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MANAGEMENT OF HEREDITARY ANGIOEDEMA TYPE 1 AND 2 FOR CANADIAN ALLERGY AND IMMUNOLOGY PRACTITIONERS

Background

Hereditary angioedema (HAE) is a rare and debilitating disorder characterized by recurrent episodes of angioedema, without the presence of urticaria. These attacks can occur unexpectedly or as a result of various triggers, such as stress and surgery. The symptoms of HAE can significantly impact the quality of life of those affected; in severe cases, edema of the upper airway can be fatal.[1]

HAE type 1 and 2 are due to mutations in the SERPING1 gene leading to a deficiency in C1 inhibitor (C1- INH) and will be the focus of this article. HAE type 1 (HAE-1) is due to a decrease in the plasma level of C1-INH and type 2 (HAE-2) is due to a decrease in the function of C-INH. Other forms of hereditary angioedema have been identified with normal C1-INH (HAE nC1-INH) and are considerably rarer than HAE-1 and HAE-2. Their pathophysiology is not as well understood but pathogenic variants in certain genes have been identified in some families.

The prevalence of HAE is estimated at approximately 1 in 50,000 individuals and has been reported in all races. Both HAE-1 and HAE-2 are inherited in an autosomal dominant manner, although up to 25% of cases may occur *de novo* without a prior family history.[2,3] HAE-1 is estimated to occur in 80% to 85% of patients and HAE-2 in the remaining 15% to 20%.

A diagnosis of HAE-1 and HAE-2 can be confirmed by measuring levels of complement C4 and C1-INH antigen and functional levels on 2 occasions separated by at least 1 month. In these disorders, C4 levels are reduced as C4 is consumed by dysregulated C1-INH activity. Most HAE-1 and HAE-2 patients will have a reduced C4 level between attacks, and nearly all will have a reduced level during attacks. While C1-INH function will be reduced in both HAE-1 and HAE-2, the conditions are distinguished by a reduced C1-INH antigen level in HAE-1, and a normal or increased level in HAE-2. Genetic testing also plays an important role in confirming the diagnosis and may help identify the heritability of the condition.

It is imperative for allergists and immunologists to accurately confirm the diagnosis of HAE and coordinate individualized, patient-centred treatment. The 2019 International/Canadian Hereditary Angioedema Guideline, provides an evidence-based approach to managing HAE patients.[4] The objective of this article is to further assist healthcare providers in caring for patients with a confirmed diagnosis of HAE by outlining an approach to patient counselling and reviewing the principles of therapy.

We propose 5 essential items to consider in the management of all HAE patients: 1) Patient education; 2) On-demand therapy; 3) Short-term prophylaxis (STP); 4) Long-term prophylaxis (LTP); and 5) Genetic testing. We will also discuss special considerations for pregnant patients.

1. Patient education

Patients with HAE-1 and HAE-2 should understand the basic pathophysiology of the disease. Specifically, it is important for practitioners to communicate to them that they have a pathogenic variant in a gene responsible for the production of the C1 INH which, when absent, leads to the accumulation of bradykinin, which produces angioedema.

It is essential to discuss potential triggers with patients, such as trauma, physical pressure, emotional stress, menstruation and pregnancy. Patients should be advised to inform their healthcare team of any planned dental procedures or surgeries. A list of approved therapies to use in outpatient or inpatient procedures follows below.

The use of medication should be carefully reviewed with patients, as several drug classes that affect bradykinin metabolism may exacerbate the symptoms of HAE. Patients should be informed to avoid all angiotensin converting enzyme inhibitors (ACEis), angiotensin receptor-neprilysin inhibitors (ARNIs) such as sacubitril, and dipeptidyl peptidase-4 inhibitors (DPP-4is) such as sitagliptin and saxagliptin. Similarly, oral contraceptive use should be avoided as estrogen can trigger attacks. In follow-up appointments, healthcare providers should inquire about any interim diagnoses of hypertension or diabetes and ensure that potentially triggering medications are avoided.

2. On-demand therapy

"On-demand therapy" is a term that refers to the treatment of acute angioedema attacks, either at home or at a local healthcare facility. In Canada, there are several options available for this purpose.

