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CLINICAL PRACTICE OF HEREDITARY ANGIOEDEMA IN BELGIUM: OPPORTUNITIES FOR OPTIMIZED CARE

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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 the diagnosis and management of HAE was recently updated and provides up-to-date guidance for the management of. In this paper, we 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 we acquired on Belgian clinical practice, a Belgian patient registry and expert opinion analysis. The Belgian patient registry was developed with the involvement of eight Belgian reference centers for HAE patients. Eight Belgian experts, physicians in the participating centers, included patients in the patient registry and participated in the expert opinion analysis.

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Results: The main action points to further optimise the Belgian clinical practice of HAE are 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 universally used assessment including multiple aspects of the disease (e.g. quality of life assessment) in daily clinical practice; and (5) continue and expand an existing patient registry to assure continued data availability on C1-INH-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 C1-INH-HAE.

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 [Citation1–4]. 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 [Citation5]. 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 (LT) prophylactic treatment, as the new treatment lanadelumab (anti-kallikrein monoclonal antibody) has become available in Belgium in July 2022 and other new treatment options like berotralstat and garadacimab might follow.

The objective was to set up a Belgian expert panel and compare the HAE guidelines with available information on the current Belgian clinical practice (a Belgian patient registry and Belgian expert opinion analysis). We aimed to identify opportunities for optimised care, leading to specific action points for the Belgian clinical practice of HAE. Methods

visualizes the overall approach.

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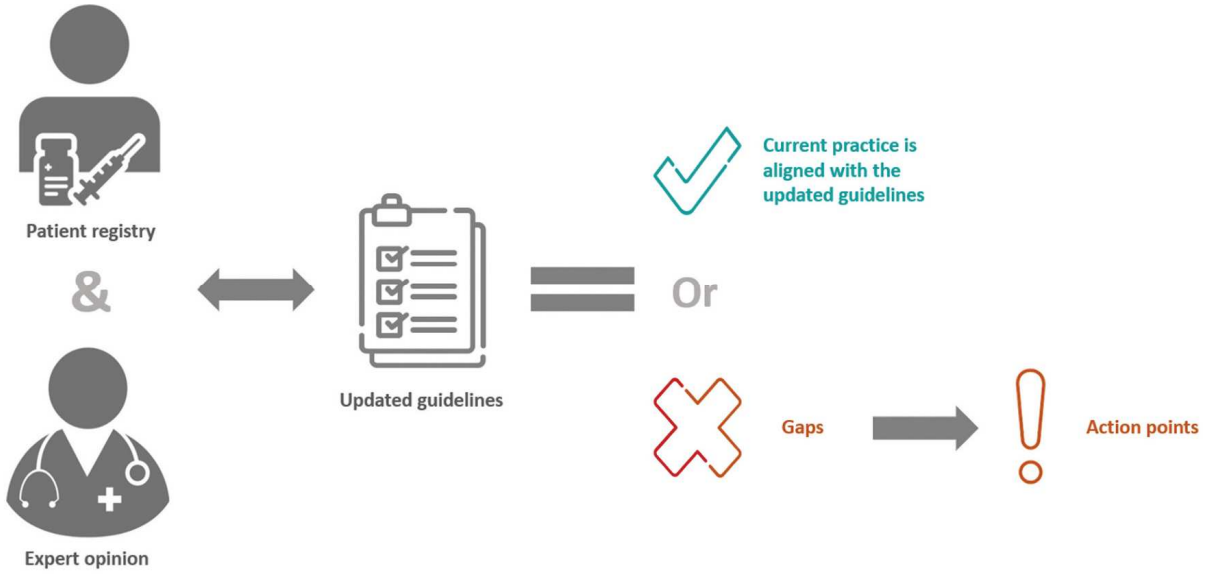
Figure 1. *By comparing all available sources (the Belgian patient registry, the Belgian expert opinion analysis, and the updated guideline), action points were identified to further optimise the Belgian clinical practice in C1-INH-HAE.*



1.1. C1-INH-HAE PATIENT REGISTRY

1.1.1. APPROACH

The primary objective of the retrospective patient registry was to collect data on Belgian clinical practice, as no epidemiological data on C1-INH-HAE for Belgium was available.

A nation-wide, multicentric study was initiated and coordinated by the 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), Center Hospitalier Universitaire Brugmann (CHU/UVC Brugmann), Center Hospitalier Universitaire de Saint-Pierre (CHU/UMC Saint-Pierre), Cliniques Universitaires Saint-Luc (UC Louvain), Center Hospitalier Régional de la citadelle Liège (CHR Citadelle) and, Center Hospitalier Universitaire de Liège (CHU Liège).

Patients or their legal caretakers completed a questionnaire that was composed by the participating experts. centerTime frame

The patients filled out the questionnaire between 2018 and 2021.

Participants

One hundred eighty C1-INH-HAE patients were invited to fill out the questionnaire. One hundred twenty-five patients completed the questionnaire.

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1.1.3. 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.

1.2. EXPERT OPINION ANALYSIS

1.2.1. APPROACH

The expert opinion analysis aimed to gain a better understanding of 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. Eight centers that treat the vast majority of C1-INH-HAE patients in Belgium were invited to participate in the expert opinion analysis, of which 7 centers participated. A follow-up 1-to-1 interview was performed with all experts who completed the survey.

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

TIME FRAME

Data were collected between June and September 2021.

1.2.3. 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.

