HICT

Clinical practice of HAE in Belgium

OPPORTUNITIES FOR OPTIMISED CARE

OPTIMISING HEALTHCARE

This white paper is the result of the expert panel discussion on hereditary angioedema (HAE) organized on June 13th, 2022 at Takeda Belgium (Zaventem)

Ghent, November 2022

Abstract

Introduction. Hereditary angioedema (HAE) is a rare disorder characterized by unpredictable painful and potentially life-threatening swelling episodes. The international WAO/EAACI guideline on HAE was recently updated. It was assessed to what extent the Belgian clinical practice was aligned with the revised guideline, and whether there were opportunities to optimise Belgian clinical practice in HAE.

Methods. We compared the updated international guideline for HAE with information available on Belgian clinical practice (i.e. a Belgian patient registry and expert opinion analysis). The Belgian patient registry was developed with the involvement of eight Belgian hospitals. Eight Belgian physicians from the centers included in the patient registry participated in the expert opinion analysis.

Results. The main action points to further optimise the Belgian clinical practice of HAE are: (1) Work towards total disease control and normalize patients' life by considering the use of new and innovative long-term prophylactic treatment options; (2) inform HAE patients about new long-term prophylactic therapies; (3) assure the availability of on-demand therapy for all HAE patients; (4) implement a more formal assessment including multiple aspects of the disease in the daily clinical practice; and (5) continue and expand an existing patient registry to assure continued data availability on HAE in Belgium.

Conclusions. In light of the updated WAO/EAACI guideline, five action points were identified and several other suggestions were made to optimise the Belgian clinical practice in HAE.

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1. Introduction

Hereditary angioedema (HAE) due to C1–inhibitor (C1-INH-HAE) deficiency or dysfunction, also referred to as HAE type 1 or type 2, is a rare autosomal dominant disorder characterized by recurrent, unpredictable, transitory, and painful swelling episodes that can become life-threatening in case of oropharyngeal involvement. The prevalence of C1-INH-HAE is estimated between 1.41 and 1.54 per 100 000 inhabitants (Nordenfelt et al., 2016; Schöffl et al., 2019; Bygum et al., 2009; Zanichelli et al., 2015). Considering the current Belgian population size, this translates to approximately 175 C1-INH-HAE patients (type 1 and 2) in Belgium.

The international WAO/EAACI guideline for managing HAE was revised and updated in 2021 (Maurer et al., 2022). To what extent the Belgian clinical practice aligns with the revised guideline was unclear. Moreover, changes in the clinical practice are expected, especially regarding long-term prophylactic treatment, as the new innovative treatment Takhzyro® (lanadelumab, anti-kallikrein monoclonal antibody) has become available in Belgium in July 2022 and other new treatment options like berotralstat and garadacimab might follow.

1.1. Objective

To set up a Belgian expert panel, aiming to identify opportunities for optimised care, leading to specific action points for the Belgian clinical practice of HAE, based on a comparison of the 2021 HAE guidelines with available information on the current Belgian clinical practice (a Belgian patient registry and Belgian expert opinion analysis).

2. Methods

Figure 1 visualizes the overall approach.

2.1. HAE patient registry

2.1.1. Approach

The primary objective of the retrospective patient registry was to collect data on Belgian clinical practice, as no epidemiological data on HAE for Belgium was available.

A nation-wide, multicentric study was initiated by Antwerp University Hospital (UZA) and involved the eight largest Belgian hospitals responsible for the follow-up of the majority of patients with C1-INH-HAE. Included hospitals were:

- Antwerp University Hospital (UZA),
- Ghent University Hospital (UZ Gent),
- Leuven University Hospital (UZ Leuven),
- Centre Hospitalier Universitaire Brugmann (CHU/UVC Brugmann),
- Centre Hospitalier Universitaire de Saint-Pierre (CHU/UMC Saint-Pierre),
- Cliniques Universitaires de Saint-Luc (UC Louvain),
- Centre Hospitalier Régional de la citadelle Liège (CHR Citadelle),
- Centre Hospitalier Universitaire de Liège (CHU Liège).

