.6–414; p < 0.001). Functioning: 42.4 (30–54.9; p < 0.001). Fatigue/mood: 23 (4.8–13; p < 0.001). Fears/shame: 30.6 (6–18; p < 0.001). Nutrition: 22.73 (7.9–37.6; p = 0.004).
Lumry et al. (2021)[49]	USA	Phase 3	C1-INH(SC) 40 IU/kg (n = 63) or 60 IU/kg (n = 63) twice weekly	52 weeks	EQ-5D-3L, HADS, WPAI, TSQM	EQ-5D – baseline and end of study mean change (95% CI): Health state value: 0.07 (0.01–0.12). Visual analogue scale: 7.45 (3.29–11.62). HADS – baseline and end of study mean change (95% CI): Anxiety scale: −1.23 (−2.08 to −0.38). Depression scale: −0.95 (−1.57 to −0.34). WPAI – baseline and end of study mean change (95% CI): Presenteeism: −23.33% (−34.86 to −11.81) Work productivity loss: −26.68% (−39.92 to −13.44). Activity impairment: −16.14% (−26.36 to −5.91).

						TSQM – baseline and end of study mean change (95% CI): Effectiveness: 19.74 (7.94–31.54). Overall satisfaction: 18.93 (10.68–27.18).
Watt et al. (2021)[46]	–	NR	Rollovers: lanadelumab 300 mg on day 0, then 300 mg every 2 weeks after their first attack (regular dosing stage). Nonrollovers: lanadelumab 300 mg every 2 weeks from day 0.	132 weeks	AE-QoL, TSQM	AE-QoL - day 0 to end of study mean change (SD): Rollovers: total score −10.2 (17.9), functioning −11.1 (24.3), fatigue/mood −7.4 (23.8), fears/shame −12.9 (19.2), nutrition −7.2 (26.1). Nonrollovers: total score −19.5 (21.3), functioning −26.2 (27.7), fatigue/mood −11.6 (25.8), fears/shame −22.2 (24.3), nutrition −18.3 (24.4). Mean TSQM-9 scores Rollovers and nonrollovers: very satisfied with treatment effectiveness (>90), perceived treatment was convenient (>81), very satisfied with lanadelumab (>87).
Wedner et al. (2021)[42]	Europe	Phase 3	Berotralstat 150 mg, 110 mg, or placebo in part 1; berotralstat 150 mg, 110 mg, in part 2.	24 weeks in Part 1; plus 24 weeks in part 2	AE-QoL, TSQM	After 48 weeks, 67% of patients on the berotralstat arm achieved the AE-QoL MCID. TSQM: improvements in global satisfaction in placebo arm patients rerandomized to berotralstat

(continued)

Author, Year	Country	Type of study	Treatment	Follow up	QoL instrument	Results summary
Lumry et al. (2021)[44]	USA	Phase 3	Lanadelumab 150 mg every 4 weeks (q4wks; n = 28), 300 mg q4wks (n = 29), 300 mg every 2 weeks (q2wks; n = 27), or placebo (n = 41)	182 days	AE-QoL, EQ-5D-5L	AE-QoL - day 0–182 mean change (p-value): Lanadelumab total group: total score −19.47 ± 2.02 (p < 0.01), functioning −29.28 ± 2.48 (p < 0.01), fatigue/mood −13.0 ± 2.51 (p < 0.05), fears/shame −18.75 ± 2.58 (p < 0.05), nutrition −17.01 ± 2.42 (p < 0.01). Placebo: total score −4.71 ± 2.91 (p > 0.05), functioning −5.41 ± 3.58 (p > 0.05), fatigue/mood −1.79 ± 3.52 (p > 0.05), fears/shame −9.05 ± 3.74 (p > 0.05), nutrition 0.49 ± 3.50 (p > 0.05). Lanadelumab 300 mg q2wks vs. placebo group: highest proportion (81%; p = 0.001) and 7.2 times more likely to achieve MCID.
Banerji et al. (2018)[45]	USA	Phase 3	Lanadelumab (SC): 150 mg every 4 weeks (n = 28), 300 mg every 4 weeks (n = 29), 300 mg every 2 weeks (n = 27). Placebo (n = 41).	26 weeks	AE-QoL	AE-QoL - Proportion of patients that achieved the MCID in total score: 150-mg every-4-week group: 65.4% (p = 0.047); 300-mg every-4-week group: 63.0% (p = 0.07);

