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Gepants as a New Therapeutic Option for Migraine

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ABSTRACT

Background. Migraine is a common neurological disorder characterized by recurrent, often unilateral, throbbing headaches accompanied by other symptoms. It arises from sensory processing disorders involving activation of the trigeminal-vascular system and release of pro-inflammatory neuropeptides such as calcitonin gene-related peptide (CGRP), which is a key therapeutic target. Gepants are small-molecule CGRP receptor antagonists that block CGRP-induced pain amplification in trigeminal pathways and other related structures. Their efficacy in migraine treatment has been the focus of many recent clinical studies.

Aim. The aim of this study was to review the latest data on the therapeutic potential of gepants in acute and preventive migraine treatment, assess their safety profile, and compare their clinical utility with established therapies such as triptans and monoclonal antibodies targeting CGRP.

Material and methods. We conducted a review of the literature from 2017-2025 available in the PubMed database, using the keywords “migraine,” “CGRP,” and “gepants.”

Results. Clinical trials have shown that ubrogepant, rimegepant, and atogepant are effective in aborting acute migraine attacks, while rimegepant and zavegepant are effective in preventing migraines. Compared to currently available targeted therapies, they are less effective than triptans and comparably effective to monoclonal antibodies targeting CGRP.

Conclusions. Gepants are a safe class of medications that can be used both for prevention and for aborting migraine attacks. Although less effective than triptans, they can be used in patients who cannot be treated with them. They also have a more convenient oral form of administration compared to monoclonal antibodies, with comparable efficacy. Further research is still needed to more accurately assess the efficacy of gepants, compare them to currently approved therapies, and evaluate their potential for application in clinical practice.

Keywords: migraine, CGRP, gepants

Introduction

Migraine is a condition that causes repeated, severe headaches, usually unilateral and often with a throbbing or pulsing feeling. These headaches can be accompanied by nausea, vomiting, and sensitivity to light or sound [1]. The symptoms are intensified by physical activity [2]. About

15% to one-third of people with migraine experience an aura, which is a temporary and reversible neurological dysfunction. It can cause visual, sensory, speech, or motor symptoms occurring before the headache phase [2,3]. Diagnostic criteria for migraine without and with aura are shown in Table 1 and Table 2, respectively.

Table 1. Diagnostic criteria for migraine without aura from the International Classification of Headache Disorders, 3rd edition (ICHD-3) [4].

A	At least five attacks fulfilling criteria B–D
B	Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C	Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity
D	During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis.

Table 2. Diagnostic criteria for migraine with aura from the International Classification of Headache Disorders, 3rd edition (ICHD-3) [4].

A	At least two attacks fulfilling criteria B and C
B	One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal
C	At least two of the following four characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession

2. each individual aura symptom lasts 5-60 minutes1
3. at least one aura symptom is unilateral2
4. the aura is accompanied, or followed within 60 minutes, by headache

D Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

According to the Global Burden of Disease 2019 study, about 1.1 billion people worldwide are affected by migraine, with a prevalence of around 14%. Migraine is the second leading cause of years lived with disability among all diseases and is more common in women, especially those of childbearing age [2]. Migraine can be classified as episodic (fewer than 15 headache days per month) or chronic (15 or more headache days per month) [2].

The biological mechanisms underlying migraine are not yet fully understood and involve a complex interaction of environmental, biochemical, genetic, and epigenetic factors [1]. It is believed that migraine is a sensory processing disorder triggered by activation of the trigeminovascular system and the release of pro-inflammatory neuropeptides such as calcitonin gene-related peptide (CGRP). This initiates a neural cascade involving the brainstem, hypothalamus, and sensory cortex, resulting in the symptoms previously described [2].

CGRP

CGRP is a neuropeptide broadly present in both the peripheral and central nervous systems (CNS). Its α-isoform is mainly located in somatosensory peripheral nerves and the CNS, whereas the β-isoform is predominantly found in motor neurons and the enteric nervous system [5]. Both isoforms express similar activity [6]. Within the trigeminovascular system, CGRP is released from nerve fibers along meningeal and cerebral arteries as well as other blood vessels. It is also present in the trigeminal ganglion. In the CNS, neurons containing CGRP are found in the spinal trigeminal nucleus, locus coeruleus, raphe nuclei, certain thalamic nuclei, and the cerebellum [6]. Importantly, CGRP does not appear to cross the blood–brain barrier [6]. CGRP is well known to play an important role in vasodilation, neurogenic inflammation, and nociceptive modulation, however it is not directly algogenic [5,7]. The actions of CGRP in migraine involve both peripheral and central mechanisms, forming a bidirectional loop of communication between the trigeminovascular system and the CNS [7]. The trigeminal ganglia are a key site where CGRP signaling initiates or sustains migraine pain [8]. Although the exact mechanisms underlying CGRP-induced migraine attacks are not fully understood, extensive clinical data indicate that CGRP is a key contributor to migraine pathophysiology [5,7]. Studies

have shown that CGRP levels are elevated in the jugular vein during migraine attacks and remain higher between attacks in migraine patients compared to individuals without migraine. Chronic migraine patients show even greater interictal CGRP elevations than those with episodic migraine [5]. Moreover, it has been demonstrated that intravenous CGRP injections induced migraine-like attacks [7]. For these reasons, CGRP has become a potential target for anti-migraine drugs such as gepants [6].