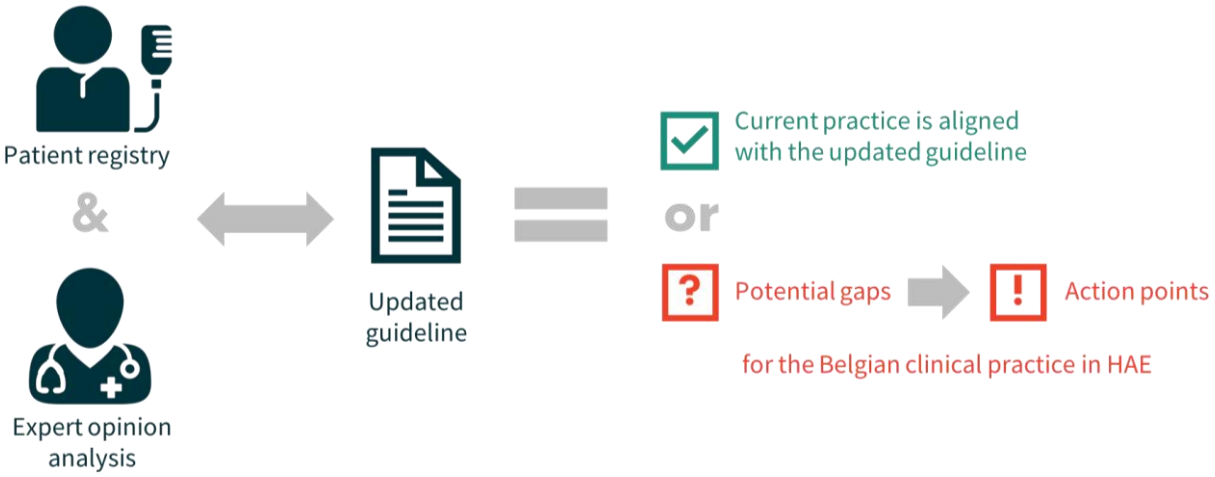

Figure 1. By comparing all available sources (the Belgian patient registry, the Belgian expert opinion analysis, and the updated guideline), action points were identified to further optimise the Belgian clinical practice in HAE.

HAE patients or their relatives filled in a questionnaire. There were no restrictions on age or type of C1-INH-HAE. The treating physician was contacted by UZA to collect additional clinical data on participants to the HAE patient registry.

2.1.2. Time frame

The patients filled out the questionnaire between 2018 and 2021.

2.1.3. Participants

One hundred eighty HAE patients were invited to fill in the questionnaire. One hundred twenty-five patients completed the questionnaire.

2.1.4. Reporting

Results of the patient registry were shared and discussed during the expert panel meeting (see supra). A separate publication will describe the results of the prefinal patient registry.

2.2. Expert opinion analysis

2.2.1. Approach

The expert opinion analysis aimed to better understand the current and future clinical practice and decision process for treating C1-INH-HAE in Belgium, particularly on prophylactic treatment. Questions in the expert opinion analysis aligned with the patient registry questionnaire, allowing to compare physician and patient perspectives on specific topics. A survey was developed by Hict, an independent company, based on exploratory literature review and critically reviewed during a pilot interview with a physician with expert knowledge on HAE (prof. Dr. DG Ebo). Eight centres that treat the vast majority of HAE patients in Belgium were invited to participate in the expert opinion analysis, of which 7 centres participated. A follow-up 1-to-1 interview was performed with all experts who completed the survey. Hict processed the answers and any additional information provided.

The survey and interviews focused on adult and adolescent C1-INH HAE patients of type 1 and 2.

2.2.2. Time frame

Data were collected between June and September 2021.