						300-mg every-2-week group: 80.8% (p = 0.001); Placebo: 36.8%.
Aygören-Pürsün et al. (2018)[48]	Germany	Phase 2	Berotralstat: 350 mg, 250 mg, and 125 mg, once daily. This dose could be reduced for 62.5 mg.	28 days	AE-QoL	AE-QoL - least-squares mean change (p-value) from baseline 125-mg dose group: total score: −29.0 placebo group: −4.5 (difference: −24.5 points; p < 0.001) Across the four domains: Functioning: −26.7 points, p = 0.002 Fatigue and mood: −11.6 points, p = 0.054 Fears and shame: −33.8 points, p < 0.001 Food: −24.4 points, p = 0.006.
Lumry et al. (2018)[5044]	Europe	Phase 3	C1-INH(SC) 40 or 60 IU/kg twice weekly	16 weeks preceded or followed by 16 weeks of twice weekly placebo injections	EQ-5D-3L, HADS, WPAI, TSQM	EQ-5D – mean treatment difference at week 14 (95% CI): Health state value: 0.04 (−0.01-0.08). Visual analogue scale: 8.53 (4.10–12.97). HADS – mean treatment difference at week 14 (95% CI): Anxiety scale: −1.05 (−1.79 to −0.31). Depression scale: −0.55 (−1.11- 0.01). WPAI – significant mean treatment difference at week 14 was observed for

(continued)

Author, Year	Country	Type of study	Treatment	Follow up	QoL instrument	Results summary
						presenteeism, work productivity loss and activity impairment domains TSQM – significant mean treatment difference at week 14 was observed for effectiveness and overall satisfaction domains.
Weller et al. (2017)[51]	USA	NR	C1-INH 1000 U with 24,000 U of rHuPH20 or C1-INH 2000 U with 48,000 U of rHuPH20 every 3–4 days	8 weeks and then crossed over for another 8 weeks	AE-QoL	AE-QoL – baseline and last available assessment mean change (95% CI; p-value): Total score: −8.11 (−13.72 to −2.50; p = 0.007). Functioning: −12.80 (−20.87 to −4.73; p = 0.003). Fatigue/mood: −1.95 (−8.66-4.76; p = 0.572). Fears/shame: −10.26 (−17.06 to −3.46; p = 0.005). Nutrition: −7.62 (−13.29 to −1.95; p = 0.012). The 2000 U arm showed higher mean AE-QoL score reductions in the functioning and nutrition domains vs 1000 U arm.
Greve et al. (2016)[52]	Germany	Observational	Wash-in: C1-INHc (1000 UI) Individual prophylactic treatment regimens (n = 7): C1-INHc from 6.67 × 1000 to	Doses and frequency were set up for 12 weeks. After that, the patients continued with	AE-QoL	AE-QoL - paired differences (SD): Functioning: 25.0% (27.7) Fatigue/mood: 10.7% (13.4)

Study	Country					Outcome
Lumry et al. (2014)[5347]	USA	NR	C1-INH-nf (1000 UI) or placebo every 3-4 days	12 weeks and then crossed over for another 12 weeks	SF-36	C1 INH-nf prophylaxis: Significantly better HRQoL than angioedema attack acute treatment.
			13 × 1000 U per month with a mean of 9.7 × 1000 U	this therapy for an additional 6 months		Fears/shame: 37.7% (23.3; p = 0.005) Nutritions: 10.7% (11.2; p = 0.045) Total score: 31.2% (22.9; p = 0.011)

Table 2. (Continued) Summary of studies assessing the impact of prophylactic treatment in quality of life AE-Qol: Angioedema Quality of Life; AECT: angioedema control test; C1-INH: C1-INHibitor; EQ-5D-3L: European Quality of Life-5 Dimensions Questionnaire; HADS: Hospital Anxiety and Depression Scale; NR: Not reported; WPAI: Work Productivity and Activity Impairment Questionnaire; TSQM: Treatment Satisfaction Questionnaire for Medication; rHuPH20: recombinant human hyaluronidase; C1-INH-nf: nano fitered C1-INH; SF-36: thirty-six-item short form; SD: standard deviation.

experienced delayed educational advancement; 40% were restrained from applying for specific jobs; 36% have experienced a reduction in career development; 9% have switched positions in the same company; and 10% have quit their jobs.[22]

In Brazil, Nunes et al (2021) conducted a study aiming to analyze effects of a systematic intervention in HAE patients' management and only mild-to-moderate impairment on productivity was reported. No impairment (0 score) was reported by 88.1%, 73.8%, 73.8%, and 57.2% of patients for absenteeism, presenteeism, work productivity loss and activity impairment domains, respectively.[24] Different study designs may explain divergences between results from Brazil and Japan and Sweden; however, further analysis to determine the reasons for such regional differences are still needed.[14,23,24] In addition, the Brazilian study was conducted aiming to analyze the effect of an intervention and reinforces the importance of access to treatment.

