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REVIEW PAPER

The latest therapeutic reports on short-term and long-term prophylaxis in the treatment of hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare but serious condition that manifests itself as self-limiting swelling of the subcutaneous and submucosal tissue. Symptoms can occur on various parts of the body, including the gastrointestinal tract, face and extremities, with the most dangerous form being swelling of the larynx and airways, which can be life threatening for the patient. Triggers can be trauma, surgical procedures, excessive stress or exposure to estrogen. The diagnosis of HAE is based on a thorough medical history, analysis of the family history, specialized laboratory tests and genetic analysis. Various medications are used in the treatment and prevention of HAE, both for short- and long-term prevention. Patients with HAE must be aware of the need to receive medication promptly in the event of an attack, as well as the importance of regular prophylactic therapy, which can significantly reduce the frequency and severity of attacks, allowing them to lead normal lives. Modern research and development of therapy help to improve the quality of life of patients with HAE, giving them better control of the disease.

KEY WORDS

treatment, prophylaxis, hereditary angioedema, long-term, hereditary angioedema, short-term.

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INTRODUCTION

Hereditary angioedema (HAE) is an ultra-rare, autosomal dominantly inherited disease with an incidence of 1/50,000-150,000, which is diagnosed on the basis of the medical history, clinical symptoms and levels of complement components C1-INH, C4 and C1q and C1-INH activity. The detailed classification of edemas is presented in Table 1. HAE type 1 accounts for about 2% of all cases of angioedema. It manifests as recurrent episodes of edema involving subcutaneous and submucosal tissue occupying mainly the extremities, face, genitourinary area, as well as the respiratory tract and gastrointestinal tract, so if not treated in a timely manner with appropriate medications, it can pose a serious threat to the patient's health and life [1–3].

TABLE 1. Classification of angioedema according to WAO/EAACI [3]

Bradykinin-induced AE				Mast cell mediator-induced AE		Unknown mediator
C1-INH deficiency/defect		C1-INH normal		IgE-mediated	Non-IgE-mediated	Idiopathic AE
Inherited	Acquired	Inherited	Acquired			
HAE-1 HAE-2	AAE-C1-INH	HAE-nC1-INH (HAE-FXII, HAE-PLG, HAE-KNG1, HAE-HS3ST6, HAE -ANGPT1+, HAE-MYOF+, HAE-UNK)	ACEI-AE Other drug-induced AE*	Angioedema with anaphylaxis Angioedema with or without wheals (urticaria)	Angioedema with or without wheals (urticaria)	

HAE-1 – hereditary angioedema due to C1-inhibitor deficiency, HAE-2 – hereditary angioedema due to C1-inhibitor dysfunction, AAE-C1-INH – acquired angioedema due to C1-inhibitor deficiency, HAE-nC1-INH – hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII (Factor 12), ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin) and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6) or unknown (UNK). + HAE-ANGPT1 and HAE-MYOF are due to mutations involving the vascular endothelium and the role of bradykinin as a mediator of angioedema symptoms seems to be an indirect or conditional one. ACEI-AE – angiotensin-converting enzyme inhibitor-induced angioedema, *other drugs like angiotensin II receptor blockers, gliptins, neprilysin inhibitors or tissue plasminogen activators are thought to potentially induce bradykinin-mediated AE [3].

TABLE 2. Comparison of histamine and bradykinin-induced edemas [10]

Feature	Bradykinin	Histamine
Effectiveness of GCS, antihistamines, epinephrine	Ineffective	Effective
The rate of increase of symptoms	Gradually	Fast
Duration of symptoms	> 3 days	< 3 days

HOW IS BRADYKININ EDEMA DIFFERENT FROM HISTAMINE EDEMA?

Both types of edemas differ in the mediators that cause them, and a detailed comparison is shown in Table 2. In both cases, prompt and correct medical diagnosis is essential due to the possibility of clinical symptoms that can threaten the life and health of the patient.

