SUPPLEMENTARY MATERIAL

METHODS

Systematic review

Table A 1. Literature search terms, strategy and characteristics.

Nº	POPULATION: HEREDITARY ANGIOEDEMA
#1	"Hereditary angioedema types I and II" [MESH]
#2	"Hereditary angioedema type I"
#3	HAE
#4	HAE-C1INH
#5	"Hereditary C1-inhibitor deficiency"
#6	"C1-INH deficiency"
#7	"Deficiency of C1-esterase inhibitor"
#8	"C1-inhibitor deficiency"
#9	"C1-esterase inhibitor deficiency"
Nº	**OUTCOMES: DISEASE CONTROL GOALS**
#10	"Therapy goals"
#11	"Therapeutic goals"
#12	"treatment target*"
#13	"Clinical response"
#14	"Clinical remission"
#15	"disease activity"
Nº	**OUTCOMES: BIOMARKERS**
#16	Biomarkers [MESH]
#17	Markers
Nº	**OUTCOMES: PATIENT-REPORTED OUTCOMES INSTRUMENTS**
#18	"Patient Reported Outcome Measures" [MESH]
#19	"Patient Reported Outcome*"
#20	PROs
#21	"Quality of Life" [MESH]
#22	"Health-related quality of life"
#23	HRQOL
#24	HAE-QoL
#25	"Activity score"
#26	"Control Test"
#27	AE-QoL

SEARCH STRATEGY
("Hereditary angioedema types I and II"[MESH] OR "Hereditary angioedema type I" OR HAE OR HAE-C1-INH OR "Hereditary C1-inhibitor deficiency" OR "C1-INH deficiency" OR "Deficiency of C1-esterase inhibitor" OR "C1-inhibitor deficiency" OR "C1-esterase inhibitor deficiency") AND ("Therapy goals" OR "Therapeutic goals" OR "treatment target*" OR "Clinical response" OR "Clinical remission" OR "disease activity" OR "Patient Reported Outcome Measures"[MESH] OR "Patient Reported Outcome*" OR PROs OR "Quality of Life"[MESH] OR "Health-related quality of life" OR HRQOL OR Biomarkers[MESH] OR Markers OR "Activity score" OR "Control Test" OR "guidelines" OR "recommendations" OR "consensus")
CHARACTERISTICS OF THE SEARCH
Database: PubMed
Applied filter: Human
Text availability: Abstract
Publication year: Published in the last 20 years
Language: English and Spanish

Delphi consultation

A Scientific Committee consisting of five Spanish allergologists with extensive experience in HAE met online in November 2020 to discuss available evidence and experience and to develop and propose recommendations for the treatment of patients with HAE-C1INH based on a T2T approach to be included in a Delphi survey.

A Delphi questionnaire was developed and implemented online, and included 45 recommendations divided into four domains: 1) on-demand treatment; 2) short-term prophylaxis; 3) long-term prophylaxis; and 4) general management. For each statement, the participants were asked to indicate their degree of agreement on a Likert scale from 1 to 9, with 1 representing “I totally disagree” and 9 representing “I totally agree”.

A panel of 65 experts in the management of HAE were invited to take part in the Delphi survey, almost all of whom were allergologists. Only two were immunologists, reflecting the fact that HAE-C1INH in Spain is mainly managed by allergologists. Sociodemographic variables were included to describe the panel and ensure sufficient expertise on the topic. Province, number of years in clinical practice, and number of patients with HAE-C1INH seen in their practices were collected. Mean, standard deviation, median, interquartile range, minimum and maximum values were calculated.

After each round, the appropriateness of each statement and panel consensus was assigned using the RAND/UCLA method (1). Thus, a statement was defined as “appropriate” when the median score was between 7 and 9, “inappropriate” when the median score was between 1 and 3, and “undetermined” when it was between 4 and 6. “Agreement” was achieved if at least one third of the sample responded within the same score range as the median, “disagreement” if the median score fell in either of the two extremes and more than one third of the sample responded in the opposite extreme interval, or if the median fell in the central interval, and at least one third of the sample responded in one of the two other intervals, and “neutral” if it did not meet any of the previous criteria. Items that did not achieve “agreement”

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(consensus), were entered in the second-round questionnaire, in which panelists were asked to score the items again on a 9-point Likert scale, but this time they could see the results from the entire panel, and thus change their scoring to reach consensus. Additionally, one question was submitted to the panel, which was not subject to consensus, asking them to score the importance of a series of criteria for the initiation of LTP.

