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REVIEW

Prevention of Recurrent Attacks of Hereditary Angioedema (HAE): Berotralstat and Its Oral Bioavailability

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Abstract: Hereditary angioedema (HAE) is a condition characterized by episodes of cutaneous and submucosal edema. Angioedema of the extremities and abdominal attacks are the most common manifestations of the disease. It can also affect the upper airways with the potential of becoming life-threatening. The two most common causes of HAE are a deficiency of C1 inhibitor (classified as type 1 HAE) or a dysfunction of C1 inhibitor (type 2 HAE). A malfunction or deficiency of C1 inhibitor leads to an overactivated plasma kallikrein (an inflammatory vasoactive peptide), that increases bradykinin, mediating the angioedema episodes in patients with HAE. To minimize the difficulties of this pathology and to improve patients' quality of life, prevention of this condition is essential. Berotralstat is a unique option for oral administration for routine prophylaxis. This drug acts by binding to kallikrein and reducing its plasma activity, lowering bradykinin levels. Open-label studies have demonstrated the effectiveness of a single daily dose of berotralstat 150 mg in preventing HAE attacks. This review aims to examine studies performed to elucidate the efficacy, safety, and tolerability of berotralstat.

Keywords: hereditary angioedema, berotralstat

Introduction

Hereditary angioedema (HAE) is characterized by episodes of cutaneous and submucosal angioedema; it is considered a rare disease with an estimated prevalence of less than 1 in 50,000 people if proper diagnosis is available.[1–3] The most common causes of HAE are a deficiency of C1 inhibitor protein (C1-INH), classified as type 1 HAE, or a dysfunction of C1-INH (type 2 HAE). They can be caused by autosomal dominant or de novo pathogenic variants in the SERPING1 gene.[3,4] C1 inhibitor inactivates plasma kallikrein, therefore a decreased or dysfunctioning C1-INH results in overactivated plasma kallikrein that causes an increase in bradykinin.[1–4] The excess of bradykinin induces recurrent angioedema events, which are characterized by vasodilation and localized swelling. Patients with HAE experience recurrent attacks of angioedema of the extremities, face, and abdomen. Attacks can also involve the upper airway and become life-threatening.[3]

Berotralstat is a small molecule that binds to plasma kallikrein and decreases its enzymatic activity, reducing bradykinin levels and preventing HAE attacks.[5–13]

Patients that live with HAE report significant discomfort, pain, and diminished quality of life (QoL)[2] due to the recurrent attacks and the stress of anticipating another attack. Various treatments have been used in attempts to decrease the disease burden in these patients. Clinical guidelines recommend, as a first line therapy for long-term prophylactic treatment of HAE type 1 and 2, plasma-derived C1-INH, lanadelumab, and berotralstat.[1]

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We reviewed the mechanism of action, safety, efficacy, pharmacodynamics, and clinical trial results of the drug berotralstat, which is a new oral pharmacologic agent for the prevention and treatment of recurrent HAE attacks approved by the Food and Drug Administration (FDA) in December 2020.[6]

Mainstays of Treatments

On-demand treatment is the mainstay therapy of acute attacks, and these should be treated as early as possible.[1] Treatments for acute attacks must be given intravenously or subcutaneously, and available options include ecallantide (kallikrein inhibitor), intravenous C1 inhibitor protein, and icatibant (bradykinin B2 receptor antagonist).[1,4] Icatibant and intravenous C1 inhibitor protein can be self-administered; only treatment with ecallantide requires administration by a health-care professional. Some of these have undesirable side effects, including hypersensitivity reactions, anaphylaxis, and/or a burning sensation at the injection site.[2,4]

Long-term prophylactic treatment is one of the goals of treatment of HAE. Preventing attacks can decrease complications of an acute attack but also allow patients to have a normal lifestyle.

