An update on the treatment of hereditary angioedema in Brazil

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Dear editor,

Given the recent changes in treatment of hereditary angioedema (HAE) in Brazil, we understand that it is extremely important to update the information of the latest Brazilian Guidelines for Hereditary Angioedema (2022).[1]

HAE is characterized by recurrent edema of the subcutaneous and submucosal tissues. It affects the face, extremities, genitals, and gastrointestinal and respiratory tracts, and can even lead to death when affecting the upper airways.[2] Angioedema results from an uncontrolled release of bradykinin, which binds to its receptor on the vascular endothelium, resulting in plasma leakage. Growing knowledge about the mechanisms involved in the pathogenesis of HAE has enabled the development of new therapies.[3]

Drug treatment for HAE is divided into on-demand and short- and long-term prophylaxis. The goal of long-term prophylaxis should be to completely control the disease and normalize the patient's quality of life. Several drugs have been approved for long-term HAE prophylaxis, with national and international guidelines classifying them as first- or second-line therapies according to their safety profile and evidence of efficacy. Brazilian and international guidelines, both updated in 2022, include intravenous and subcutaneous plasma-derived C1 inhibitor (pdC1INH) and lanadelumab as first-line therapies for long-term prophylaxis. Although the international guidelines also include berotralstat among the main therapies for long-term prophylaxis, the Brazilian guidelines do not, since, at the time of publication, this drug had not been approved by the Brazilian National Health Surveillance Agency.[1,3]

Berotralstat is a small synthetic molecule that specifically inhibits plasma kallikrein. Its pharmacokinetic profile allows a single daily oral dose.[4] It was licensed in December 2020 by the U.S. Food and Drug Administration, in April 2021 by the European Medicines Agency, and was approved in Brazil in April 2024. It is recommended at a dose of 150 mg per day in patients 12 years and older who have HAE with C1INH deficiency (HAE-C1INH). Berotralstat demonstrated resposnse from the first month of treatment and, after 6 months, it significantly reduced the monthly frequency of HAE attacks compared to placebo (1.31 versus 2.65; $p < 0.001$). Quality of life scores, although improved, did not statistically differ from placebo. In the phase 3 study of berotralstat, gastrointestinal events, including abdominal pain, vomiting, and diarrhea, were among the most frequently reported adverse effects, although most symptoms were mild and transient. The drug is not recommended during pregnancy and breastfeeding.[5]

Unlike other currently available treatment options, berotralstat is an oral medication, which may help overcome the challenges associated with parenteral medications and improve the quality of life of patients with HAE. A relevant fact about long-term prophylaxis with berotralstat is that it is effective in preventing attacks in patients who have HAE with normal C1INH (HAE-nC1INH) and in those with HAE due to variants in *F12* (AEH-FXII).[4]

Although first-line medications for long-term prophylaxis are available in Brazil, access remains a significant challenge. Most patients with HAE are treated at reference centers associated with the Unified Health System, and < 25% of Brazilians have access to supplementary health insurance, making this scenario even more challenging. All first-line medications for long-term prophylaxis of HAE are very expensive and none are incorporated into the Unified Health System, and only second-line therapies available, with no short-term changes expected. Recently, patients with access to supplementary health insurance achieved a victory when lanadelumab was incorporated into the National Supplementary Health Agency list, with coverage being mandatory for adults and adolescents (+12 years) with HAE-C1INH, while pdC1INH, as a blood product, may be covered.

Regarding access to attack treatment, 2 major advances have occurred: the National Commission for the Incorporation of Technologies into the Unified Health System recommended incorporating icatibant and intravenous pdC1INH. This recommendation is reserved for treatment of attacks of HAE-C1INH types I and II, according to an as yet unpublished Ministry of Health protocol.

Despite recent improvements, groups of patients still lack HAE treatment options. The only option for long-term prophylaxis among pregnant and breastfeeding women is pdC1INH (classified as category C by the U.S. Food and Drug Administration). It can also be used for short-term prophylaxis and to treat attacks in this population.

Icatibant is not approved for on-demand treatment in pregnant and breastfeeding women, despite its good safety profile.[6] The only long-term HAE prophylaxis for children under 12 years of age is intravenous pdC1INH, except for subcutaneous pdC1INH, which can be used in patients 8 years and older. For attacks in this age group, intravenous pdC1INH and icatibant can be used. Pregnant and breastfeeding women and children can use tranexamic acid, but it is less effective for attack prevention and involves thrombosis risk, especially in pregnant women. There is still no approved therapy for HAE-nC1INH.[1]

As stated in the latest Brazilian Guidelines for Hereditary Angioedema, several drugs have been developed in recent decades, while several others are in development or are undergoing clinical trials.[1] The authors hope that as treatment possibilities expand, access to these resources be achieved.

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