Eur J Dermatol 2022; 32(4): 487-94

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Article accepted on 14/03/2022

Patients with hereditary angioedema and their treatment patterns in Germany: a Delphi consensus study

Background: Little is known about how many patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) receive on-demand and/or prophylactic treatment and what their clinical features are. Here, we estimated, using Delphi-based consensus, prevalence and treatment patterns in Germany as well as patient features linked to long-term prophylaxis. *Materials & Methods:* Eight experts, who together treat approximately 75% of all German HAE-C1-INH patients, participated in a classic, two-round Delphi survey. Consensus was defined as agreement between at least 75% of participants. *Results:* Experts agreed that an estimated 1,350 patients in Germany have HAE-C1-INH, *i.e.* 1.62 per 100,000. One in four patients was estimated to receive long-term prophylaxis. Patient features linked to the use of prophylactic treatment included reduced quality of life, frequent swellings and swellings that affect the upper airways, and >two attacks per month. *Conclusion:* The rate of prophylactic treatment in Germany is low, but is expected to increase. The level of disease activity and its impact and control are and should be considered in the choice for prophylactic treatment.

Key words: hereditary angioedema, Delphi consensus, prevalence, long-term prophylaxis, HAE

Angioedema is a vascular reaction of deep dermal/subcutaneous tissues or mucosal/submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling [1-3]. Hereditary angioedema is caused by mutations in the gene encoding C1 inhibitor (HAE-C1-INH), resulting in the deficiency (HAE type I) or dysfunction (HAE type II) of C1-INH protein [4]. HAE-C1-INH is characterized by recurrent swelling attacks. These attacks affect the skin and mucosa including the airway, gastrointestinal tract, and genitourinary region [5]. Approximately every second patient with HAE-C1-INH will suffer from a laryngeal attack at some point in his/her lifetime, which is potentially life-threatening [3, 4]. HAE-C1-INH is classified as a rare disease. Based on two population studies from Denmark and Italy, the prevalence of HAE-C1-INH in Europe is estimated to be 2 per 100,000 individuals [6, 7]. Therapy for HAE-C1-INH includes on-demand treatment of attacks, which should be combined with long-term prophylaxis in severely affected patients [1]. Since February 2019, three new drugs have been approved for long-term prophylaxis, thus current therapy options for long-term prophylaxis include intravenous and subcutaneous plasma-derived C1-inhibitor, the monoclonal antibody, lanadelumab, and oral berotralstat 150 mg daily [5]. The recommended starting dose for lanadelumab is 300 mg every two weeks. In patients who are stable and attack-free on treatment, an interval prolongation with 300 mg lanadelumab every four weeks may be considered, especially in patients with low weight [8].

The 2017 HAE guidelines update and revision of the World Allergy Organization and the European Academy of Allergy and Clinical Immunology recommends that patients are evaluated for the indication of long-term prophylaxis at every visit. Disease burden and patient preference should be taken into consideration [1]. However, current data from Germany regarding HAE-C1-INH prevalence are lacking and the proportion of patients on long-term prophylaxis is currently unknown - as is the distribution of patients over the different treatment intervals with lanadelumab. Also, criteria for considering long-term

doi:10.1684/ejd.2022.4272

To cite this article: Martinez-Saguer I, Dominas N, Straben U, Greve J, Brehler R, Magerl M, Knipps LM, Knop J, Flemming A, Schubert T, Maurer M. Patients with hereditary angioedema and their treatment patterns in Germany: a Delphi consensus study. *Eur J Dermatol* 2022; 32(4): 487-94 doi:10.1684/ejd.2022.4272

prophylaxis are ambiguous, as is the definition of "attack-free" patients. The aim of the present Delphi survey was therefore to obtain an estimate, as accurately as possible, of the number of HAE-C1-INH patients in Germany, expert opinion on the current rate of patients who receive long-term prophylaxis and different treatment intervals with lanadelumab as well as expected changes over the next three years, and to evaluate criteria used in daily practice for starting long-term prophylaxis in patients with HAE-C1-INH.