Berinert® (CSL Behring, Ottawa, ON) is a plasma-derived C1-INH (pdC1-INH) agent approved for use in adults and children. It replaces the deficient C1-INH protein in patients and is administered as a single intravenous push at a dose of 20 U/kg (rounded to the nearest 500 mg). Berinert may be administered by patients, caregivers or healthcare professionals. Patient and caregiver training may be required to establish and use an intravenous line.[5]

Icatibant (Firazyr® [Takeda, Minneapolis, MN]) is a bradykinin 2 receptor antagonist approved for use in Canada in patients 2 years and older. Dosing is 30 mg subcutaneously. The product is supplied in pre-loaded syringes.[6]

Cinyrze (Takeda, Minneapolis, MN) is a plasma-derived C1-INH agent approved for use in Australia and the European Union for the treatment of acute HAE. It is approved in Canada for long-term prophylaxis only. However, it may be used off-label for rescue in Canada if supply issues are present.[7] Initial dosing is 1,000 U intravenously initially, followed by an additional 1,000 U if there is no response.[8]

Ecallantide (Kalbitor® [Takeda, Minneapolis, MN])) is a selective, reversible inhibitor of plasma kallikrein. This agent is not currently licensed in Canada; it can be requested by the Special Access Program of Health Canada if required. Dosing is 30 mg subcutaneously, administered as three 10 mg pre-filled syringes.[9]

Frozen plasma should not be used for HAE attacks as the evidence for its effectiveness is limited.[10] Although plasma contains C1-INH, the protein that is deficient in patients with HAE, the level of C1-INH in frozen plasma is not sufficient to provide effective treatment. In Canada, frozen plasma is not widely available and the process of obtaining it can be time-consuming. As such, guidelines do not recommend this as treatment unless other evidence-based therapies are not available. Additionally, other proteins that are present in plasma may have negative effects on patients with HAE.

Based on the agent selected, a care plan should be created and implemented at a local healthcare facility.

3. Short-term prophylaxis

Short-term prophylaxis (STP) reduces the risk of an angioedema attack in response to an anticipated trigger, such as medical or dental procedures. It is essential for patients to be educated about the potential triggers of an attack, and to be aware that even with the administration of STP, an attack may still occur within 72 hours of the procedure. Patients should also be informed about other potential triggers, such as emotional stress.[4]

Guidelines recommend considering STP for any medical, surgical, or dental procedure.[4] Furthermore, HAE-specific acute treatment should be made available during and after any procedure. The decision to initiate STP should be made collaboratively between the patient and their healthcare team. In cases where STP is not used, two doses of on-demand therapy should be readily available.

Intravenous plasma-derived C1-INH agents (Berinert or Cinryze) are recommended for STP, administered at a dose of 20 U/kg IV within an hour before a procedure.[4] If plasma-derived C1-INH is not accessible, attenuated androgens or frozen plasma can be considered, particularly in situations where on-demand therapies are not available.

4. Long-term prophylaxis

Patients with recurrent angioedema attacks may benefit from regular treatment with long-term prophylaxis (LTP) to reduce the frequency and severity of attacks. Even with LTP, patients should continue to have access to at least two doses of on-demand therapy, as breakthrough symptoms may occur.

There are no set criteria regarding the initiation of LTP. The decision to initiate LTP should be made collaboratively between the patient and their healthcare team, considering factors such as the number and frequency of attacks, the severity of previous attacks, access to emergency treatment (particularly in remotely located patients), and the impact of the attacks on the patient's quality of life.

In patients with HAE-1 and HAE-2, plasma-derived C1-INH administered intravenously or subcutaneously is an effective therapy for LTP. Subcutaneous administration may be preferred as it offers patients greater convenience; additionally, recent literature has proven it to be more efficacious.[11] Options available in Canada include Haegarda, Cinryze, and Berinet (off-label).[5]

Haegarda® (CSL Behring, King of Prussia, PA), a form of subcutaneous (human) C1-INH, is approved in Canada for use in patients 12 years of age and older at a dosage of 60 U/kg subcutaneously every 3-5 days.[12]

Cinryze® (Takeda, Minneapolis, MN), is a form of plasma-derived C1-INH approved for patients 12 years and older at a dosage of 1,000 U intravenously every 3-4 days.[8] Although it is not approved for LTP,

Berinet® (CSL Behring, Ottawa, ON) may also be used in a similar fashion at a dose of 20 U/kg.[4,5]