Prophylactic medications traditionally used include danazol, an androgen therapy contraindicated in infants and pregnancy. This treatment has been known to lead to treatment discontinuation due to side effects such as hepatotoxicity, hypertension, hyperlipidemia, and virilization.[2,4]

Clinical guidelines for long-term prophylaxis in HAE recommend plasma-derived C1-INH, lanadelumab, and berotralstat as first line medications.[1] C1-INH replacement therapy has been used as treatment for the acute HAE attacks but can be used as well as a prophylactic treatment. In acute attacks it is administered IV with a high tolerability, providing relief to the patient's symptoms. Earlier treatment with this medication provides better results, decreasing the time and symptoms of the attack. The medication has also been used as a primary medication for prophylaxis of HAE attacks, with a dosage twice per week subcutaneously.[1,2,4]

More recently, a fully human monoclonal antibody to plasma kallikrein, lanadelumab, was approved for prophylaxis with a significantly longer duration of action, allowing dosing every 2–4 weeks.[4,5]

In an effort to provide a medication with oral bioavailability and improved patient QoL, a new therapy has been developed. This is the case of small molecule medications like berotralstat (previously called BCX7352), a small synthetic molecule that affects bradykinin synthesis by blocking plasma kallikrein activity. This treatment is administered orally once a day, which represents a different drug administration route from those previously available.

Berotralstat

General Characteristics

This drug is FDA-approved for adults and pediatric patients older than 12.[6] Berotralstat has shown evidence that it lowers the recurrence of HAE attacks considerably and appears to be well tolerated by patients with a low side effect profile, with mostly reported gastrointestinal symptoms like diarrhea, nausea, and abdominal pain. The recommended dosage is 150 mg as a capsule once daily with food; it can be adjusted to 110 mg in patients with liver impairment.[6]

Mechanism of Action

This drug is a small molecule that binds to plasma kallikrein. By doing so, it decreases kallikrein plasma activity and prevents it from completing proteolytic activity. This reduces the levels of activity of bradykinin[5] (see Figure 1), a potent vasodilator unregulated in HAE, which increases vascular permeability leading to swelling and pain.[6]

Pharmacodynamics

In individuals with HAE, oral dosing of berotralstat once daily resulted in concentration-dependent suppression of plasma kallikrein, as evaluated by a decrease from baseline enzyme activity.[6]

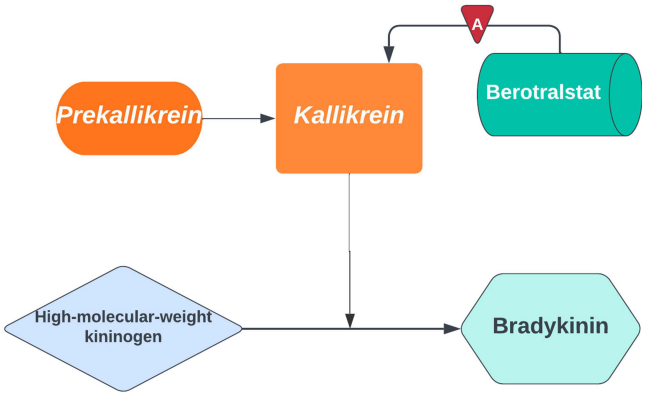

Figure 1 Mechanism of action of berotralstat. A. Berotralstat binds to plasma kallikrein and decreases its enzymatic activity. Repritned from *Ann Allergy Asthma Immunol*, 104, Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. 104:193–204, Copyright (2010), with permission from Elsevier.[14]

Pharmacokinetics

When the medication is taken with food, the median time to maximum plasma concentration (Tmax) is 5 hours, with a range of 1 to 8 hours. With high-fat meal consumption, Tmax increased up to 3 hours. The distribution of the drug is 99% bound to plasma proteins, and the medication has a half-life of 93 hours (range: 39 to 152 hours). Berotralstat is metabolized by CYP2D6 and CYP3A4 and is excreted at 9% in urine and 79% in feces.[6–13]