Materials and methods

Study design

A classic, two-round Delphi panel [9] of clinical experts was held between August and October of 2020 to reach consensus on current HAE prevalence in Germany and on the current and future number of patients in long-term prophylaxis among German centres with expertise in HAE treatment. As a Delphi panel does not generally require the presence of individuals for discussion, this approach ensured anonymity with minimized peer-group pressure effects on opinions expressed.

The panel consisted of eight experts with extensive experience in: (i) treating HAE patients in outpatient or hospital care; and (ii) publication of, or participation in clinical trials in HAE. Participating experts were from five different federal states, for geographical balance, and major relevant HAE-related specialties, including dermatology, allergology, otorhinolaryngology, and paediatrics.

The eight panel experts were invited via e-mail to join the Delphi panel; their identities remained blinded to each other, and their responses remained anonymous throughout the entire process. Participants were informed that the aggregated results and the distribution of answers of the first round would be shared with the participants in the second round. Results of the first round were aggregated by the investigators and given as feedback to the participants in the second Delphi round with the revised questionnaire [10, 11]. This process was repeated until consensus was reached. The study did not require approval from an ethics committee due to its design.

Questionnaire for first Delphi round

The questionnaire for the first Delphi round included half-open questions on the number of patients with HAE in Germany and their distribution related to on-demand and long-term prophylaxis treatment. The questionnaire consisted of three parts. In the first part, panellists were asked about their medical specialty, their experience in treating HAE, the number of HAE patients currently treated within their centre, and the number of patients with long-term prophylaxis. The second part was designed to provide the median values used in the second round for reaching consensus. Panellists were asked about their estimate regarding the number of diagnosed HAE patients in Germany and their estimate of the proportion of HAE patients with long-term prophylaxis. Panellists were presented with previous estimates used in a recent assessment of the Federal Joint Committee for these two evaluations, since providing a common starting point may help group cohesion and is therefore advised in consensus groups [11]. Next, panellists were asked, based on their own estimate for 2020, how the proportion of long-term prophylaxis patients will change over the next three years. In the final part of the questionnaire, experts were asked about their management of "freedom from attacks" and how this influences decisions about long-term prophylaxis. Specifically, they were asked for patient criteria for starting long-term prophylaxis and to consider a dose reduction in patients treated with lanadelumab. The request for criteria was based on open questions so the experts could enter free text.

Questionnaire for second Delphi round

In September 2020, the first round of questioning was completed and evaluated, aggregated and adapted for the second round of questioning. Panellists were presented with the median response for each question alongside a histogram that included the answers from all eight participants (see *figure 1* for an example of the questionnaire). Approval of these median values was assessed with a 5-point Likert scale from "very inaccurate" to "very accurate" [12]. For the two questions on possible change over 2021-2023, the average annual rate of increased probability of change was based on a rating scale ("very unlikely" to "very likely"). Criteria mentioned in the first round for starting long-term prophylaxis, to manage attack-free patients, and to consider dose reduction in lanadelumab patients were summarized by the study team and thus answers were combined under a generic term.

Consensus definition

Consensus was defined in advance of establishing the questionnaire such that at least 75% of the experts answered with at least a "4" on the five-point scale [13, 14].

Data analysis

Descriptive statistics (median, minimum, maximum and interquartile range) were used to analyse consensus between Delphi rounds. Median values and histograms were used as feedback from the first round. All data were analysed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2019 16.4, Microsoft Corporation, Redmond (Washington), USA.

Results

The panel consisted of eight HAE experts from dermatology, otorhinolaryngology and paediatrics

The Delphi survey consisted of two rounds and was carried out between July 2020 and October 2020 via an online survey. Eight experts participated and all eight experts answered both survey rounds. Panel attrition between the two survey rounds was therefore 0%.

