Ubrogepant: The First Gepant to Pass Food and Drug Administration for Acute Migraine

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Abstract

Migraine is one of the most common and disabling forms of primary headache disorders. It is characterized by the presence of unilateral pulsatile headache associated commonly with nausea, vomiting, photophobia, and phonophobia lasting for about 4–72 h. Currently, nonsteroidal anti-inflammatory drugs, ergot alkaloids, and triptans are the most commonly used drugs to abort an acute attack of migraine. Management of acute migraine is becoming a challenging task to physicians and patients due to several drawbacks faced with the use of aforementioned drugs. This lacuna is being filled up by developing drugs against novel targets such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide. In December 2019, the US Food and Drug Administration (FDA) approved ubrogepant for the treatment of acute migraine with or without aura in adults. Ubrogepant belongs to a new class of drugs called "Gepants" which are small molecules targeted against the CGRP receptor. The recommended initial dose is 50 mg or 100 mg orally. It follows first-order kinetics and is metabolized to a major extent by CYP3A4-mediated mechanisms. Compared to placebo, ubrogepant causes significant and rapid freedom from headache, pain and absence of migraine-associated most bothersome symptoms. Nausea, vomiting, and dry mouth are some of its common adverse effects. Ubrogepant with advantages such as good oral bioavailability, lack of vasoconstrictor action, and lack of hepatotoxicity might emerge as a promising drug for terminating an acute attack of migraine in the future. However, long-term clinical studies are needed to ascertain its safety profile.

Keywords: Acute migraine, calcitonin gene-related peptide antagonist, gepant, ubrogepant

Introduction

Migraine is a form of primary headache disorder and it is characterized by the presence of unilateral pulsatile headache associated commonly with nausea, vomiting, photophobia, and phonophobia. It is prevalent in about 11.6% of global population. Due to its chronic nature and severity, the quality of life and work efficiency are impaired causing economic burden.[1] Nonsteroidal anti-inflammatory drugs, ergot alkaloids, and triptans which are the currently used drugs to abort an acute attack of migraine carry the following disadvantages such as poor tolerability and varied efficacy among patients and they are also contraindicated in ischemic heart disease patients. These drawbacks led to the development of a new class of drugs called "Gepants" which are small molecules targeted against the calcitonin gene-related peptide (CGRP) receptor. Unfortunately, the clinical trials done earlier with other gepants such as olcegepant and telcagepant were terminated due to poor oral bioavailability of olcegepant and hepatotoxicity caused by telcagepant.[2] Ubrogepant is the first gepant to be approved by the Food and Drug Administration (FDA) in December 2019 for the treatment of acute migraine with or without aura in adults.[3]

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Mechanism of Action

Ubrogepant is an antagonist of the neuropeptide CGRP receptor. During an acute attack of migraine, trigeminal nerve stimulation causes release of CGRP, leading to vasodilation and neurogenic inflammation in meninges. Ubrogepant, by blocking the CGRP receptor counteracts the vasodilation mediated by CGRP without causing any vasoconstriction.[2,4]

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Pharmacokinetics

On oral administration, ubrogepant was absorbed well with good bioavailability. No significant food–drug interaction was observed except for the delay in time to reach maximum plasma concentration by fatty food intake. Ubrogepant is metabolized to a major extent by CYP3A4 and is excreted through bile. Its half-life is about 5–7 h and follows the first-order kinetics. It is also a substrate of efflux transporters such as breast cancer resistance protein and P glycoprotein.[3]

Clinical Trials

Currently, two phase 3 (ACHIEVE I and II) randomized, multicentric, double-blind, placebo-controlled clinical trials were conducted in patients with migraine comparing ubrogepant at varying doses of 25 mg, 50 mg, and 100 mg for the treatment of acute migraine. The primary endpoints were pain relief and absence of migraine-associated most bothersome symptoms (MBS) such as nausea, photophobia, and phonophobia 2 h after the first dose. The secondary endpoints were sustained freedom from headache pain and absence of MBS from 2 to 24 h after the first dose. The proportion of patients in ubrogepant groups who experienced freedom from pain and absence of MBS were higher than those in the placebo group. [5,6]

Adverse Effects

Nausea, somnolence, and dry mouth were the most common adverse events reported by patients in clinical trials.[5-7] Serious adverse events such as appendicitis, pericardial effusion, seizure, and spontaneous abortion occurred in very few patients in ubrogepant group.[5] None of the patients were withdrawn from the study due to treatment-related adverse events. Unlike the other gepants, ubrogepant did not cause a significant rise in serum liver enzymes.[5-7]

Drug Interactions and Contraindications

Since ubrogepant is metabolized by CYP3A4, when it was coadministered with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, and clarithromycin, there was a significant rise in ubrogepant plasma levels. Hence, it should not be administered along with strong CYP3A4 inhibitors. It is also advised to avoid the use of ubrogepant along with strong CYP3A4 inducers such as rifampin, phenytoin, and barbiturates. It is contraindicated in end-stage renal disease with creatinine clearance <15 ml/min. Dose modification is required in patients with severe liver and kidney dysfunction (CLcr 15–29 ml/min). There is no sufficient data available to support the use of ubrogepant in pregnant women.[3]

Advantages and Limitations

The advantages of ubrogepant are good oral bioavailability, lack of vasoconstrictor action, and lack of hepatotoxicity. Unlike triptans and ergot alkaloids, it can be safely used in patients with ischemic heart disease and peripheral vascular disorders. Its efficacy and safety on frequent use for multiple migraine episodes (more than 8 migraine attacks in a month) have not been assessed in clinical trials. It is not indicated for prophylaxis of migraine. [2,4,8]

Current Status

In December 2019, the FDA has approved ubrogepant (Ubrelvy 50 and 100 mg tablets) for the treatment of acute migraine with or without aura in adults. During an acute attack, the recommended initial dose is 50 mg or 100 mg and if required a second dose can be administered 2 h after the first dose. The recommended maximum dose is 200 mg per day.[3]

Conclusion

Ubrogepant is the first CGRP receptor antagonist to enter the pharmaceutical market for the treatment of acute migraine. Even though it carries several advantages, large-scale clinical trials including special populations have to be conducted to compare its efficacy with the currently used drugs and also to evaluate the long-term safety of ubrogepant in patients with acute migraine.

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Conflicts of interest

There are no conflicts of interest.

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