Clinical Trials

ApeX-1 Trial and ZENITH-1 Trial

These two studies were double-blind and randomized trials (Table 1). The first study, a phase II dose-ranging, placebo-controlled trial, identified the safety and efficacy dose of the molecule to prevent an acute attack.[7] The study comprised 77 subjects, where four doses were evaluated including 62.5 mg, 125 mg, 250 mg, and 350 mg.[5] During this time, the patients were reviewed, and a paper diary was made for every patient to report HAE attacks. In addition, the Angioedema QoL Questionnaire was performed on every patient.[8] The first results of this study showed that a dosage of 125 mg reduced HAE attacks in 73.8% of patients compared with the placebo group, and 43 patients did not record or report any episode after 28 days. Overall, they had an improvement in quality of life (QoL) with 125 and 250 mg dose (difference of −24.5 and −20.5 points reduction in negative symptoms compared to placebo).[7]

There was an increase in gastrointestinal symptoms that were more severe and frequent with the 250 mg and 350 mg dosage. Finally, the lower dosage (62.6 mg) did not present a significant difference compared to the placebo.

The second study (ZENITH-1 trial) emphasizes studying a safe dose range to proceed with a phase III trial. This study included 58 patients.[9] They used other dosages including 500 mg and 750 mg. This study demonstrated that the use of the medication decreased the use of acute treatments used by the patients in 50% compared with placebo; fewer attacks were reported in the group of 250 mg dosage. There were no severe adverse events reported.

Table 1 Clinical Trials of Berotralstat

Trial Name	Year of Publication	Design	Sample Size	Decrease rate of Angioedema Attacks
APeX-1	2018	Phase II, double-blind, and randomized trials	77	74%
ZENITH-1	2019	Phase II, double-blind, and randomized trials	58	50%
APeX-2	2020	Phase III, double-blind, parallel group in 11 countries	121	67%
APeX-S	2021	Phase II, open-label study conducted in 22 countries	227	50%
APeX-J	2021	Phase III, randomized, double-blind, placebo-controlled, parallel group, conducted in Japan	19	100% (after 12 months of treatment)

APeX-2

This study was a phase III, multicenter, double-blind trial performed in 11 countries.[10,11] It was divided in two parts. The first one was to identify the efficacy and safety with a control placebo group. The second part also measured the safety, tolerability, and effectiveness with a control group. Two arms were assigned different dosages, 150 mg and 110 mg, for 48 weeks. In the first 24 weeks, the patients with the 110 mg dose showed a 30% reduction in attacks compared to the placebo group; in the 150 mg dose group, 44% presented with a reduction of the attacks (Table 1). Those patients who completed 48 weeks of the study had a reduction of 52% in patients with the 110 mg dose and 67% in patients with the 150 mg dose. This study reported less than 10% adverse events including upper respiratory tract infection, diarrhea, dyspepsia, and nausea. Regarding drug-related adverse events they were reported in 43% of patients who completed the 48 weeks of treatment (8).

APeX-J

This study is similar to the APeX-2 study but was performed in Japan.[12] It is also a phase III randomized and double-blind trial divided into two phases. The first phase sought to review the 110 mg and 150 mg dosages in 19 Japanese over 24 weeks. The second phase took an additional 28 weeks with the same dosages. They reported that the 150 mg dosage reduced the HAE attacks in 50% compared with the placebo. The main treatment-related adverse effects were GI symptoms and nasopharyngitis; however, they remained mild.

APeX-S Trial

This open-label study evaluated the long-term safety and tolerability in 227 patients in 22 countries.[13] They studied the 110 and 150 mg dosages during a period of 48 weeks to evaluate the medication's long-term safety and effectiveness (Table 1). This study found that 91% of emergent adverse events occurred in 227 patients. The main drug-related adverse events were upper respiratory tract infection, abdominal pain, diarrhea, and headache – similar symptoms compared to the APeX-2 trial; however, those symptoms were mild, and patients reported a good tolerability. Eight percent of patients discontinued the 150 mg dosage, and 10% discontinued the 110 mg. Regarding the causes for discontinuation of the drug, the most common cause was the perceived lack of efficacy, followed by laboratory abnormalities (ALT elevation being the most frequent). This study shows that a long-term treatment with 150 or 110 mg doses is well tolerated in most patients.