Lanadelumab (Takhzyro® [Takeda, Minneapolis, MN]) is a fully humanized anti-active plasma kallikrein monoclonal antibody that is approved in Canada as LTP. Funding for lanadelumab is available for patients who have had at least three HAE attacks requiring injectable on-demand treatment within any 4-week period in their disease.[13] Dosing is 300 mg subcutaneously every 2 weeks. This is reassessed at the 6-month mark, at which time the interval can be prolonged to up to every 4 weeks if the patient is stable.[14]

Berotralstat (Orladeyo [BioCryst®, Durham, NC) is an oral plasma kallikrein inhibitor approved by Health Canada in 2022 for LTP in adults and pediatric patients 12 years of age and older. The dosage is one 150 mg tablet daily. Abdominal side effects associated with this product typically subside following the first 2 weeks.[15] Public funding has not yet been approved but the product is available through the manufacturer's patient support program or private payers.[16]

Historically, androgens such as danazol (Cyclomen®, Sanofi, Bridgewater Township, NJ) have been used for LTP. Although it is not first-line therapy, danazol may be used as LTP at a low dose of 200 mg or less per day. Routine bloodwork and repeated abdominal ultrasounds are required for patient monitoring. Further guidance regarding monitoring is outlined in the 2019 International/Canadian HAE guideline.[4]

Currently there are no guidelines for LTP in patients with HAE nC1-INH, due to a lack of sufficient data.

5. Genetic testing

Patients with HAE-1 and HAE-2 should be informed that their condition is inherited in an autosomal dominant manner, with the explanation that the offspring of individuals with this condition have a 50% chance of inheriting the condition. It is important for all family members, including the extended family, to have screening bloodwork performed. Due to the unreliability of biochemical testing in children,[17] C1-INH testing should be performed after 1 year of age. At our center, patients interested in family planning are referred to a genetic counsellor.

Pregnancy

Patients with HAE may experience varying attack frequency during pregnancy, with no definitive pattern. Due to ethical concerns, no randomized trials have been conducted in this population. The recommended treatment for acute symptoms in pregnant HAE-1 and 2 patients is plasma-derived C1-INH.[4] Routine short-term prophylaxis (STP) is not recommended for uncomplicated vaginal deliveries, as clinical studies have not shown an increased attack frequency in pregnant HAE patients. However, STP may be considered for patients with recurrent attacks in their third trimester or a history of genital angioedema due to mechanical trauma. Additionally, STP is recommended for patients undergoing a C-section or intrapartum instrumentation. Dosing may need to be repeated based on the timing of delivery, and two doses of on-demand therapy should be readily available during and post-delivery including for patients who receive STP.

Summary

The management of patients with HAE is a multifaceted process that requires a thorough understanding of the underlying genetic causes and the various treatment options available.

In addition, dose monitoring and regular follow-up with a healthcare provider are essential for ensuring proper management of HAE and to minimize the risk of complications. With appropriate care, patients with HAE can lead fulfilling lives, despite the challenges that accompany this rare, unpredictable disorder.

Clinical pearls

1. Patient education about HAE is necessary. Patients must understand potential triggers for angioedema attacks.
2. Multiple agents are available for acute attack management, including intravenous pdC1-INH (Berinert®, off-label Cinryze®) and subcutaneous icatibant (bradykinin 2 receptor antagonist). It is recommended that a care plan is formulated information on the patient's local hospital Emergency Department or urgent care centre to ensure that therapies are readily available when needed.
3. Intravenous pdC1-INH products (Berinert®, Cinryze®) are recommended for STP prior to anticipated triggers (e.g., medical procedures). A second of dose of on-demand therapy should be available post-procedure.
4. LTP should be considered in patients with significant disease burden and access to acute care. Agents currently available for LTP include subcutaneous or intravenous pdC1-INH (Haegarda®, Cinyrze®, off-label Berinert®); the subcutaneous plasma kallikrein inhibitor lanadelumab; and the oral plasma kallikrein inhibitor berotralstat. Danazol may be an option for some patients.
5. All immediate and extended family members of HAE-1 and HAE-2 patients should have genetic screening performed as it is an autosomal dominant disease. Referral to a genetic counsellor should be considered.
6. Pregnant patients do not routinely require STP for uncomplicated vaginal delivery, although STP may be considered based on attack frequency, and should be used if a C-section or intrapartum instrumentation occurs.

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