1.3. PANEL DISCUSSION

The expert panel was organized on 13 June 2022th. During this meeting the updated guideline was presented, focusing on the newly added or revised recommendations. Next, the results of the patient registry were presented for expert opinion analysis. Potential gaps in the current Belgian clinical practice concerning the recently updated guideline were identified and discussed. Finally, an interactive discussion with all participants took place in order to identify clear, tangible action points to further upgrade and support the Belgian clinical practice in HAE.

2. Results

Table 1 provides an overview of the revised guideline [5]

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Table 1. *Thematically ordered overview of the revised WAO-EAACI guideline [5]. Bold highlighted text indicates adaptations, and recommendations put in italics were newly added (vs. the previous guideline [6]).*

	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-C1-INH.*
20	We recommend testing children from HAE-affected families to? be carried out as soon as possible and all offspring of an affected parent to? 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 the patient 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 preferences into consideration.
19	*We suggest all patients who are using long-term prophylaxis to 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 short-term 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 to** 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.

2.1. 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 recommendation 13 of the revised guideline, stating that the treatment goal is to achieve total disease control and normalize patients' lives. Maurer et al. [Citation5] 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 the synthetic antifibrinolytic tranexamic acid (Exacyl®)

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or the use of a second-line product danazol, a synthetic steroid derived from ethisterone (Figure 2). Another explanation could be limited compliance to current therapy, potentially related to the intravenous administration route of current prophylactic treatment options.

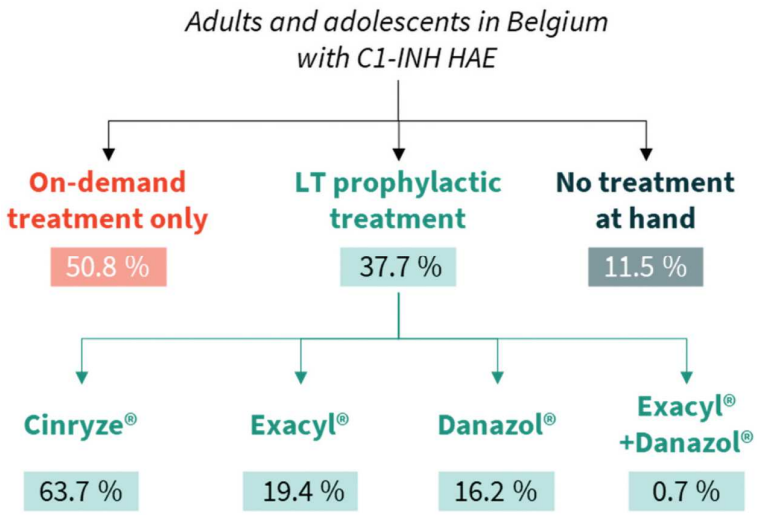
Early treatment in C1-INH-HAE is crucial. Self-administration can facilitate early treatment [5]. On-demand treatment should be considered for all attacks (recommendation 4), and patients should have OD treatment at hand for at least two attacks (recommendation 9). Based on the expert opinion analysis (Figure 2.) and the patient registry, 11.5% to 16% of C1-INH-HAE patients, respectively, do not have OD treatment at hand despite being recommended and/or prescribed.

The updated WAO EAACI guideline states that LT prophylactic treatment is the only way to achieve total disease control (recommendation 13). This finding also contrasts with the Belgian C1-INH-HAE patients still experiencing 5 attacks (median) per year, while less than 40% of them are currently on LT prophylactic treatment. In order to achieve this treatment goal in C1-INH-HAE, LT 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 C1-INH-HAE patients have a medical evaluation at least once a year [5]. Specifically for patients using LT 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 these patients.

The revised guideline recommends plasma-derived C1-INH, lanadelumab, or berostralstat as first-line treatment for LT 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.

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



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2.2. 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 [Citation5], 2022), namely that the treatment goal in C1-INH-HAE is to achieve total disease control and normalize patients' lives. To achieve this, LT 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 QOL, availability of health care resources, and failure to achieve adequate control by appropriate OD therapy.

New and innovative LT prophylactic treatment options are expected to be a gamechanger in the clinical practice of C1-INH-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 LT prophylactic treatment in patients not adequately controlled with OD 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) available from: https://acare-network.com/project/shaerpa/.

In order to manage this significant shift towards total disease control, and with lanadelumab that has become commercially available as from July 1st 2022, 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 C1-INH-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 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.

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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 OD therapy should be improved.

All physicians should re-evaluate the availability of 2 doses of OD 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 OD therapy for a household with multiple C1-INH-HAE patients rather than each 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 OD 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 center and physician is free to add questions or increase the frequency of assessment.

Practical implementation should be done individually and may differ between centers 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.

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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, this can also contribute to the continued availability of novel LT 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.

2.3. ADDITIONAL SUGGESTIONS FOR THE BELGIAN CLINICAL PRACTICE

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

All physicians treating C1-INH-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 C1-INH-HAE patients should be aware of the recommendation to consider intubation or surgical airway intervention early in the case of progressive upper airway oedema (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 centers [Citation5]. The formation of expert centers is not easy in Belgium, but accreditation through international entities like ACARE, a Ga^2 len/HAE network [Citation7] may be the first step towards this goal.

2.4. 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 LT 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 [Citation8], 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 C1-INH-HAE.

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3. 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 centers.

Abbreviation

AECT: Angioedema Control Test

AE-QOL: Angioedema Quality Of Life questionnaire

C1-INH: C1 inhibitor

C1-INH-HAE: hereditary angioedema due to a functional C1-INH deficiency HAE: hereditary angioedema

LT: long term

OD: on-demand

QOL: quality of life

WAO/EAACI: World Allergy Organization/ European Academy of Allergy and Clinical Immunology.

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Disclosure statement

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