Four of eight of the participants were otorhinolaryngologists, three of the experts were dermatologists, and one was a paediatrician (*table 1*). According to their own information, the experts currently treat a total of 1,025 HAE patients

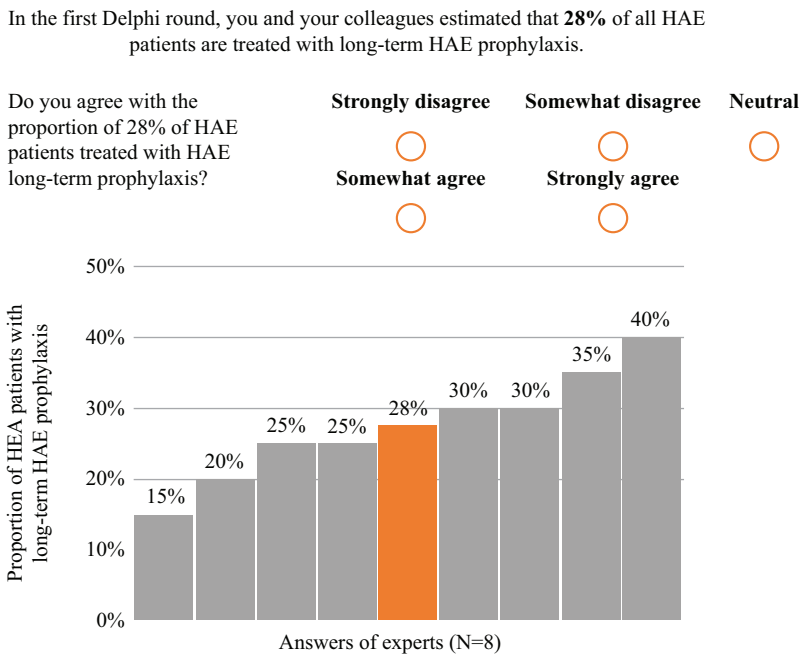

Figure 1. Screenshot from second Delphi round with feedback. In the second round, experts were presented with a median value and an anonymized histogram from the first round. They were then asked whether they agree with the median value from the first round.

(mean: 146 patients; median: 100 patients). The experts stated that a total of 239 of these 1,025 patients (23.3%) were treated with long-term HAE prophylaxis in their centres. The proportion of long-term HAE prophylaxis among all patients in their centres varied between 13% and 50%, with a considerable smaller spread of 21-30% among the four experts with the most HAE patients.

In Germany, 1,350 patients are estimated to have HAE-C1-INH

The experts estimated that 1,350 patients are currently diagnosed with HAE-C1-INH in Germany (mean: 1,375; minimum: 1,000; maximum: 1,800) (*table 2*), which reached consensus in the second round (7/8; 87.5%) (*table 3*). The participating experts reported treating a total of 1,025 patients, *i.e.* about 75% of all patients with HAE-C1-INH.

Table 1. Delphi panel characteristics.

	Frequency	Percent
N	**8**	**100**
Gender		
Female	3	37
Male	5	63
Medical specialty		
Otorhinolaryngology	4	50
Dermatology	3	37
Pediatrics	1	13
Experience in treating HAE-C1-INH		
Less than 1 year	0	0
1 to <5 years	1	13
5 to <10 years	1	13
10+ years	6	76
Treatment setting		
Inpatient/hospital	7	87
Outpatient/medical office	1	13

HAE-C1-INH: hereditary angioedema due to C1 inhibitor deficiency.

In Germany, one in four patients with HAE is on long-term prophylaxis, but this rate will increase

The experts estimated that, in Germany, 28% of patients with HAE-C1-INH use long-term prophylaxis (mean: 28%; minimum: 15%; maximum: 40%) which reached consensus in the second round (8/8; 100%). Based on expert estimates, the rate of HAE patients in Germany who use long-term prophylaxis will increase during the next three years compared to 2020 by 5% per year, based on consensus in the second round (8/8; 100%).

Patient features linked to the use of prophylactic treatment

In the first round, the experts indicated different criteria for starting long-term prophylaxis. Criteria stated at least once were: reduction in quality of life due to frequent swelling, frequent swellings and swellings in the throat/pharynx area, HAE attack frequency >two/month, insufficient effectiveness of on-demand medication, sufficient compliance of the patient and a high burden of disease. After summarizing similar responses, the most important criteria in the second round were frequent swelling of the throat/pharynx (larynx) (average rank: 2.0) and other frequent attacks, despite on-demand medication (HAE attack frequency >two/month) (average rank: 2.1) (*table 4*).

Table 2. Results from the first Delphi round.