2.2.3. Participants

Following Belgian physicians participated, from the same centres that were included in the patient registry:

- Prof. Dr. DG Ebo & dr. A Van Gasse & dr. ML van der Poorten (UZA),
- Prof. Dr. F Haerynck & Dr. J Willekens (UZ Gent, adolescent population),
- Prof. Dr. C Hermans (UC Louvain),
- Prof. Dr. H Lapeere (UZ Gent, adult population),
- Prof. Dr. O Michel (CHU/UVC Brugmann),
- Prof. dr. M Moutschen (CHU Liège),
- Prof. Dr. R Schrijvers (UZ Leuven),
- Dr. H Simonis (CHR Citadelle).

2.2.4. Reporting

The results of the expert opinion analyses were discussed during the panel discussion. Together with the patient registry, this was used to identify gaps in the Belgian clinical practice.

2.3. Panel discussion

The expert panel was organized on June 13th and moderated by Hict. Prof. Dr. Ebo, Prof. Dr. Hermans, Prof. Dr. Schrijvers, Prof. Dr. Michel, Dr van der Poorten and Dr. Willekens participated in the meeting. Prof. Dr. Moutschen did not attend the meeting but endorsed the results of the panel discussion.

During the expert panel, Prof. Dr. Hermans presented the updated guideline, focusing on the newly added or revised recommendations. Next, Prof. Dr. Ebo and Hict presented the results of the patient registry and the expert opinion analysis. Potential gaps in the current Belgian clinical practice concerning the recently updated guideline were identified and discussed. Finally, Hict moderated an interactive discussion with all participants to come to clear, tangible action points to further upgrade and support the Belgian clinical practice in HAE.

3. Results

Table 1 provides an overview of the revised guideline (Maurer et al., 2022).

*Table 1. Thematically ordered overview of the revised WAO-EAACI guideline (Maurer et al., 2022). **Red highlighted text** indicates adaptations, and recommendations with a red no. were newly added (vs. the previous guideline (Maurer et al., 2017)).*

	Diagnosis
1	We recommend that all patients suspected to have C1-INH-**HAE** are assessed for blood levels of C1-INH function, C1-INH protein, and C4.
2	We **suggest** that testing for C1-INH function, C1-INH protein, and C4 is repeated **in patients who test positive**, to confirm the diagnosis of HAE-1/2.
3	We recommend that patients who are suspected to have C1-INH-HAE and have normal C1-INH levels and function are assessed for known SERPING1 mutations underlying HAE-nC1-INH.
20	We recommend testing children from HAE-affected families be carried out as soon as possible and all offspring of an affected parent be tested
28	We recommend screening first-degree family members of patients for HAE.
	Treatment approach
4	We recommend that all attacks are considered for on-demand treatment.
5	We recommend that any attack affecting or potentially affecting the upper airway is treated.
6	We recommend that attacks are treated as early as possible.
9	We recommend that all patients have sufficient medication for on-demand treatment of **at least** two attacks and carry on-demand medication at all times.
10	We recommend considering short-term prophylaxis before **medical, surgical, or dental procedures as well as exposure to other angioedema attack-inducing events**.
12	We suggest considering prophylaxis prior to exposure to patient specific angioedema inducing situations.
13	We recommend that the goals of treatment are to achieve total control of the disease and to normalize patients' lives.
14	We recommend that patients are evaluated for long-term prophylaxis at every visit, taking **disease activity**, burden, and **control** as well as patient preference into consideration.
19	We suggest all patients who are using long-term prophylaxis be routinely monitored for disease activity, impact, and control to inform optimization of treatment dosages and outcomes.
23	We recommend that all patients have an action plan.
24	We **recommend** that HAE-specific comprehensive, integrated care is available for all patients.
25	We recommend that patients are treated by a specialist with specific expertise in managing HAE.
27	We recommend that all patients should be educated about triggers that may induce attacks.
	Therapies
7	We recommend that attacks are treated with either **intravenous** C1 inhibitor, ecallantide, or icatibant.
8	We recommend that intubation or surgical airway intervention is considered early in progressive upper airway edema.
11	We recommend the use of intravenous plasma-derived C1 inhibitor as first line shortterm prophylaxis.
15	We recommend the use of **plasma-derived** C1 inhibitor as first-line long-term prophylaxis.
16	We recommend the use of lanadelumab as first-line long-term prophylaxis.
17	We recommend the use of berotralstat as first-line long-term prophylaxis.
18	We **recommend** the use of androgens **only** as second-line long-term prophylaxis. For more information see also SHAERPA (Stopping androgen treatment in patients with HAE – Characterization of rationale, protocols and development of advice for patients and physicians).
21	We recommend C1 inhibitor **or icatibant** be used for the treatment of attacks in children under the age of 12.
22	We recommend **plasma-derived** C1 inhibitor as the preferred therapy during pregnancy and lactation.
26	We recommend that all patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer.