Anxiety and depression

The levels of anxiety and depression of HAE patients are higher than within the general population. A survey of 242 patients with HAE across eight countries, in majority male with a mean age of 43.8 years, reported on the basis of the HADS score that 38% of these patients experienced moderate to severe anxiety and 17.4%, depression. These patients had the diagnosis with the mean age of 11.5 years and reported the occurrence of a mean of 12.5 attacks in a 6-month period.[15]

A study in the United States, which included in majority male individuals with the diagnosis of HAE type 1, showed that 39% of adult HAE patients had depression, and 15% of patients, anxiety.[25] Anxiety and depression were also frequent comorbidities in a noninterventional US survey of 445 adult individuals, most frequently females, with HAE type I, affecting 35.3% and 20.9% of patients, respectively. In addition, 7.6% of anxiety patients and 3.4% of depression patients had severe conditions (HADS score ≥ 15). Mean age at diagnosis of the US survey was 12.5 years and a mean of 11.1 attacks in a 6-month period was reported.[16]

Another study evaluated using HADS, 186 European patients with HAE with depression reported in 23%, 8% and 10% and anxiety reported in 46%, 39% and 24% of Spanish, German, and Danish patients respectively. Regarding demographic characteristics, the samples from all countries were composed by female adults, with the exception of patients from Denmark that were in majority male adults. Anxiety and depression levels correlate with HAE severity. The intensity of pain from the most recent attack indicated a strong correlation with the anxiety degree regarding future attacks. In addition, HAE patients showed distress, panic, and anxiety about HAE transmission to descendants. During the study, access to therapy for German and Danish patients was easier than for other patients. Thus, as the Spanish patients showed more depression and anxiety, improvements in therapy can probably reduce the prevalence of these mental disorders in HAE. Furthermore, tension, anxiety, and a negative mood could trigger attacks, creating a vicious cycle of angioedema causing more anxiety and even more angioedema.[26] HAE patients' self-control sense and anxiety improved as a result of access to self-administered acute attack and prophylaxis treatment.[27]

A Canadian study found high rates of under-recognized psychiatric symptomatology in patients with HAE. Mania, anger, sleep disorders, somatic symptoms, and impaired personality functioning are among these disorders. It is suggested that physicians treating HAE patients should ask about mental health on a regular basis and refer patients to experts as needed.[28]

A Brazilian study also indicated that it is critical to reinforce the expertise of HAE patient health-care professionals. Patients' QoL improves with prompt HAE attack treatment and continued focus on psychological and psychiatric disorders. These researchers recommended that physicians and other healthcare professionals undertake major efforts worldwide to provide effective medications to prevent and treat HAE attacks, prevent deaths, and provide healthy and productive life to these patients.[24]

These data highlight the need for a multidisciplinary approach for HAE patients, not only focused on medical treatment. However, most of the studies are still conducted using the HADS questionnaire.[15,16,25,26] Saez-Flores et al (2018) assessed HADS' factor structure in a sample of adolescents and young adults with cystic fibrosis and reported poor ability to distinguish between symptoms of anxiety and depression, suggesting that instruments such as Generalized Anxiety Disorder 7 (GAD-7) and Scale and the Patient Health Questionnaire-9 (PHQ-9) would be more appropriate.[29] Indeed, Zarnowski et al (2021) conducted a study to investigate the prevalence of depression and anxiety in patients with HAE in Germany using both instruments (HADS and GAD-7) and reported discrepant results, 43.2% through HADS anxiety scale and 25% using GAD-7 score.[30] Additionally, PHQ-9 and GAD-7 include aspects related to suicidal ideation, which is a limitation of other instruments. Thus, further analyses on this issue are still needed.

Validated questionnaires for assessing the quality of life in hereditary angioedema

There are several generic instruments to assess HRQoL such as the thirty-six-item short form (SF-36) and the Pediatric Quality of Life Inventory (PedsQL). SF-36 is an instrument that measure eight scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and provides two summary measures, the Physical Component Summary and the Mental Component Summary.[31] PedsQL is an instrument developed to assess quality of life among individuals aged 5–18 years and assesses the following domains: physical functioning, emotional functioning, social functioning, and school functioning.[32]

Despite the ability of generic questionnaires to compare HRQoL between different diseases, they generally have low sensitivity when assessing a particular aspect of the disease and do not measure key challenges of the population. Therefore, HRQoL impact assessment requires specific questionnaires about the impairment caused by the disease. Specific instruments are available and validated for angioedema (AE-QoL) and HAE (HAE-QoL).[33]

