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LETTER TO THE EDITOR

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Progress in treating migraines: promising prospects for a better tomorrow

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Abstract

Background Migraine is a debilitating disorder that undoubtedly has a significant impact both clinically and socially. New treatment options are necessary in Iran due to issues with tolerance, interactions, contraindications, and the lack of effectiveness of current medications.

Main text and a short conclusion Gepants are small compounds that target calcitonin gene-related peptide and are currently in further clinical development as preventive treatment alternatives for migraine. However, their development was halted due to hepatotoxicity, so this process still needs to be completed. Recent clinical trials have demonstrated the effectiveness, safety, and general patient tolerability of the latest generation of gepants. In light of this information, we aim to provide readers with a concise and helpful overview of the two types of gepants and their potential side effects.

Keywords Migraine, Gepants, Atogepant, Zavegepant, CGRP

Dear Editor

Migraine is a type of headache manifesting itself with frequent episodes of mild or severe headache usually associated with other symptoms, such as nausea, vomiting, photophobia, and hyperacusis (Ahadiat et al. 2022). This disorder accounts for 22.5% and 26.9% of all headaches in men and women, respectively, and causes substantial disturbances in the quality of life of the affected patients, such as social function, relationship with family members, and functionality in the workplace (Chądzyński et al. 2019). Migraine is more prevalent in adolescent boys compared to girls of the same age group. However, the prevalence become higher in adult women compared to men, with a substantial decline in pregnant and postmenopausal women. Thus, it has been hypothesized that hormonal fluctuations play a role in the development of migraine (Szewczyk et al. 2023).

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The pathophysiology of migraine is not fully understood yet. However, it is usually treated with ordinary analgesics, such as acetaminophen. In case of progressive or severe disease that is non-responsive to analgesics, other medications, such as triptans and ergotamine, are recommended. Up to now, most therapeutic approaches for migraine have relied on medications not specifically designed for this disease. However, our growing understanding of the pathophysiology of migraine has shown the benefits of several neurotransmitters in the treatment of migraine (Ripa et al. 2015).

According to the neovascular concept, the activity of perivascular nerves in migraine is affected by the release substance P, neurokinin A, calcitonin-producing peptide (CGRP), and nitric oxide, leading to vasodilatation and vascular inflammation. Moreover, vasoactive intestinal peptide (VIP) was the first neuropeptide found to be a potent vasodilator that affects the cranial vessels. This substance helped researchers in obtaining novel information on neuropeptides (Edvinsson 2021). VIP has been detected in the cerebral circulation and parasympathetic perivascular nerves. In recent years, it has been found to

be involved in the pathophysiology of migraine and cluster headaches.

Another peptide involved in the pathophysiology of migraine, calcitonin gene-related peptide (CGRP), is produced by the hypothalamus and exerts a hormonal effect. Researchers have detected the CGRP mRNA in the central and peripheral nervous systems. It is a potent vasodilator of cerebral arteries and arterioles, exerting its effects through the activation of adenylyl cyclase in vascular smooth muscle cells. Moreover, it has been shown that the stimulation of the trigeminal nerve in response to cerebral vasoconstriction increases CGRP production, which can be inhibited by antimigraine drugs. Also, intradermal injection of CGRP increases microvascular expansion and perfusion (Ma 2004; Moreno-Ajona et al. 2022; Altamura et al. 2022a; Ala et al. 2021; Wattiez et al. 2019). As a potent vasodilator released by sensory nerves, CGRP can be a key molecule in modifying the pain pathway in migraine. It has been shown that the CGRP released from trigeminal nerve fibers causes vasodilation in meningeal blood vessels, which are involved in migraine pain (Wattiez et al. 2020).

The novel findings on CGRP prompted researchers to perform deeper investigations on neuropeptides through animal studies and clinical trials, which led to the development of first (olcegepant and telcagepant), second (ubrogepant, rimegepant, and atogepant), and third (zavegepant) generations of CGRP receptor antagonists (Lassen et al. 2002).

Several of these drugs have shown promising results in terms of both efficacy and safety (Ailani et al. 2021). The present study discusses the most recent evidence on two of these drugs, of which one belongs to the first generation, while the other one is from the second generation.