3.1. Main opportunities to optimize the Belgian clinical practice

Most (82%) of the Belgian C1-INH-HAE patients still experienced multiple attacks in the last year (median of 5 attacks per year). Both patients and experts acknowledged a significant impact on patient lives: work, hobbies, school, and living in fear. This finding contrasts with recommendation 13 of the revised guideline, stating that the treatment goal is to achieve total disease control and normalize patients' lives. Maurer et al. (2022) define complete control as "no longer having attacks." The use of less preferred treatment options might explain the occurrence of attacks: the experts reported almost 40% off-label use tranexamic acid (Exacyl®) or the use of a second-line product danazol (Danazol®) (Figure 2). Another explanation could be limited compliance to current therapy, potentially related to the intravenous administration route of current prophylactic treatment options.

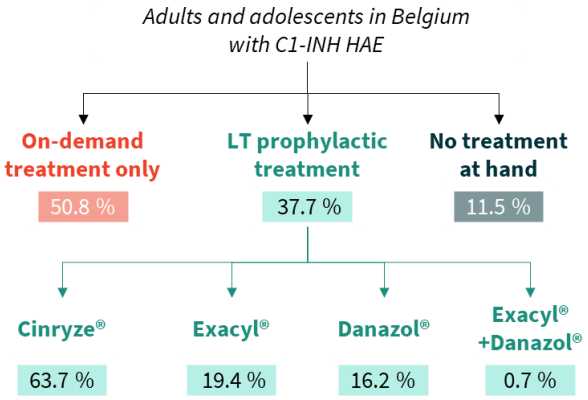

Figure 2. Used long-term prophylactic treatment options, as estimated in the expert opinion analysis.

Early treatment in C1-INH-HAE is crucial. Self-administration can facilitate early treatment (Maurer et al., 2022). On-demand treatment should be considered for all attacks (recommendation 4), and patients should have on-demand treatment at hand for at least two attacks (recommendation 9). Based on the expert opinion analysis (Figure 2) and the patient registry, 11.5% to 16% of HAE patients, respectively, do not have on-demand treatment at hand despite being recommended and/or prescribed.

The updated WAO EAACI guideline states that long-term prophylactic treatment is the only way to achieve total disease control (recommendation 13). This finding also contrasts with the Belgian HAE patients still experiencing 5 attacks (median) per year, while less than 40% of them are currently on long-term prophylactic treatment. In order to achieve this treatment goal in HAE, long-term prophylactic treatment should be considered at each visit based on a variety of elements (recommendation 14), including quality of life (QOL). Based on the expert opinion analysis, there is a lack of formal assessment of QOL during visits. Most experts (n=5) indicated that this is due to a lack of time.

It is recommended that HAE patients have a medical evaluation at least once a year (Maurer et al., 2022). Specifically for patients using long-term prophylactic treatment, routine monitoring is recommended (recommendation 19). However, experts indicated that several HAE patients are lost to follow-up. It is unclear if other physicians follow up these patients.

The revised guideline recommends plasma-derived C1 inhibitor, lanadelumab, or berostralstat as first-line treatment for long-term prophylactic treatment (recommendation 15-17), androgens as a second-line treatment only (recommendation 18) and does not recommend tranexamic acid. As shown in Figure 2, the current clinical practice is not entirely in line with these recommendations. It should be noted that, at the time of data collection, only one of the recommended first-line therapies (i.e. plasma-derived C1-INH) was available in Belgium.

3.2. Proposed action points

The expert panel identified five concrete action points to optimise the Belgian clinical practice in HAE.