The first questionnaire developed specifically for angioedema was the Angioedema Quality of Life Questionnaire (AE-QoL), which addresses

high-impact areas for the loss of quality of life in recurrent angioedema patients. The AE-QoL has 17 questions in functioning, fatigue/mood, fears/shame, including appearance of swellings, and nutrition domains, with recall period of 4 weeks.[30,33,34] Values define no (0–23), small (24–38) or moderate to large effect (≥39) on recurrent angioedema patients' QoL.[34-36] The minimal clinically important difference of the AE-QoL is 6 points. The AE-QoL total scores show a significant correlation with the annual angioedema attacks ($r = 0.46$; $p < 0.0001$), a total internal consistency of 0.89, and a test-retest reliability of 0.83, which shows the ability of the instrument to discriminate groups that are assumed to be different. The AE-QoL assists with assessment and development of better therapeutic strategies for patients with the disorder.[34]

The first questionnaire addressed specific for HAE-C1-INH is the Hereditary Angioedema Quality of Life (HAE-QoL).[37] This is a 25-item questionnaire with 7 domains (mental health; disease-related stigma; treatment difficulties; perceived control over illness; emotional role and social functioning; concern about offspring; and physical functioning and health). The development of this instrument was based on a qualitative methodology, with a patient-centered perspective.[37] The HAE-QoL has Cronbach's alpha internal consistency of 0.92 and test-retest reliability of 0.87, in addition to good discriminant validity in the psychometric analysis.[37] Higher scores means improved QoL. The HAE-QoL has good reliability, and it is available in 18 languages.[37] This is the most used instrument by the Brazilian Study Group in HAE (GEBRAEH).

Regarding the pediatric HAE population, there are no validated instruments designed to specifically determine the impact of the disease on QoL, to date. Considering that generic instruments are not able to describe HAE QoL with an appropriate confidence, this is still an unmet need in the area.

Quality of life with treatments for acute attacks and long-term prophylaxis

There are 3 treatment approaches for HAE. On-demand therapy reduce attacks severity and duration with treatment options as ecallantide, icatibant, and plasma-derived or recombinant C1-INH. If these options are not available, frozen plasma can be used, but it has lower efficacy and frequent adverse events.[38] Prevention to angioedema attacks is also possible through long-term prophylaxis with antifibrinolytics (ie, tranexamic acid), attenuated androgens (ie, danazol), C1-INH replacement, berotralstat, and lanadelumab.[38] Finally, when patients are aware of a potential trigger exposure, they can use short-term prophylaxis to reduce the attack risk. Except for lanadelumab and berotralstat, all long-term prophylactic options can be utilized for short-term prophylaxis.[38]

Treatments for acute attacks

Acute attacks treatments are plasma-derived and recombinant human C1-INH, bradykinin B2 receptor inhibitor and inactivate plasma kallikrein.[1] Previously, prophylaxis treatment options were antifibrinolytic agents and attenuated androgens.[1] These treatments are effective, but are not able to normalize patients' lives, and still pose a risk of serious adverse events. At present, these agents are considered second-line therapies.[1] International WAO/EAACI guidelines recommends that all attacks should be considered for on-demand therapy, using either intravenous C1-INH, ecallantide or icatibant.[39]

Table 1 summarizes studies assessing the impact of attacks treatment on QoL. Nunes et al. (2021) assessed the impact of a systematic intervention (that could include icatibant, pdC1-INH concentrates, antifibrinolytics, increase dosage of attenuated androgen to manage attacks or no treatment) among Brazilian HAE patients. The comparison with the baseline showed an increase in HAE-QoL total scores by 15.2 (mean, 95% credible interval [CrI]: 1.23–29.77) at 8 months and 26 (mean, 95% CrI: 14.56–39.02) at 14 months. Improvement in the SF-36 questionnaire role-emotional domain score was also reported. However, no significant differences were noted in the Pediatric Quality of Life Inventory (PedsQL) scores.[24]

The SABHA was an observational, single-center, and prospective study. Plasma-derived nano-filtered C1-INH (C1-INH-nf) self-infusion safety and feasibility were the primary endpoints; the secondary was the evaluation of self-infusion effect on QoL through the HAE-QoL questionnaire. Fifteen

patients completed the study, and 189 attacks were registered in 12 months. There was a median of 2 h between the symptom's onset and self-administration and a median of 6 h for the attack resolution. The baseline median HAE-QoL score was 86 (IQR: 76–103), and it had increased (94; QR: 86–113) after 12 months, with no statistically significant difference. Concerns about offspring, perceived control over disease, and mental health showed the largest increases after 6 months, with stability between the third and last assessment.[40]