The first Delphi round was conducted in February 2021 and the second round in March-April 2021.

RESULTS

Delphi consultation

Sixty-one HAE experts agreed to participate, 53 of whom completed both rounds of the Delphi questionnaire. Participants represented 10 different Spanish regions and 42 hospitals and had been practicing their specialty for a median of 21 years (IQR: 17-29). The median number of years of experience was close to the mean (22; SD: 7), and each specialist treated a median of 10 patients with HAE-C1INH (IQR: 3-20).

After the first round, 41 of the 45 statements were classified as *appropriate* and reached agreement. Three items that were considered *appropriate* in the first round but did not reach agreement were reconsidered during the second round, at which stage they achieved consensus (agreement). The fourth, which was initially classified as *undetermined* and did not reach agreement**,** did not change its status after the second round.

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Table A2. Results of the Delphi rounds regarding recommendations agreed by the panel of experts for on-demand treatment (ODT).

Recommendation	Median score	Participants voting in the "appropriate" range (%)
1. The goal of ODT for angioedema attacks should be to minimize associated morbidity and mortality.	9	100
2. The most appropriate ODT should be chosen by the clinician and a well-informed patient working together, based on his/her specific needs and preferences.	9	94.2
3. All angioedema attacks are candidates for ODT.	8	84.6
4. All angioedema attacks should be treated as early as possible.	9	86.5
5. All patients diagnosed with HAE-C1INH should have 2 complete doses of angioedema-specific medication at their disposal at all times.	9	84.6
6. The patient should be adequately trained in the self-administration of angioedema ODT.	9	98.1
7. The patient's competence in ODT self-administration should be periodically evaluated.	9	98.1
8. A patient with an upper airway angioedema attack should attend the emergency room after treatment, in order to monitor the degree of airway involvement.	9	98.1
9. The need for naso- or orotracheal intubation or tracheotomy should always be considered in the case of an upper airway angioedema attack.	9	94.2
10. An abdominal echography is advisable in case of an abdominal angioedema attack that does not improve after specific angioedema ODT.	9	98.1

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Table A3. Results of the Delphi rounds regarding the recommendations for short-term prophylaxis (STP).

Recommendations	Median score	Participants voting in the "appropriate" range (%)
1. The objective of STP should be to prevent angioedema attacks associated with known triggers, such as medical, surgical, or dental procedures, and stressful life events.	9	100
2. STP should be administered before medical or surgical procedures to prevent angioedema attacks.	9	94.2
3. STP should be administered before dental procedures with a risk of triggering angioedema attacks.	9	100
4. STP may be administered before or during any stressful life event that may worsen HAE-C1INH activity to prevent angioedema attacks.	9	98.1
5. Despite previous administration of STP, at least 2 doses of angioedema ODT should be available during and after medical, surgical, or dental procedures.	9	98.1
6. An urgent surgical intervention should never be delayed, even if STP has been administered less than one hour before.	8	88.5
7. The upper airway must be monitored after extubation in the case of procedures that required intubation.	9	100

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Table A 4. List of possible adverse events that might be included in the adverse event follow-up checklist

Possible adverse events	
Acne	Impotence
Allergic reactions	Weight gain
Alopecia	Infectious disease transmission
Anaphylaxis	Injection site reactions
Breast atrophy/hypotrophy	Insomnia
Cholestatic hepatitis	Altered libido
Complicated venous access	Liver adenocarcinoma
Decreased growth rate	Muscle cramps
Diarrhea	Myalgia
Dizziness	Nausea
Dysmenorrhea	Polycythemia
Dyslipidemia	Premature closure of epiphyseal plates
Gynecomastia	Rash
Headache	Rhabdomyolysis
Hematocrit increase	Seborrhea
Hematuria	Sexual dysfunction
Hepatic enzyme alterations (high ALT, AST)	Thrombosis
Hepatocellular adenoma	Transient increases in muscle enzymes (creatine phosphokinase and aldolase)
High blood pressure	Virilization in women
Mood changes	Voice deepening
Hypersensitivity	Vomiting
Hypotension	Other

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Table A5. Results of the Delphi rounds regarding recommendations for long-term prophylaxis (LTP).