Question	Minimum	Median (basis for 2nd round)	Maximum	Interquartile range	Data not available
How many HAE diagnosed patients do you estimate there to be in Germany? (*n*)	1,000	1,350	1,800	325	-
What is your estimate of the proportion of HAE patients with long-term HAE prophylaxis in Germany? (%)?	15	28	40	7.5	-
Of all HAE patients in Germany, the proportion with long-term prophylaxis will likely change by what percentage in 2021, 2022, and 2023? (%)	5	5	5	0	1

HAE: hereditary angioedema.

Table 3. Results from the second Delphi round.

Statement/ Question	Frequency (%) of responses (*n*=8)					Mean (SD)	Frequency (%) of agreement
	1	2	3	4	5		
There are currently 1,350 diagnosed HAE patients in Germany		1 (13)		5 (62)	2 (25)	4.0 (0.9)	7 (87)
28% of all diagnosed HAE patients are treated with long-term HAE prophylaxis				7 (87)	1 (13)	4.1 (0.4)	8 (100)
The proportion of HAE patients on long-term HAE prophylaxis will increase by 5% annually over the next three years				3 (37)	5 (62)	4.6 (0.5)	8 (100)
The proportion of patients treated with 300 mg lanadelumab every 4 weeks will increase by 3% annually over the next three years		2 (25)		5 (62)	1 (13)	3.6 (1.1)	6 (75)
The treatment interval with 300 mg lanadelumab every 4 weeks will be used more frequently in the future compared to the *status quo*.				1 (13)	7 (87)	4.9 (0.4)	8 (100)

Questions that achieved consensus approval have been highlighted in bold text. Percentages may not sum up to 100 due to rounding. HAE: hereditary angioedema; SD: Standard Deviation.

Table 4. Criteria for considering long-term prophylaxis: results from the second round.

Criteria for considering long-term prophylaxis	Average rank	Frequency (%) of rank (*n*=8)					
		1	2	3	4	5	6
Frequent swelling of the throat / pharynx (larynx)	2.0	4 (50)	1 (13)	2 (25)	1 (13)		
Other frequent attacks, despite on-demand medication (HAE attack frequency >2/month)	2.1	3 (38)	2 (25)	2 (25)	1 (13)		
Failure of on-demand therapy for reasons other than those previously mentioned (frequent throat/pharyngeal swelling, facial swelling, or other attacks)	3.0		4 (50)	2 (25)	1 (13)		1 (13)
Frequent swelling of the face	4.0		1 (13)	1 (13)	3 (37)	3 (37)	
Sufficient compliance of the patient	5.3				1 (13)	4 (50)	3 (38)
Patient request for long-term HAE prophylaxis	4.6	1 (13)		1 (13)	1 (13)	1 (13)	4 (50)

Percentages may not sum up to 100 due to rounding. HAE: hereditary angioedema

For the management of attack-free patients, the experts stated the following criteria in the first round (all criteria were stated at least once): no HAE symptoms at all, no visible swellings, documentation according to diary, angioedema activity score, only minor restriction of quality of life, no abdominal complaints, no prodromal signs, AECT, environment or family affected, and individual patient assessment. In the second round, quality-of-life measures (*e.g.*, AE-QoL, average rank 1.4) and angioedema activity score were considered most important in defining attack-free patients (average rank: 2.0) (*table 5*).

Table 5. Criteria for defining attack-free patients and switching to 300 mg lanadelumab every four weeks: results from the second round.