CLINICAL PICTURE

The clinical manifestation of HAE can last up to 5 days and may be accompanied by prodromal symptoms such as fatigue, malaise, joint and muscle pain or mood changes and erythema marginatum. Self-limiting edema affects subcutaneous and submucosal tissue and some of the most common locations are the extremities, gastrointestinal tract, trunk and face. Swellings localized around the larynx and respiratory tract are potentially life threatening for the patient. HAE attacks are usually spontaneous; however, they can be triggered by trauma, surgical and dental procedures, excessive stress and exposure to estrogens (oral contraceptives) [4–6]. Most patients experience their first attack before the age of 20, which can be a useful fact when making a diagnosis, but should not be a criterion for excluding or confirming a diagnosis [6, 7].

DIAGNOSTICS

The diagnosis of HAE is a complex process, requiring precise identification and differentiation from other types of edema and diseases, e.g., urticaria, allergic reactions, cancer. A typical diagnosis of HAE begins with a detailed medical history, including analysis of the family history and clinical symptoms. Then, specialized laboratory tests are required, such as measurement of the concentration and activity of C1 inhibitor and C4 concentration of complement proteins, and, if possible, genetic analysis. Diagnosis of HAE can be extremely difficult, especially for rare types of the disease, so it is important to have close cooperation between doctors of different specialties and to use state-of-the-art diagnostic methods, such as CT scans and MRIs, to rule out other potential causes of edema.

TREATMENT OF HAE ATTACKS ON DEMAND

A HAE attack can pose a serious threat to a patient's life and health if the interruption drugs (Berinert® – a plasma C1inhibitor, Ruconest® – a recombinant C1 inhibitor, Firazyr® – a bradykinin B2 receptor antagonist; icatibant [8] and Ecallantide, Kalbitor® – plasma kallikrein inhibitor [9] are not administered quickly enough, especially when the swelling occurs in the abdominal region, neck, throat or larynx. The time required for the drugs to take

effect, from the time they are administered, varies from 30 min to 2.5 h. Because of the need to inject the drug quickly, the patient should be trained in self-administering C1-INH safely and have it with them at all times [8].

However, preparations that interrupt an HAE attack are not always available, hence the use of fresh frozen plasma (FFP) is an option in such situations. However, this carries a risk of hypersensitivity reactions, transmission of viral infection (hepatitis A, B, C, HIV virus) or Creutzfeldt-Jakob disease [8, 10, 11]. It also seems controversial that the symptoms of edema could theoretically be exacerbated due to the delivery, along with FFP, of high-molecular-weight kininogen, which is a substrate during the bradykinin release reaction [12].

With the patient's written consent, adrenal androgens or tranexamic acid, which is less effective but available in most hospitals, can also be administered in emergencies. Depending on the location of the edema and the severity of the disease, symptomatic treatment is administered with antiemetics, analgesics, antispasmolytics and fluid therapy [8].

HAE PREVENTION METHODS

In the prophylaxis of HAE, we can distinguish between drugs used for both short-term prophylaxis and long-term prevention. The former group includes plasma-derived C1-INH (pd-C1-INH) concentrate (Berinert®) and the latter, the human monoclonal antibody, plasma kallikrein inhibitor lanadelumab (Takhzyro®) and Ecallantide (Kalbitor®). Plasma-derived C1-INH concentrate (Berinert®) in Poland for long-term prophylaxis is still an off-label drug. We also have other off-label drugs: tranexamic acid (Exacyl®) and a synthetic steroid, an ethinyl-testosterone derivative (Danazol® – the only androgen derivative preparation available in Poland) [10].

SHORT-TERM PREVENTION

Short-term prophylaxis for HAE focuses on preventing and minimizing symptoms before specific situations that may trigger an attack, such as surgery, skin or mucosal disruption, or stress. First-line treatment includes the administration of pd-C1-INH at a dose of 15–30 U/kg body weight, up to 6 h before the scheduled surgery. Due to the risk of an attack during surgery, which could prevent postoperative wound care, one more dose of the drug should be prepared. In the absence of pd-C1-INH, FFP can be used, as in the case of flare-up interruption. In the past, tranexamic acid or adrenal steroids were used when both drugs were unavailable, which is now not recommended [1, 13].

LONG-TERM PREVENTION

Long-term prophylaxis is aimed at preventing chronic and recurrent attacks of edema and is indicated in patients with attacks occurring 1–2 per week requiring medication [1].