Recommendation	Median score	Participants voting in the "appropriate" range (%)
LTP indication and switch criteria		
1. LTP requirements should be considered at each follow-up visit.	9	100
2. The decision to initiate LTP should be shared between the physician and the patient.	8	86.5
3. The selection of the most appropriate LTP treatment should be shared between the clinician and a properly informed patient.	9	94.2
4. The criteria for LTP indication are the same in adults and children.	8	76.0
5. The desired effectiveness will influence the selection of LTP type	8	72.0
6. If the patient has an insufficient response to the treatment, it should be adjusted or switched.	9	96.2
LTP goals and outcome measurement		
1. LTP goals should be established by the clinician and the patient working together.	9	96.2
2. A goal for LTP is to reduce the angioedema attack rate.	9	98.1
3. LTP response is assessed based on the decrease in the angioedema attack rate.	8	90.4
4. A goal for LTP is to reduce the rate of severe angioedema attacks.	9	98.1
5. A goal for LTP is to reduce the duration of angioedema attacks.	8	82.7
6. The Hereditary Angioedema-Activity Score (HAE-AS) should be used as a tool to assess overall disease activity and the AngioEdema Control Test (AECT) for the assessment of disease control	8	82.7
7. The LTP response with respect to any of the aforementioned goals should be assessed between 3 and 6 months after starting the treatment.	8	94.2
Health-related quality of life (HRQoL)		
1. HRQoL should be assessed at least every 6 months.	8	84.6
2. HRQoL should be assessed by the specific questionnaire Hereditary Angioedema-Quality of Life (HAE-QoL) or the Angioedema-Quality of Life (AE-QoL).	9	92.3
3. The LTP response should be considered appropriate when HAE-QoL or AE-QoL scores improve.	7	80.8
4. If the LTP response in terms of the HAE-QoL score is not sufficient, treatment adjustment or switch should be considered.	7	84.6
Adverse events (AE)		
1. AEs associated with LTP should be monitored at every follow-up visit.	9	96.2
2. AEs associated with LTP should be monitored using an *ad hoc* checklist.	9	94.2
3. The probability of experiencing certain AEs or side effects will influence the choice of LTP treatment.	9	96.2

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Table A6. Results of the Delphi rounds regarding recommendations on general aspects of HAE-C1INH treatment.

Recommendation	Median score	Participants voting in the "appropriate" range (%)
Patient satisfaction with treatment		
1. Patient satisfaction with treatment should be assessed periodically.	9	100
2. Patient satisfaction should be considered as a criterion for considering the maintenance/switching of treatment.	9	94.2
3. Patient satisfaction should be assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM) in its original (14 items) or abbreviated (9 items) version.	7	68
Cost and accessibility of treatment		
1. Treatment cost influences the treatment choice.	7	63.5
2. All patients should have access to all treatments independently of their place of residence.	9	98.1
Patient diary		
1. Patients should keep a diary to record the characteristics of each angioedema attack (location, severity, duration, ODT administration, and response to ODT), whether STP was administered and reason, or if the patient is receiving LTP.	9	96.2
2. Analysis of the patient diary may help optimize treatment and identify unknown triggers.	9	98.1

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Table A3. Complete list of Delphi panelists and corresponding place of work.