Bewtra et al. (2012) assessed HRQoL using SF-12 for an I.M.P.A.C.T.2 study subgroup. The analysis reported a positive impact of the use of C1-INH concentrate single-dose to manage acute attacks in the lifestyle and emotional domains.[41]

The results suggest that treatment for acute attacks promotes an improvement on HAE patients' QoL. However, statistically significant differences are not always observed and further analysis on the impact of treatment in different QoL domains are still needed.[24,40,41]

Prophylactic treatment

Prophylactic treatment, besides treating angioedema attacks, may benefit HAE patients. It aims to reduce the likelihood of edema in the presence of triggers (short-term prophylaxis) or to reduce the intensity and burden of angioedema attacks (long-term prophylaxis). Even if they are effectively controlled on a prophylactic treatment plan, patients are advised to continue to seek effective on-demand attack treatment.[10] The WAO/EAACI latest guidelines recommends both short or long-term prophylactic treatment. The document recommend short-term prophylaxis before medical, surgical or dental procedures and after exposure to other angioedema attack-inducing events, using plasma-derived C1-INH (pdC1-INH) as first-line option.[39]

Considering long-term prophylaxis, the latest WAO/EAACI guideline recommends that it shall be evaluated for all patients at every visit, taking into consideration aspects such as disease activity, burden, control and patient preference.[39] There are first- and second-line long-term prophylaxis drugs. Intravenous (pdC1-INH), subcutaneous pdC1-INH, and plasma kallikrein inhibitors, such as lanadelumab and berotralstat, compose the first line. Antifibrinolytics like tranexamic acid, and anabolic androgens, like danazol, are considered second-line therapies.[10,39,42] The summaries of studies that assessed the prophylactic treatment impact in HRQoL are shown in Table 2.

Buttgereit et al (2021) analyzed lanadelumab treatment outcomes in real-life through reporting their experience in hospital-based cohort. The previous medication was switched to lanadelumab in 24 HAE and four acquired C1-INH deficiency angioedema patients, assessed through the angioedema control test (AECT) and the AE-QoL during the adjustment. The AE-QoL of 24 patients was assessed before and during lanadelumab treatment, and the result was a significant reduction from 45.8 to 13.8 (mean change score, 32; $p < 0.001$). The baseline AE-QoL total values were similar between groups that switched from on-demand treatment to lanadelumab or with previous prophylactic treatment (AE-QoL total 46 vs. 45.7; $p = 0.73$), but the QoL impairment trend after lanadelumab treatment (AE-QoL total 9.6 vs. 14.8; $p = 0.71$; not statistically significant) was lower.[43] Other analyses with lanadelumab treatment showed a significantly increased HRQoL for treated patients.[44,45]

The HELP study assessed the effect of lanadelumab on HRQoL. Patients received either lanadelumab 150 mg or 300 mg every 4 weeks, 300 mg every 2 weeks, or placebo for 26 weeks (days 0–182).[44] Watt et al (2021) reported data from the HELP Open-label Extension Study in a long-term follow-up (132 weeks).[46] A minimum clinically important difference (MCID) sustained improvement in AE-QoL total and domain scores was observed from day 0 till the study's end, as well as during the study's follow-up.[44,46] In addition, patients also reported being satisfied with their treatment as measured by Treatment Satisfaction Questionnaire for Medication (TSQM-9).[42,44]

In part 1 of the APeX-2 study, 24 weeks of berotralstat treatment showed effectiveness and a favorable benefit-to-risk profile.[42,47,48] After 48 weeks, part 2 of the ApeX-2 trial validated berotralstat's safety, tolerability, and efficacy.[42] Starting as early as week 4, berotralstat treated patients in parts 1 and 2 exhibited AE-QoL total score improvement, which lasted until week 48.[42]

