WeAreHAE

HAE Patients' Treatment Experience Log: A Guide for Healthcare Professionals

This guide has been developed in conjunction with a patient questionnaire which is available via: https://wearehae.eu/ and https://hae-patient.eu/ (for patients prescribed Ruconest® only).

The questionnaire is designed to help patients record their experiences of treating their HAE attacks, and to encourage them to share their responses with you – their healthcare provider – at their next appointment. The information they provide may give you a better understanding of any issues they may be experiencing with HAE and their treatment(s) and enable you to provide more guidance on how they can best manage their HAE attacks.

Patients with hereditary angioedema (HAE) who are self-treating at home may be experiencing issues with controlling their condition. These may be disease or treatment related. One issue in particular which may be worrying for patients is the need to redose, because of a failure of the first on-demand treatment dose to resolve their symptoms. Patients need to feel confident that their HAE treatment can be relied-upon to work first time when they start to experience an attack.

The questions for patients are listed below along with some brief guidance on each one to help you interpret the answers that patients may give. We hope you find that both the questionnaire and this guide are helpful in stimulating conversations between you and your HAE patients regarding their treatment experience.

Questions for HAE patients with HCP guide

1 On average how often do you experience an HAE attack?

HCP guide: *HAE attacks can affect multiple parts of the body and, importantly, attacks are unpredictable.[1,2] This means that attacks will rarely be regular, so patients may give an attack frequency covering a long time period, such as a year, especially if their attacks are not very frequent. Patients who are taking prophylactic medication may still have 'break-through' attacks.[3-5] International guidelines recommend that all patients using long-term prophylaxis should also have on-demand medication (intravenous C1-INH, icatibant).[1,3]*

2 Where in your body do your attacks occur?

HCP guide: *Cutaneous (face and extremities) and abdominal attacks are the most common in HAE patients, although other areas may be affected including the tongue, larynx, and genitals, and in rare cases, bladder, muscle, or joints.[6] Although laryngeal episodes account for approximately 0.9% of all attacks, all patients are at risk of a laryngeal attack, and more than 50% have a laryngeal attack during their lifetime.[6] Laryngeal attacks are particularly worrying as they can be fatal if not treated promptly.[6] It is particularly important, therefore, that all patients have sufficient medication for on-demand treatment of at least two attacks and carry on-demand medication at all times, as recommended by guidelines.[1,3]*

Hereditary angioedema with C1-inhibitor deficiency typically develops in childhood (mean age at onset: 8–12 years), usually worsens during puberty, and can fluctuate during a patient's lifetime.[6] Therefore, regardless of the patient's response to this question, other bodily sites may be affected in the future, including the larynx.[6] This highlights the importance of patients having an on-demand treatment that works first time.

WeAreHAE

3 At what point do you treat the attack – do you wait until you see swelling, or feel pain, or do you treat as soon as you 'sense' that an attack is coming?

HCP guide: *Early treatment is associated with a shorter time to resolution of symptoms and shorter total attack duration, regardless of attack severity.[3] International guidelines therefore recommend that attacks are treated as early as possible.[3]*

Survey data indicate that 57-83% (N=40-52) of HAE patients experience early signs and symptoms (prodomes), and can therefore predict an oncoming attack all or most of the time.[7] Early detection by a prodrome can help the patient initiate timely treatment that may delay or diminish the intensity of attacks.[8] Some of your patients may therefore report that they often treat when they first sense an attack is coming, rather than waiting for swelling to appear or for abdominal pain. Perception of prodromes is mostly subjective and unique for each individual patient depending on their experience.[8] The most common early symptoms include fatigue, erythema marginatum, skin 'tightness', prickling sensation, and nausea.[8] Early treatment of signs and symptoms of an HAE attack is therefore recommended.[3]

4 Does your on-demand treatment ever fail, so that you need to give yourself a second dose? If 'yes', how often do you need to do this, in general? How does this affect your daily life?

HCP guide: *It is well documented that on-demand treatments for HAE will sometimes fail to provide patients with the necessary symptom relief, and a second dose is needed[9-11] (occasionally even a second dose is inadequate and different on-demand therapy or medical assistance is needed).[11] Patients using prophylactic medication will also experience breakthrough attacks periodically and need to take on-demand rescue medication[4] – these patients should report on how often a second dose of on-demand medication was needed.*

Patients need to feel confident that their acute HAE treatment will work first time. The possible failure of the first treatment dose and the need for redosing is a concern that may impact not only patients' quality of life, but also the cost of treatment and patient safety.[12]

HAE treatment redosing rates with plasma-derived C1-INH have been reported to be 1.1-30.9% (N=1085 and N=609 attacks, respectively),[9,10] while redosing with icatibant has been shown to occur in 22-31.9% (N=27-72) of patients (due to new or worsening attacks within 48 hours of the initial dose[11,13] – note that this is a cross-trial comparison as no direct head-to-head studies have been carried out).