Conclusions

Patients who suffer from HAE are burdened by its recurring attacks. Therefore, the need for preventative treatments is essential for enhancing patients' QoL. Plasma-derived C1-INH, lanadelumab, and berotralstat are the three medications indicated as first-line therapy for long-term prophylactic treatment.[1] The three medications are widely available and effective in the prevention of acute attacks. The difference of berotralstat is the oral route of administration . Side effects reported seem to be limited to the gastrointestinal tract and improve upon treatment continuation. The use of one of those options is reserved for specific cases and based on the doctor's decision. Clinical guidelines recommend new studies that compare the safety and effectiveness between these three medications.[1]

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Disclosure

The authors declare that they have no relevant conflicts of interest in this work.

References

1. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77:1961–1990. doi:10.1111/all.15214
2. Valerieva A, Longhurst HJ. Treatment of hereditary angioedema-single or multiple pathways to the rescue. *Front Allergy*. 2022;3:952233. doi:10.3389/falgy.2022.952233
3. Busse PJ, Christiansen SC. Hereditary Angioedema. *N Eng J Med*. 2020;382:1136–1148. doi:10.1056/NEJMra1808012
4. Arruda LK, Ferriani MPL. Treatment of hereditary angioedema: when the goal is having a normal life. *J Allergy Clin Immunol*. 2021;148:80–82. doi:10.1016/j.jaci.2021.05.023
5. Hwang JR, Hwang G, Johri A, Craig T. Oral plasma kallikrein inhibitor BCX7353 for treatment of hereditary angioedema. *Immunotherapy*. 2019;11:1439–1444. doi:10.2217/imt-2019-0128
6. BioCryst Pharmaceuticals I ORLADEYO™ (berotralstat) capsules, for oral use. U.S. Food and Drug Administration website. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214094s000lbl.pdf. Accessed February 27, 2023. 2020.
7. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, et al. Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema. *N Engl J Med*. 2018;379:352–362. doi:10.1056/NEJMoa1716995
8. Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012;67:1289–1298. doi:10.1111/all.12007
9. Longhurst H, Moldovan D, Bygum A, et al. Oral Plasma Kallikrein Inhibitor BCX7353 is Safe and Effective as an On-Demand Treatment of Angioedema Attacks in Hereditary Angioedema (HAE) Patients: results of the ZENITH-1 Trial. *J Allergy Clin Immunol*. 2019;143:AB36. doi:10.1016/j.jaci.2018.12.112
10. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled Phase 3 trial. *J Allergy Clin Immunol*. 2021;148:164–172.e169. doi:10.1016/j.jaci.2020.10.015
11. Wedner HJ, Aygören-Pürsün E, Bernstein J, et al. Randomized Trial of the Efficacy and Safety of Berotralstat (BCX7353) as an Oral Prophylactic Therapy for Hereditary Angioedema: results of APeX-2 Through 48 Weeks (Part 2). *J Allergy Clin Immunol Pract*. 2021;9:2305–2314.e2304. doi:10.1016/j.jaip.2021.03.057
12. Ohsawa I, Honda D, Suzuki Y, et al. Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: a phase 3 randomized trial. *Allergy*. 2021;76:1789–1799. doi:10.1111/all.14670
13. Farkas H, Stobiecki M, Peter J, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: the open-label APeX-S study. *Clin Transl Allergy*. 2021;11:e12035. doi:10.1002/clt2.12035
14. Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:193–204. doi:10.1016/j.anai.2010.01.007