Name	Hospital
Andalucía	
Inmaculada Doña	Hospital Regional Universitario, Malaga
Blanca Sáenz de San Pedro	Complejo Hospitalario de Jaén, Jaén
Stefan Cimbollek	Hospital Universitario Virgen Del Rocío, Seville
Krasimira Baynova	Hospital Universitario Virgen Del Rocío, Seville
Macarena Piñero	Hospital Juan Ramón Jiménez, Huelva
Lourdes Fernández Delgado	Hospital Universitario Reina Sofía, Cordoba
Vanesa Saíz	Hospital Universitario Reina Sofía, Cordoba
Principado de Asturias	
Carmen Díaz Donado	Hospital Universitario Central de Asturias, Oviedo
Islas Baleares	
Jaume Pons	Hospital Universitari Son Espases, Palma de Mallorca
Canarias	
Lourdes Almeida	Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria
Cantabria	
Isabel Jiménez	Hospital Universitario Marqués de Valdecilla, Santander
Castilla y León	
Pedro Carretero	Hospital Universitario de Burgos, Burgos
Castilla-La Mancha	
Ángel del Moral	Complejo Hospitalario de Toledo, Toledo
María del Mar Jiménez Lara	Complejo Hospitalario de Toledo, Toledo
Jesús Jurado	Hospital General Nuestra Señora Del Prado, Talavera de la Reina
Paz Flores	Hospital General de Almansa, Almansa
Patricia Prieto	Complejo Hospitalario Universitario de Albacete, Albacete
Cataluña	
Joan Bartra	Hospital Clínic de Barcelona, Barcelona
Paula Galván	Hospital Universitari Vall d'Hebrón, Barcelona
Anna Sala-Cunill	Hospital Universitari Vall d'Hebrón, Barcelona
Blanca Andrés	Hospital Universitari Bellvitge, L'hospitalet de Llobregat
Lluís Marqués	Hospital Universitari Santa María and Hospital Universitari Arnau de Vilanova, Lleida
Comunidad Valenciana	
Gemma Mencía Sánchez	Hospital Clínico Universitario, Valencia
Dolors de las Marinas	Hospital General Universitario, Valencia
Ana Ferrer Franco	Hospital Universitario Doctor Pesset, Valencia
Ethel Ibáñez Echevarría	Hospital Universitario La Fe, Valencia
Ramón Almero	Hospital Universitario La Fe, Valencia
Mónica Antón Gironés	Hospital General Universitario del Vinalopó, Elche
Carlos Hernando de Larramendi	Hospital Marina Baixa de la Vila Joiosa, Villajoyosa
Extremadura	
Sergio Luis Porcel Carreño	General Universitario San Pedro De Alcántara, Cáceres
Galicia	
Beatriz Veleiro	Complexo Hospitalario Universitario A Coruña, A Coruña
María Rosario López Rico	Complexo Hospitalario Universitario A Coruña, A Coruña

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Virginia Rodríguez Vázquez	Complexo Hospitalario Universitario de Santiago, Santiago de Compostela
Carmen Marcos Bravo	Complejo Hospitalario Universitario de Vigo, Hospital Meixoeiro, Vigo
Pilar Iriarte Sotés	Complexo Hospitalario Universitario de Ferrol, El Ferrol
Raquel López Abad	Complexo Hospitalario Universitario de Ferrol, El Ferrol
Celsa Pérez Carral	Complexo Hospitalario Universitario de Eoxi Pontevedra-O Salnés, Pontevedra
María Teresa Soto Mera	Complexo Universitario Hospitalario de Eoxi Pontevedra-O Salnés, Pontevedra
Susana Varela	Complexo Hospitalario de Ourense, Ourense
Comunidad de Madrid	
Ruth Mielgo	Hospital Universitario 12 De Octubre, Madrid
María Luísa Baeza	Hospital Universitario Gregorio Marañón, Madrid
Alicia Prieto García	Hospital Universitario Gregorio Marañón, Madrid
Rosario Cabañas	Hospital Universitario La Paz, Madrid
Carmen Gómez Traseira	Hospital Universitario La Paz, Madrid
Nieves Prior	Hospital Universitario Severo Ochoa, Leganés
Comunidad Foral de Navarra	
Ana Isabel Tabar Purroy	Complejo Hospitalario de Navarra, Pamplona
Blanca García Figueroa	Complejo Hospitalario de Navarra, Pamplona
País Vasco	
Teresa Macías	Hospital de Galdakao-Susunsolo, Galdakao
Gonzalo Bernaola	Hospital de Galdakao-Susunsolo, Galdakao
Olga Uriel Villate	Hospital Universitario Araba, Vitoria
María Dolores Martínez Antón	Hospital Universitario de Cruces, Bilbao
Pedro Gamboa	Hospital Universitario de Cruces, Bilbao
La Rioja	
Teófilo Lobera Labairu	Complejo Hospitalario San Millán San Pedro, Logroño
Idoia González Mahave	Complejo Hospitalario San Millán San Pedro, Logroño
María Dolores del Pozo Gil	Complejo Hospitalario San Millán San Pedro, Logroño

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