For patients on the prophylactic HAE medication, lanadelumab, breakthrough attacks requiring on-demand 'rescue' medication has been reported to occur in 20.2% of patients.[4]

Patients who report a high rate of redosing may benefit from a treatment review and a change considered, taking patient preference, disease activity and burden into consideration.[3]

5 Do you always use the same on-demand medicine for the second dose as you did for the first dose? If 'no', please make a note here of the second medicine you have used

HCP guide: *Although many patients using on-demand treatment may redose with the same medication as administered for the first dose, some patients may have a different medicine for situations where the first treatment dose fails to improve their HAE symptoms. It is important that the patient tells you exactly which medications are being used for redosing, so that you can assess their level of control and make any revised treatment recommendations accordingly.*

WeAreHAE

6 When you have to give yourself a second dose, does it always work?

HCP guide: *It would be hoped that a second dose of HAE medication would work and relieve the patient's symptoms, but published evidence indicates that this is not always the case. For example, in the 31.9% (N=72) of patients who reported redosing with icatibant, 4 attacks (1.2% of all attacks) needed 3 doses for symptom resolution.[11] When even a second dose does not work to relieve symptoms, it must be very worrying for the patient, and life-threatening if the larynx is involved.[3] All laryngeal attacks must be regarded as a medical emergency, and after the injection of on-demand medication, intubation or surgical intervention should be considered early in all progressive HAE attacks affecting the upper airway.[3] If a patient records such events in the questionnaire, it may be appropriate to reassess their treatment options to prevent future occurrences.*

Permitted redosing varies among C1-INH preparations: Berinert 500 IU (plasma-derived C1-INH) can be dosed more than twice to treat an attack,[14] but Cinryze 500 IU (plasma-derived C1-INH) and RUCONEST® (recombinant C1-INH) cannot be administered more than twice in a 24 hour period.[15,16]

References

1. Busse PJ, *et al.* US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract* 2021 Jan;**9**(1):132-150.e3.
2. Caballero T, *et al.* Practitioners Corner: Triggers and Prodromal Symptoms of Angioedema Attacks in Patients With Hereditary Angioedema. *J Investig Allergol Clin Immunol* 2016;**26**(6):383-386.
3. Maurer M, *et al.* The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. *Allergy* 2022;**77**:1961-1990.
4. Banerji A, Riedl MA, Bernstein JA, *et al.* Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. *JAMA* 2018 Nov 27;**320**(20):2108-2121.
5. Zuraw BL, Busse PJ, White M, *et al.* Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;**363**:513-22.
6. Busse PJ, Christiansen SC. Hereditary Angioedema. *N Engl J Med* 2020;**382**(12):1136-1148.
7. Reshef A, Prematta MJ, Craig TJ. Signs and symptoms preceding acute attacks of hereditary angioedema: results of three recent surveys. *Allergy Asthma Proc* 2013;**34**(3):261-6.
8. Leibovich-Nassi I, Reshef A. The Enigma of Prodromes in Hereditary Angioedema (HAE). *Clin Rev Allergy Immunol* 2021;**61**(1):15-28.
9. Craig TJ, Bewtra AK, Bahna SL, *et al.* C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks--final results of the I.M.P.A.C.T.2 study. *Allergy* 2011;**66**(12):1604-11.
10. Riedl MA, Hurewitz DS, Levy R, *et al.* Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. A*nn Allergy Asthma Immunol* 2012;**108**(1):49-53.
11. Malbrán A, Riedl M, Ritchie B, *et al.* Repeat treatment of acute hereditary angioedema attacks with open-label icatibant in the FAST-1 trial. *Clin Exp Immunol* 2014;**177**(2):544-53.
12. Longhurst H. Optimum Use of Acute Treatments for Hereditary Angioedema: Evidence-Based Expert Consensus. *Front Med* (*Lausanne*) 2018;**4**:245.
13. Cicardi M, Banerji A, Bracho F, *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010 Aug 5;**363**(6):532-41.
14. Berinert. Summary of Product Characteristics. CSL Behring UK, Dec 2021. Available at: https://www.medicines.org.uk/emc/product/7043/smpc
15. Cinryze. Summary of Product Characteristics. Takeda UK, Dec 2022. Available at: https://www.medicines.org.uk/emc/product/2808
16. Ruconest. Summary of Product Characteristics. Pharming Group N.V., Jun 2021. Available at: https://www.medicines.org.uk/emc/product/8580/smpc#gref

RUC-INT-2023-0017V2 October 2023