	Average rank	Frequency (%) of rank (*n*=8)								
		1	2	3	4	5	6	7	8	9
Criteria for defining attack-free patients										
Quality-of-life measures (*e.g.*, AE-QoL)	1.4	6 (75)	1 (13)	1 (13)						
Angioedema activity score	2.0	2 (25)	4 (50)	2 (25)						
No abdominal discomfort	4.1		2 (25)	2 (25)	1 (13)	1 (13)		2 (29)		
No visible swelling	4.8			1 (13)	3 (38)	2 (25)	1 (13)	1 (14)		
Patient diary	4.9			2 (25)	2 (25)	1 (13)	1 (13)	2 (29)		
AECT	5.1		1 (13)		1 (13)	2 (25)	1 (13)	2 (29)		
Individual patient assessment	5.7				1 (13)	2 (25)	3 (38)		1 (14)	0 (0)
Suitable patient environment, *e.g.*, family situation	7.6						2 (25)		5 (71)	1 (14)
No prodromal signs	8.9								1 (14)	6 (86)
Criteria for a potential switch from 300 mg lanadelumab every 2 weeks to every 4 weeks										
Freedom from attack	1.0	8 (100)								
Patient satisfaction	2.6		3 (38)	4 (50)						
Patient safety in dealing with the disease	3.6		1 (14)	1 (14)	5 (50)					
Quality of life	3.8		4 (50)		1 (14)	2 (29)			1 (14)	
Patient preference	5.1			1 (14)		4 (50)	1 (14)	1 (14)		
Practicability for the patient	5.9				2 (29)	1 (14)	2 (29)	2 (29)	1 (14)	
Costs	6.1			1 (14)			4		2 (29)	
Side effects	7.5			1 (14)				2 (29)	2 (29)	3 (38)
Fixed, increasing treatment intervals	8.3							2 (29)	1 (14)	4 (50)

Percentages may not sum up to 100 due to rounding and a lack of available data. AE-QOL: Angioedema Quality of Life Instrument (AE-QoL); AECT: Angioedema Control Test

Treatment schedule of 300 mg lanadelumab every four weeks is expected to increase

The experts indicated that 60% of all patients treated in their own centre with lanadelumab are currently treated with 300 mg lanadelumab every four weeks and 40% with 300 mg lanadelumab every two weeks.

The experts also estimated that the proportion of patients receiving 300 mg lanadelumab every four weeks among all lanadelumab patients in their own centre will increase in 2021, 2022, and 2023 compared with 2020. On average, an increase in 3% per year was assumed, which in the second round, six out of eight experts evaluated as likely or highly likely (75% consensus reached).

All experts agreed with the statement: "The treatment interval with 300 mg lanadelumab every four weeks will be used more frequently in the future compared to the status quo" (100% consensus).

Discussion

Based on this Delphi survey, experts' assessments on current prevalence and therapy of hereditary angioedema were evaluated, and the views of treatment providers of approximately 75% of all diagnosed HAE patients in Germany were reported. The experts estimated, by consensus, that there are 1,350 diagnosed HAE patients living in Germany and that 28% of these are treated with long-term HAE prophylaxis. Based on the estimate of 1,350 HAE patients in Germany, this implies that approximately 350 to 400 patients currently receive long-term prophylaxis in Germany.

The previous European HAE-C1-INH prevalence estimate of 2 in 100,000 [6, 7] would yield a prevalence of 1,640 HAE-C1-INH patients in Germany based on a population of 82 million people (1:50,000). Previous estimates in Germany have revealed that at least 1,200 individuals in Germany are affected by HAE-C1-INH (1.46 per 100,000; 1:68,000) [15, 16].

Our estimate of 1,350 diagnosed HAE-C1-INH patients is within the midrange of these figures, which could be due to the focus on HAE-C1-INH patients already diagnosed. Since a hurdle for the diagnosis of HAE-C1-INH is initial suspicion by the primary care or emergency physician, and given the low prevalence of the disease and the non-specific symptoms, particularly during attacks of abdominal pain [17], there might be a significant number of undiagnosed HAE-C1-INH patients. Our estimate is consistent with a prevalence of 1.62 patients diagnosed with HAE per 100,000 inhabitants (1 in 62,000).

Based on consensus, the experts expect that the proportion of patients receiving long-term prophylaxis will increase by 5% per year over the next three years. Based on the consensus of 28% (378 patients in Germany) in 2020, this would mean an increase up to 33% (446 patients), 38% (513