Outcomes from the COMPACT open-label extension study also found significant and consistent improvements in multiple estimates by HRQoL after long-term subcutaneous C1-INH [C1-INH(SC)] replacement therapy in C1-INH-HAE patients. The final results showed that the mean total AE-QoL score was between 13.39 and 17.89, while the mean global scores of the HAE-QoL were between 115.7 and 122.3, close to the best possible score, that is, 135.[49] Another study with C1-INH(SC) showed that self-administration of C1-INH(SC) twice a week is more effective than just on-demand therapy for the improvement of specific HAE conditions. Thus, this study confirmed the HRQoL benefits observed in the COMPACT study. Therefore, prophylactic treatment with C1-INH(SC) proved to be a major advance in the management of HAE. This treatment also improved HAE patients' parameters related to anxiety (assessed through HADS) and empowerment for an active and productive lifestyle.[50] Improvements in AE-Qol score were also observed after up to 16 weeks of C1-INH(SC) with recombinant hyaluronidase.[51] A study that assessed HRQoL with the SF-36 questionnaire demonstrated improved QoL with nanofiltered C1-INH prophylactic treatment as well.[52] Another study with nanofiltered C1-INH also showed improved QoL assessed by AE-QoL.[53]

Results showed that prophylactic treatment, either with lanadelumab, berotralstat or C1-INH(SC), is able to improve HAE patients' QoL. Using AE-QoL data, mean changes between treatment beginning and end of the follow-up ranged from 10.2 to 32 with lanadelumab and was estimated at 29 points in a single study using berotralstat.[43,44,46,48] Considering the proportion of patients that achieve minimum clinically important difference, similar results are observed with both strategies, about 60%.[42,45]

CONCLUSIONS

The reviewed literature highlights the importance of considering patients' QoL with appropriate QoL measurement tools when applying disease management strategies. Both on-demand and long-term prophylaxis treatment have shown to increase HAE patients' HRQoL, considering both global measure and specific domains such as functioning, fears/shame and nutrition. Specific tools to assess HRQoL among HAE individuals are available and shall be used in clinical practice instead of generic instruments.

Our review also assessed the frequency of anxiety and depression and found estimates that ranged from 8% to 46%, depending on the outcome assessed, and data may be underestimated due to a major use of HADS questionnaire. These results call attention to the importance of a routine assessment of quality of life and mental health using adequate instruments during HAE management. Finally, in addition to the use and/or development of tools able to identify QoL impairment among HAE patients, investments on new treatments to prevent seizures should also be considered.

Abbreviations
AECT, Angioedema control test; AE-QoL, Angioedema Quality of Life Questionnaire; C1-INH, C1 inhibitors; C1-INH-nf, nanofiltered C1-INH; CrI, credible interval; EAACI, European Academy of Allergy and Clinical Immunology; EQ-5D-3L, European Quality of Life-5 Dimensions Questionnaire; FXIIa, factor XII; GEBRAEH, Brazilian Study Group in HAE; HRQoL, Health-related quality of life; HAE, Hereditary angioedema; HAE-QoL, Hereditary Angioedema Quality of Life; HADS, hospital anxiety and depression scale; IV, intravenous; MCID, minimum clinically important difference; nC1-INH, normal C1-INH; NR, not reported; pd, plasma-derived; PedsQL, Pediatric Quality of Life Inventory; QoL, Quality of life; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous; SD, standard deviation; SF-12, twelve-item short form; SF-36, thirty-six-item short form; TSQM-9, Treatment Satisfaction Questionnaire for Medication; USA, United States of America; WPAI, Work Productivity and Activity Impairment Questionnaire; WAO, World Allergy Organization.

Availability of data and material
Not applicable.

Authors' contributions
HJC was responsible for conceptualization, investigation, methodology, funding acquisition, project administration, and writing (review and editing).

Ethics approval and consent to participate
Not applicable.

Consent for publication

All authors agree to the publication of this manuscript in World Allergy Organization Journal.

CONFIRMATION OF UNPUBLISHED WORK

The authors confirm that this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Competing interest

The authors declare that they have no competing interests.

Author details

Division of Allergy and Immunology, Complexo Hospital de Clínicas, Federal University of Paraná, Curitiba, Paraná, Brazil.

REFERENCES

1. Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med*. 2020;382(12):1136–1148. https://doi.org/10.1056/NEJMra1808012.

2. Wilkerson RG, Moellman JJ. Hereditary angioedema. *Emerg Med Clin North Am*. 2022;40(1):99–118. https://doi.org/10.1016/j.emc.2021.09.002.

3. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. *Br J Hosp Med*. 2019;80(7):391–398. https://doi.org/10.12968/hmed.2019.80.7.391.

4. Bowen T, Cicardi M, Bork K, et al. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2008;100(1):S30–S40. https://doi.org/10.1016/S1081-1206(10)60584-4.

5. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359(10):1027–1036. https://doi.org/10.1056/NEJMcp0803977.

6. Lumry WR. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. *Am J Manag Care*. 2013;19(7 Suppl):s103–s110.

7. Giavina-Bianchi P, Arruda LK, Aun MV, et al. Brazilian guidelines for hereditary angioedema management - 2017 update part 1: definition, classification and diagnosis. *Clinics*. 2018;73:5–9. https://doi.org/10.6061/clinics/2018/e310.