Action point 1

Work towards total disease control and normalize patients' life by considering the use of new and innovative long-term prophylactic treatment options.

A challenging treatment goal was added to the revised guideline (Maurer et al., 2022), namely that the treatment goal in C1-INH-HAE is to achieve total disease control and normalize patients' lives. To achieve this long-term

prophylaxis should be individualized and considered in all C1-INH-HAE patients of type 1 and 2 taking into consideration the disease activity, patient's quality of life, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy.

New and innovative long-term prophylactic treatment options are expected to be a gamechanger in the clinical practice of HAE, of which lanadelumab (Takhzyro®) is the first reimbursed in Belgium.

Based on the expert opinion analysis, a 10% increase in LT prophylactic treatment for adults and adolescents in Belgium with C1-INH-HAE (type 1 and 2) is expected. During the panel discussion, several experts expressed the need for an even larger shift towards long-term prophylactic treatment in patients not adequately controlled with on-demand treatment only.

Moreover, experts expect a significant shift from existing prophylactic therapies. Hence, the availability of new LT prophylactic treatment options should also lead to a reduced use of tranexamic acid Exacyl® (off-label product) or danazol Danazol® (second-line product). For more information see also SHAERPA (Stopping androgen treatment in patients with HAE – Characterization of rationale, protocols and development of advice for patients and physicians).

In order to manage this significant shift towards total disease control, and with lanadelumab (Takhzyro®) that has become commercially available as from July 1st 2022, HAE patients should be contacted pro-actively by the treating physicians, such as those not well controlled on current prophylactic treatment or previously not eligible for prophylactic treatment. Other patients, such as those with lower disease activity but still room for improvement on QOL or disease control, can be identified gradually during their regular consultations.

It should be noted that prioritization in HAE patients remains challenging due to the unpredictability of the disease.

Action point 2

Inform C1-INH-HAE patients about new long-term prophylactic therapies.

All physicians should inform their own HAE patients. Informing patients should be done proactively and can be done gradually taken into consideration the practical feasibility. The information from the patient registry can support physicians in this approach.

A possible approach is to reach at least one person within each family. In addition, patient days, patient organizations or digital platforms such as the Facebook community HaveYourSay and the patient website mijnhae.com can be leveraged to inform all HAE patients, including those not included in the registry or lost to follow-up. Lastly, various stakeholders can use this whitepaper for further outreach to physicians and patients.

Action point 3

Assure the availability of on-demand therapy for all C1-INH-HAE patients.

Despite some limitations (such as expiration of medication), the expert panel is convinced that the availability of on-demand therapy should be improved.

All physicians should re-evaluate the availability of 2 doses of on-demand therapy in their HAE patient population. Again, patients lost to follow-up should not be overlooked.

In some cases, it can be considered to assure the availability of on-demand therapy for a household with multiple HAE patients rather than each HAE patient individually. It is questioned if this is sufficient, for example, when one of the family members travels or if students live in another city most of the time. Hence, this solution might only apply to a limited number of families.

Lastly, it can also be useful to communicate to patients in which hospital pharmacies on-demand treatment is available.

Action point 4

Implement a more formal assessment including multiple aspects of the disease in the daily clinical practice.

The assessment should incorporate QOL, disease burden (e.g. impact on life), and quantitative information such as the number of attacks within a specified period. The Belgian expert physicians should agree on a minimal set of questions based on validated questionnaires (e.g. the Angioedema Quality Of Life questionnaire (AE-QOL), or the Angioedema Control Test (AECT)). The assessment should be performed at least once a year. Each centre and physician is free to add questions or increase the frequency of assessment.

Practical implementation should be done individually and may differ between centres or patients. Differences can include the format (e.g. on paper, electronic), the location (e.g. at home, in the waiting room, at the hospital pharmacy), and timing.

Though the primary goal of this assessment is the routine follow-up of patients and to assist in treatment decisions, this formal assessment can also serve as input for the healthcare payer or complement the patient registry.

Action point 5

Continue and expand existing patient registry to assure continued data availability on HAE in Belgium.