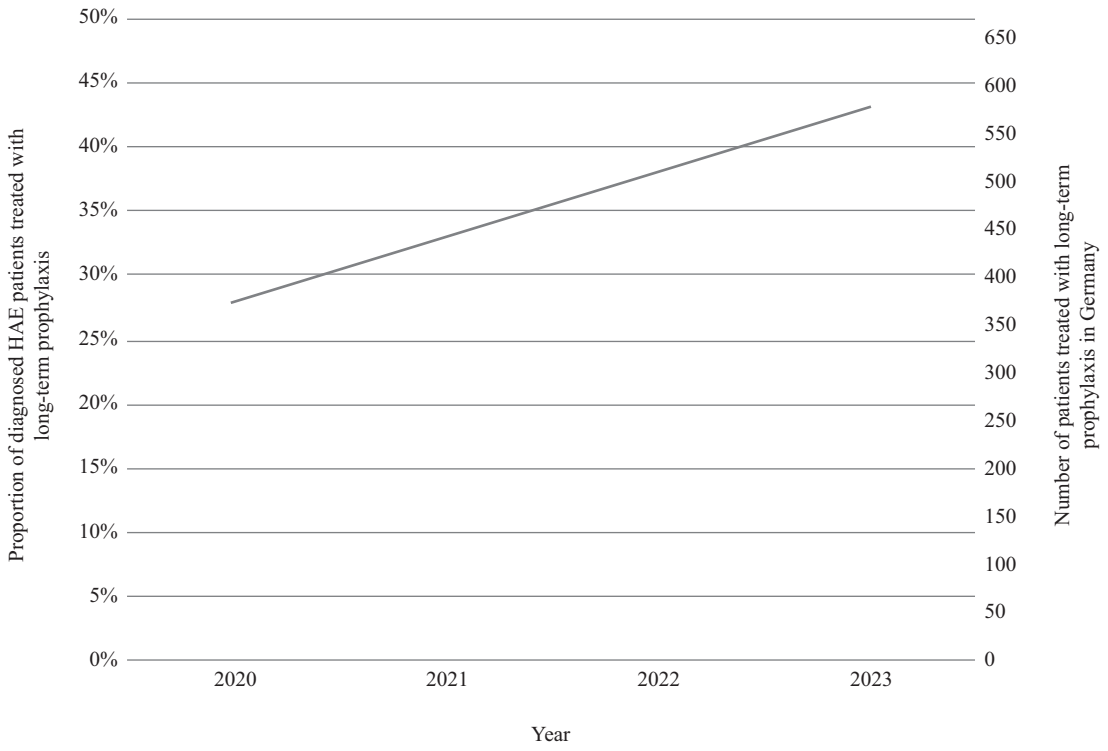

Figure 2. Number of HAE patients with long-term prophylaxis from 2020 to 2023. Based on 1,350 patients diagnosed with HAE in Germany in 2020, who are assumed to remain stable, long-term prophylaxis is predicted to increase by 5% per year for the 28% who received this treatment in 2020, based on consensus.

patients), and 43% (581 patients) in 2021, 2022 and 2023, respectively; assuming a constant point prevalence of 1,350 patients (*figure 2*).

Prior to this study, little was known about the proportion of patients treated with on-demand medication only and those who received long-term prophylaxis, especially since lanadelumab was introduced in 2019. A patient survey among participants of the United States Hereditary Angioedema Association patient summit in 2013 found that 66% of HAE-C1INH and 17% of HAE-nlC1INH patients were treated with prophylaxis treatment. These figures, however, might have been highly biased since all study subjects attended the summit, were self-selected and may have differed significantly from the general HAE population [18]. A US claims database study from 2019 of C1INH-HAE patients found that C1-INH(IV) was used for routine HAE prophylaxis by at least 25% of patients [19]. In Japan, 60% of HAE patients self-reported the regular use of long-term prophylaxis in 2016-2017 [20].

Our data on changing the treatment interval from two to four weeks in patients treated with lanadelumab are consistent with a recent analysis of pharmaceutical data [21]. Using German pharmaceutical data, it was shown that out of 44 patients with at least 12 months of lanadelumab treatment, 21 (48%) patients received dose reduction. The mean time to dose reduction was 110 days for probable and definite dose reduction and 88 days for definite dose reduction only. The questions about the dosing regimen of lanadelumab in our study were guided by the product information from the European public assessment report which states that the recommended starting dose is 300 mg lanadelumab every two weeks with possible reduction to 300 mg lanadelumab every four weeks. In practice, other treatment regimens are conceivable (*e.g.* 300 mg every three weeks), however, information related to such regimens was not available in this study.