As a CGRP antagonist with high oral bioavailability, atogepant was approved by the Food and Drug Administration (FDA) for the indication of episodic migraine prevention in September 2021 (AGN-241689/MK-8031), becoming the first drug developed exclusively as a preventive treatment for migraine (Goadsby et al. 2020). According to a placebo-controlled, double-blinded, randomized phase 2b/3 clinical trial, atogepant was safe and well tolerated over the 12-week treatment course. About 60% of the participants showed a 50% reduction or more in migraine days. In terms of side effects, constipation was the most commonly reported. Other side effects included nausea (5%), upper respiratory tract infection, and elevated ALT and AST levels (1–2%, up to 3 times higher than the upper limit of the normal range) (Ashina et al. 2023).

Atogepant does not need dose adjustment in mild renal or hepatic failure. However, the maximum daily dose should be limited to 10 mg in severe renal failure. Moreover, the drug is contraindicated in severe hepatic failure. It is hoped that this drug can be a useful medication for preventing migraine episodes, especially in those patients preferring oral treatment to injections (Ailani et al. 2021). Also, a study investigated the effect of 300 mg atogepant on QT interval compared to the placebo in 60 participants. Having used moxifloxacin, which causes a considerable and predictable QT elongation, as a positive control, the researchers reported no effect of atogepant on ventricular repolarization in the ECG (Boinpally et al. 2021).

On March 9, 2023, the FDA approved Zavzpret® (zavegepant, BHV-3500), which is in the form of a nasal spray, for treating acute migraine attacks. This drug was the first CGRP antagonist to be licensed for intranasal use. According to a recent study, 10–20 mg of zavegepant was superior to the placebo in treating acute migraine pain. Moreover, this novel medicine exhibited a satisfying safety profile with no signs of hepatotoxicity, and the most prevalent side effects reported were nausea or dysgeusia. Also, unlike triptans, it did not cause ECG changes or myocardial infarction. Thus, it is safe for patients with cardiovascular conditions (Ashina and Tfelt-Hansen 2023; Noor et al. 2022).

This drug is an appealing alternative for patients with migraine. Since several patients struggle with oral tolerance in acute attacks due to severe nausea and vomiting, they may benefit from intranasal use. In addition to its excellent safety profile and mild side effects, zavegepant is more effective compared to triptans as 20 mg of zavegepant causes a 61.2% reduction in pain following 2 h after use, while eletriptan, as the first-line treatment, causes a pain reduction of 37.9% after 2 h. Moreover, the pain-relieving response of triptans is varied in different situations. For example, they cause a 65% reduction of pain for 2 out of 3 attacks and a 34% reduction of pain for 3 out of 3 attacks (Ashina and Tfelt-Hansen 2023). Also, there is no published data on whether their effect lasts longer than 48 h (Croop et al. 2022; Ferrari et al. 2011; Scuteri et al. 2022).

On the other hand, CGRP has been shown to be involved in airway smooth muscle contraction and allergic inflammation in humans. It can reduce cellular adhesion and lead to increased endothelial permeability, pulmonary embolism, and hypoxemia by activating the receptors on the endothelial cells (Xu et al. 2022). Thus, a phase 2 clinical trial (NCT04346615) was launched in April 2020 to explore the safety and efficacy of intranasal zavegepant in COVID-19 patients who needed supplementary oxygen. Moreover, phase 1 of NCT04987944, which is currently ongoing, aims to investigate the safety and effectiveness of oral zavegepant (150 mg/day) in patients with moderate asthma (Altamura et al. 2022b).

Although the current data have proved that zavegepant is a novel migraine treatment, results from recent clinical studies and future research are required to present definite, high-quality evidence on its efficacy and safety. Similarly, a soft gel formulation of zavegepant can be an additional alternative for incomplete migraine treatment regimens. However, such an idea requires great investigation. Finally, there is a need for large-scale studies investigating the efficacy and safety of this drug in pregnant women and those with severe hepatic and cardiovascular disorders (Scuteri et al. 2022).

In conclusion, CGRP antagonists are the first oral drugs introduced for migraine prevention following 40 years of investigation. Up to 60% of the patients using these drugs have shown a 50% reduction or more in the frequency of migraine attacks. Moreover, no vascular or hepatic side effects have been documented with the FDA-approved drugs up to now. However, additional research is needed to investigate the tolerance and safety of these drugs if combined with monoclonal antibodies. Also, alternative therapeutic classes are being investigated for acute or prophylactic use. These novel preventive medicines for migraine that target the CGRP pathway are superior to traditional oral migraine prophylaxes in both safety and tolerability. We have come a long way toward recuperation, but we still have a long way to go.

Abbreviations

ARDS	Acute respiratory distress syndrome
CGRP	Calcitonin gene-related peptide
MOH	Medication-overuse headaches
VIP	Vasoactive intestinal peptide

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