This strategy involves regular, ongoing therapy, which includes the administration of pd-C1-INH 1–2 times a week, registered in the European Union for intravenous infusion. In first-line treatment, there is also lanadelumab registered in the EU and used at a dose of 300 mg twice a month. It is administered starting at the age of 12, with the possibility of administration also once a month (every 4 weeks). Another first-line option is the recently approved berotralstat, administered orally at a daily dose of 150 mg. Alternatively in the absence of access to the previously mentioned drugs: antifibrinolytics, such as tranexamic acid can also be used, albeit with limited efficacy data, in doses of 20–50 mg/kg body weight per day, divided into 2 or 3 doses. It is similar with androgens such as danazol, stanozolol, oxandrolone, and oxymetholone can be used, although their use is limited due to numerous side effects and is not recommended in children [9].

The decision to take long-term prophylaxis also takes into account access to emergency care and the presence of specific factors that exacerbate children's symptoms, such as frequent upper respiratory infections or eruption of teeth.

The treatment plan should be tailored to the individual patient's needs, with drug selection and dosage closely monitored by a specialist to minimize side effects and ensure optimal disease control. Long-term prophylaxis can significantly reduce the frequency and severity of attacks, allowing patients to lead more normal and active lives. Recent research and development of new therapies help to further expand treatment options, offering HAE patients increasingly better control over their condition [1].

THE IMPORTANCE OF PATIENT EDUCATION

Due to the lower life expectancy of a patient with HAE caused by, among other things, death from asphyxiation, patient education plays a key role in controlling the disease. Making the patient aware of the nature of the disease, triggers for attacks, available treatment options and self-care strategies can go a long way toward better managing the condition and preventing sudden attacks. Education can also help the patient self-monitor symptoms and respond appropriately, which is key to effective treatment management. Working closely with the healthcare team, an educated patient can participate in treatment decisions, increasing understanding and adherence to the

therapeutic plan. In the case of HAE, where response time can be crucial, patient and family education becomes integral to effective treatment and the prevention of serious complications [1].

CHALLENGES AND PROSPECTS OF HAE TREATMENT

Patients with HAE should undergo constant medical monitoring due to the spontaneity of disease attacks. A major challenge for HAE therapy is monitoring the quality of life (QoL) index and preventing its deterioration. Due to the clinical symptoms accompanying HAE, patients experience reduced productivity or are often forced to be absent from work [14]. The most effective HAE treatment strategy to date is long-term prophylaxis, which is still undergoing clinical trials of pdC1-INH and lanadelumab [15]. However, it is not fully effective, so patients still need to be protected with HAE attack interruption agents. Drug delivery methods, unfortunately, are still associated with burdens for patients, such as frequent injections and fatigue due to regular medications [14].

Another challenge in the treatment of HAE, is the distinctiveness of flare-ups prevention methods in women: during menopause, using hormonal contraception, planning pregnancy or pregnant and breastfeeding. If the patient is using hormonal contraception, progesterone preparations are recommended, but should not be combined with tranexamic acid and androgens due to a significant increase in the thromboembolic risk [10]. During pregnancy, women with HAE may experience an increased, decreased or unchanged number of attacks [16, 17]. Before a planned pregnancy, if patients are using tranexamic acid or androgens for long-term prophylaxis, they should be switched to C1-INH concentrates. Also during pregnancy itself, for treatment of attacks, C1-INH concentrates remain the preparations of choice [17]. During breastfeeding, there is an increase in flare-ups. This is associated with increased prolactin levels [18].

As the pathophysiology of HAE becomes better understood, therapeutic options are becoming more effective and targeted. A human monoclonal antibody in the IgG4 class that blocks activated factor XII (Garadacimab®) and the previously mentioned lanadelumab (Takhzyro®) remain under investigation, as well as gene therapies [19].

SUMMARY

HAE is a genetically inherited disease that remains incurable, and its symptoms can threaten a patient's health and life. In the therapeutic context, current global trends focus on creating effective, safe and convenient long-term prophylaxis for the patient. It is very important to educate patients about avoiding flare-up triggers, as well as skillful self-administration of medications. Special attention should be paid to selecting the right treatment for the patient, taking into account the patient's desire to become pregnant or to breastfeed.

Ever-evolving treatments for HAE offer hope for increasing control of the disease and a more comfortable life for patients. Many drugs remain in the research phase and the current outcome remains promising.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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