8. Bork K, Wulff K, Möhl BS, et al. Novel hereditary angioedema linked with a heparan sulfate 3-O-sulfotransferase 6 gene mutation. *J Allergy Clin Immunol*. 2021;148(4):1041–1048. https://doi.org/10.1016/j.jaci.2021.01.011.

9. Bernstein JA. Severity of hereditary angioedema, prevalence, and diagnostic considerations. *Am J Manag Care*. 2018;24(14):S292–S298. https://doi.org/10.1056/NEJMicm1200960.indicator.

10. 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(1):132–150.e3. https://doi.org/10.1016/j.jaip.2020.08.046.

11. Banerji A, Busse P, Christiansen SC, et al. Current state of hereditary angioedema management: a patient survey. *Allergy Asthma Proc*. 2015;36(3):213–217. https://doi.org/10.2500/aap.2015.36.3824.

12. Campos R de A, Valle SOR, Toledo EC. Hereditary angioedema: a disease seldom diagnosed by pediatricians. *J Pediatr*. 2021;97:S10–S16. https://doi.org/10.1016/j.jped.2020.10.011.

13. Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013;111(5):329–336.

14. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Björkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2014;35(2):185–190.

15. Mendivil J, Murphy R, de la Cruz M, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. *Orphanet J Rare Dis*. 2021;16(1):1–13. https://doi.org/10.1186/s13023-021-01717-4.

16. 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(6):600–607. https://doi.org/10.1016/j.anai.2020.02.018.

17. Bork K, Anderson JT, Caballero T, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. *Allergy Asthma Clin Immunol*. 2021;17(1):1–14. https://doi.org/10.1186/s13223-021-00537-2.

18. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson Da, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010;31(5):407–414.

19. Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. *Clin Rev Allergy Immunol*. 2016;51(2):230–239. https://doi.org/10.1007/s12016-016-8575-2.

20. Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104(4):314–320. https://doi.org/10.1016/j.anai.2010.01.024.

21. Lumry WR, Settipane RA. Hereditary angioedema: epidemiology and burden of disease. *Allergy Asthma Proc*. 2020;41(6):S08–S13. https://doi.org/10.2500/aap.2020.41.200050.

22. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Allergy Asthma Proc*. 2014;9:99. https://doi.org/10.2500/aap.2013.34.3685.

23. Ohsawa I, Honda D, Nagamachi S, et al. Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. *Ann Allergy Asthma Immunol*. 2015;114(6):492–498. https://doi.org/10.1016/j.anai.2015.03.010.

24. Nunes FL, Ferriani MPL, Moreno AS, et al. Decreasing attacks and improving quality of life through a systematic management program for patients with hereditary angioedema. *Int Arch Allergy Immunol*. 2021;182(8):697–708. https://doi.org/10.1159/000513896.

25. Fouche AS, Saunders EFH, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2014;112(4):371–375. https://doi.org/10.1016/j.anai.2013.05.028.

26. Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the burden of illness study in Europe. *Allergy Asthma Proc*. 2014;35(1):47–53. https://doi.org/10.2500/aap.2013.34.3685.

27. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol*. 2009;19(2):147–151. https://doi.org/10.1684/ejd.2008.0603.

28. Hews-Girard J, Goodyear MD. Psychosocial burden of type 1 and 2 hereditary angioedema: a single-center Canadian cohort study. *Allergy Asthma Clin Immunol*. 2021;17(1):61. https://doi.org/10.1186/s13223-021-00563-0.

29. Saez-Flores E, Tonarely NA, Barker DH, Quittner AL. Examining the stability of the hospital anxiety and depression scale factor structure in adolescents and young adults with cystic fibrosis: a confirmatory factor analysis. *J Pediatr Psychol*. 2018;43(6):625–635. https://doi.org/10.1093/jpepsy/jsx155.

30. Zarnowski J, Rabe M, Kage P, Simon JC, Treudler R. Prophylactic treatment in hereditary angioedema is associated with reduced anxiety in patients in Leipzig, Germany. *Int Arch Allergy Immunol*. 2021;182(9):819–826. https://doi.org/10.1159/000514973.

31. Saris-Baglama RN, Dewey CJ, Chisholm GB, et al. QualityMetric Health Outcomes™ Scoring Software. 4.0. 2010.

32. Varni JW, Seid M, Rode CA. The PedsQL™: measurement model for the pediatric quality of life inventory. *Med Care*. 1999;37(2):126–139. https://doi.org/10.1097/00005650-199902000-00003.

33. Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. *Front Med*. 2017;4:212. https://doi.org/10.3389/fmed.2017.00212.

34. Balla Z, Ignácz B, Varga L, Kőhalmi KV, Farkas H. How angioedema quality of life questionnaire can help physicians in treating C1-inhibitor deficiency patients? *Clin Rev Allergy Immunol*. 2021;61(1):50–59. https://doi.org/10.1007/s12016-021-08850-9.

35. Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012;67(10):1289–1298. https://doi.org/10.1111/all.12007.

36. Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. *Allergy*. 2016;71(8):1203–1209. https://doi.org/10.1111/all.12900.

37. Prior N, Remor E, Pérez-Fernández E, et al. Psychometric field study of hereditary angioedema quality of life questionnaire for adults: HAE-QoL. *J Allergy Clin Immunol Pract*. 2016;4(3):464–473.e4. https://doi.org/10.1016/j.jaip.2015.12.010.

38. Lee EY, Hsieh J, Borici-Mazi R, et al. Quality of life in patients with hereditary angioedema in Canada. *Ann Allergy Asthma Immunol*. 2021;126(4):394–400.e3. https://doi.org/10.1016/j.anai.2021.01.002.

39. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2021 revision and update. *Allergy Eur J Allergy Clin Immunol*. 2022;77(7):1961–1990. https://doi.org/10.1111/all.15214.

40. Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert®) in patients with hereditary angioedema: the SABHA study. *Orphanet J Rare Dis*. 2018;13(1):51. https://doi.org/10.1186/s13023-018-0797-3.

41. Bewtra AK, Levy RJ, Jacobson KW, Wasserman RL, Machnig T, Craig TJ. C1-inhibitor therapy for hereditary angioedema attacks: prospective patient assessments of health-related quality of life. *Allergy Asthma Proc*. 2012;33(5):427–431.

42. Wedner HJ, Aygören-Pürsün E, Bernstein J, et al. Randomized trial of the efficacy and safety of berotralstat (BCX7353) as an oral prophylactic therapy for hereditary angioedema: results of APeX-2 through 48 Weeks (Part 2). *J Allergy Clin Immunol Pract*. 2021;9(6):2305–2314.e4. https://doi.org/10.1016/j.jaip.2021.03.057.

43. Buttgereit T, Vera C, Weller K, et al. Lanadelumab efficacy, safety, and injection interval extension in HAE: a real-life study. *J Allergy Clin Immunol Pract*. 2021;9(10):3744–3751. https://doi.org/10.1016/j.jaip.2021.04.072.

44. Lumry WR, Weller K, Magerl M, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. *Allergy*. 2021;76(4):1188–1198. https://doi.org/10.1111/all.14680.

45. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks. *JAMA*. 2018;320(20):2108. https://doi.org/10.1001/jama.2018.16773.

46. Watt M, Maurer M, Devercelli G, et al. Long-term impact of lanadelumab on patients with hereditary angioedema (HAE) type 1/2: patient reported outcome (PRO) findings from the HELP open-label extension study (OLE). *J Allergy Clin Immunol*. 2021;147(2):AB24. https://doi.org/10.1016/j.jaci.2020.12.125.

47. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immunol*. 2021;148(1):164–172.e9. https://doi.org/10.1016/j.jaci.2020.10.015.

48. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. *N Engl J Med*. 2018;379(4):352–362. https://doi.org/10.1056/NEJMoa1716995.

49. Lumry WR, Zuraw B, Cicardi M, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. *Orphanet J Rare Dis*. 2021;16(1):86. https://doi.org/10.1186/s13023-020-01658-4.

50. Lumry WR, Craig T, Zuraw B, et al. Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of

hereditary angioedema. *J Allergy Clin Immunol Pract*. 2018;6(5):1733. https://doi.org/10.1016/j.jaip.2017.12.039, 41.e3.

51. Weller K, Maurer M, Fridman M, Supina D, Schranz J, Magerl M. Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase. *Allergy Asthma Proc*. 2017;38(2): 143–151. https://doi.org/10.2500/aap.2017.38.4025.

52. Greve J, Hahn J, Nordmann M, et al. Nanofiltrated C1-esterase-inhibitor in the prophylactic treatment of bradykinin-mediated angioedema. *Transfusion*. 2016;56(5):1022–1029. https://doi.org/10.1111/trf.13462.

53. Lumry WR, Miller DP, Newcomer S, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. *Allergy Asthma Proc*. 2014;35(5):371–376.