No consensus was achieved regarding operationalized criteria for starting long-term prophylaxis and to define attack-free patients. The criteria stated by the experts for starting long-term prophylaxis and a possible dose reduction of lanadelumab indicate that freedom from attacks is not the only focus of clinical management. The wide range of responses speaks in favour of extended therapy goals related to quality of life, disease control and symptom frequency. In practice, the decision to reduce treatment to 300 mg lanadelumab every four weeks is patient-specific and could not be brought under a common denominator based on our Delphi panel. Further research is needed to further operationalize these topics in the future.

Limitations

Limitations must be taken into account when interpreting the statements made in a Delphi survey. On the one hand, future research (including survey-based trends) is a construct based on consensus about the assessment of the future by the experts questioned [22]. Other experts may therefore arrive at different assessments. However, this risk was minimized by the selection of professional representativeness among HAE experts. There are about 20 HAE-C1-INH practitioners in Germany, and the practitioners of about 75% of all patients were included in this study. Secondly, the study results are based on a rather small sample size of $n = 8$ experts. Also, experts could be positively or negatively

biased regarding the use of new drugs for the treatment of rare diseases. This is particularly the case when more experts are involved in the research of a drug (*e.g.* in Phase III studies). However, these possible biases were minimized by aggregating individual values. The survey referred to HAE patients in Germany without specification of type I or II HAE only, or whether type III HAE (HAE with normal C1-INH) was also included. Therefore, it cannot be excluded that some experts included type III HAE patients in their estimates. However, since estimate variance in the first round was low (inter-quartile range: 325 patients) and a consensus on 1,350 patients was achieved in the second round, this risk is considered low by the authors.
Criteria used for ranking the open questions in the second round were based on a summary of the first-round responses, which was subject to researcher influence. No validated methods such as factor analyses were used to summarize the criteria for the second round.

Conclusion

Based on Delphi consensus, we estimate that 28% of German HAE-C1-INH patients are currently treated with HAE-C1-INH long-term prophylaxis. Criteria to start long-term prophylaxis treatment included quality of life, disease control, and symptom frequency in patients. Further research is needed to validate whether broader therapeutic goals, beyond pure freedom of attacks, should be defined for the clinical management of HAE-C1-INH patients. ■

Acknowledgements and disclosures. *Acknowledgements: this study was financially supported by Takeda Pharma Vertrieb GmbH & Co. KG. The sponsor was involved in the study design and wording of the questionnaire but had no role in data collection, data analysis, or data interpretation in either of the Delphi rounds. We thank Tobias Vogelmann (LinkCare GmbH, Stuttgart, Germany) for his assistance with medical writing.*
Conflicts of interest: IMS has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, Octapharma, KalVista, and Takeda/Shire and/or has served as a consultant and/or participated in advisory boards for these companies. MMau is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, ArgenX, AstraZeneca, BioCryst, Celldex, Centogene, CSL Behring, FAES, Genentech, GIINNOVATION, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, Third HarmonicBio, UCB, and Uriach. LK has received honoraria and travel grants from Takeda/Shire, CSL Behring. MMag is or was a speaker and/or advisor for Almirall, BioCryst, CSL Behring, Dyax, Novartis, Octapharma, Kalvista, Shire/ Takeda, Pharming. ND has received travel grants and speaker fees from CSL Behring, Pharming, Shire, Takeda and Viropharma. US has received travel and research grants, as well as honoraria for speaking engagements, from CSL Behring, Shire, Takeda and Viropharma. JG has received travel and research grants, as well as honoraria for speaking engagements, from CSL Behring, Shire, Takeda and Viropharma. RB has received speaker fees from ALK, Allergopharma, Astra Zeneca, Bencard, Behring, GSK, HAL, Leti, Lofarma, Novartis, Sanofi, Shire, Stallergenes, Takeda, Thermo-Fischer, and/or participated in advisory boards. JK and AF are employees of Takeda Pharma Vertrieb GmbH & Co. KG. TS is owner and employee of LinkCare GmbH, which has received honoria from Takeda Pharma Vertrieb GmbH & Co. KG.

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