It is highly relevant to assure the availability of up-to-date data to accommodate the requirements of the Belgian healthcare payer. If a new patient registry can quantify the impact of lanadelumab (Takhzyro®), this can also contribute to the continued availability of novel long-term prophylactic therapies.

A new patient registry should be as similar as possible to the current one to allow a comparison of the results. However, additional questions could be included based on learnings from the current patient registry.

3.3. Additional suggestions for the Belgian clinical practice

The expert panel raised several suggestions to further improve clinical practice.

All physicians treating HAE patients should be aware of the updated guideline and use this as a checklist to guide them in the diagnosis, treatment approach, therapy selection, and follow-up. A more visual presentation of the guideline may be helpful.

As an attack involving the larynx may be fatal, all caregivers who come into contact with HAE patients should be aware of the recommendation to consider intubation or surgical airway intervention early in the case of progressive upper airway edema (Recommendation 8).

Patient awareness, training, and motivation can help their understanding of the disease and help identify personal triggers and therapy adherence.

Due to the rarity of the disease, the time to diagnosis is often considerable. Broader awareness of the disease and a preliminary/screening C4 test may improve the time to diagnosis.

The international guideline recommends the treatment of patients by HAE experts, preferably in expert centres (Maurer et al., 2022). The formation of expert centres is not easy in Belgium, but accreditation through international entities like ACARE, a Ga²len /HAE network (Maurer et al., 2020) may be the first step towards this goal.

3.4. Limitations of this study

Two important limitations were identified.

First, regarding the comparison made, the updated guideline was only published after all data collection was performed. Moreover, none of the innovative long-term prophylactic treatment options were commercially available at the time of data collection on the Belgian clinical practice. This limitation was clearly mentioned and taken into account during the expert panel discussion.

Second, data collection via expert opinion has important limitations, therefore being the lowest level of evidence. However, expert opinion is recognized as a relevant component in evidence-based medicine (Hohmann et al., 2018), and is highly valuable to gain insights into the daily clinical practice, which fits our objective of identifying opportunities for optimised care and formulating action points specifically for the Belgian clinical practice of HAE.

4. Conclusion

Comparing the updated guideline for C1-INH-HAE with a Belgian patient registry and a Belgian expert opinion analysis during an expert panel discussion identified opportunities to further optimise the Belgian clinical practice in C1-INH-HAE. The expert panel identified five action points to support the Belgian clinical practice of HAE:

1. Work towards total disease control and normalize patients' life by considering the use of new and innovative long-term prophylactic treatment options;
2. Inform C1-INH-HAE patients about new long-term prophylactic therapies;
3. Assure the availability of on-demand therapy for all C1-INH-HAE patients;
4. Implement a more formal assessment including multiple aspects of the disease in the daily clinical practice;
5. Continue and expand existing patient registry to assure continued data availability on HAE in Belgium.

In addition, further opportunities for the Belgian clinical practice in HAE were identified related to physician awareness, broader caregiver awareness, patient awareness, time to diagnosis, and expert centres.

Abbreviations

AECT: Angioedema Control Test; **AE-QOL**: Angioedema Quality Of Life questionnaire; **C1-INH**: C1 inhibitor; **HAE**: hereditary angioedema; **QOL**: quality of life; **WAO/EAACI**: World Allergy Organization/ European Academy of Allergy and Clinical Immunology. LT, OD, ...

Contact information

This whitepaper was developed by Hict for Takeda. Hict is an independent company that provides expert advice to health care providers, health care suppliers and public services in the health care sector. The contributors from Hict were Amber Werbrouck, Ann Tanghe, Britt Callebaut.

Contact details: Amber.Werbrouck@hict.be; +32 478 29 05 79.

Acknowledgments

Hict would like to thank Takeda Belgium and prof. DG Ebo and his team for their input during the preparation of the expert opinion analysis and expert panel, and prof. C Hermans for the preparation of the expert panel.

Funding

Takeda provided financial support for the HAE patient registry, the expert opinion analysis, and the expert panel.

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