Gepants

Gepants - small molecule calcitonin gene-related peptide receptor antagonists - exert their anti-migraine effect by binding to the CGRP receptor and blocking its activation [8,9]. They do not cross the blood-brain barrier, so they mainly act on CGRP pathways outside it. Gepants disrupt the resonance of pain signals transmitted by CGRP through neuroglial, neuronal, and neurovascular signaling. In this way, they appear to block the processes of pain amplification and consolidation that occur in the trigeminal ganglion, trigeminal nerve fibers, and dura mater. Gepants also relieve symptoms associated with migraine attacks, such as nausea and autonomic activation, by acting on the postrema area and sphenopalatine ganglia, which are located outside the blood-brain barrier and are innervated by trigeminal projections [8].

After characterizing the CGRP receptor, numerous studies evaluated the therapeutic value of CGRP blockade by gepants. The first gepant, olcegepant, showed strong efficacy in preclinical models and early clinical trials, providing rapid relief from migraine without serious adverse events. However, further work on this drug was halted because of difficulties in developing an effective oral form. Telcagepant, the first oral agent, showed satisfactory efficacy in aborting migraine attack, but its development for migraine prophylaxis was discontinued due to elevated liver enzymes. Several other compounds were withdrawn due to similar concerns about hepatotoxicity, but newer agents—rimegepant, ubrogepant, zavegepant and atogepant—ultimately demonstrated favorable safety and efficacy and have since received FDA approval [8,10,11].

Gepants for acute migraine treatment

Ubrogepant

To date, two large randomized controlled trials with a placebo control group have been conducted to evaluate the efficacy of oral ubrogepant in the treatment of acute migraine attacks in adults with migraine with and without aura: the ACHIEVE I study (NCT02828020), which included 1,672 participants, and the ACHIEVE II study (NCT02867709), which included 1,686

participants. In both studies, the primary endpoints were evaluated at 2 hours after the initial dose: pain freedom and absence of the most bothersome migraine-associated symptom [12–14].

The ACHIEVE I study compared placebo with ubrogepant 50 mg and 100 mg. In this clinical trial, the percent of participants who were pain-free after 2 hours was 11.8% in the placebo group, 19.2% in the 50 mg ubrogepant group, and 21.2% in the 100 mg ubrogepant group. The percent of participants who were free of the most bothersome symptoms after 2 hours was 27.8% in the placebo group, 38.6% in the 50 mg ubrogepant group, and 37.7% in the 100 mg ubrogepant group. Adverse events occurring within 48 hours after the first or optional second dose were experienced by 12.8% of participants in the placebo group, 9.4% in the group receiving 50 mg of ubrogepant, and 16.3% in the group receiving 100 mg of ubrogepant. The most common side effects were nausea, drowsiness, and dry mouth, which occurred more frequently in the group receiving 100 mg of ubrogepant. None of the participants discontinued the study due to an adverse event [13].

The ACHIEVE II study was conducted to evaluate the efficacy of ubrogepant at doses of 25 mg and 50 mg compared to placebo. In this study, the percentage of participants who reported pain relief 2 hours after receiving the initial dose was 20.7% in the 25 mg group, 21.8% in the 50 mg group, and 14.3% in the placebo group. The percentage of participants reporting no most bothersome migraine symptoms after 2 hours was 34.1% in the 25 mg group, 38.9% in the 50 mg group, and 27.4% in the placebo group. Treatment-related adverse events were reported within 48 hours of receiving the first or optional second dose by 9.2% in the 25 mg group, 12.9% of participants in the 50 mg group, and 10.2% in the placebo group. No major adverse events were reported within 48 hours of receiving the first or optional second dose. The most commonly occurring adverse event was nausea [14].

Secondary endpoints also generally showed a benefit for ubrogepant at a dose of 50 mg or 100 mg compared to placebo. More patients achieved pain relief after 2 hours (approximately 62% compared to 49%), sustained pain relief between 2 and 24 hours (approximately 37% compared to 21%), and sustained pain-free status (approximately 14% compared to 8%). Both studies also demonstrated a reduction in photophobia and phonophobia with ubrogepant. Moreover, among participants who took an optional second dose after an insufficient initial response, more people achieved complete pain relief with ubrogepant than with placebo (34% compared to 19%). Even in people who were pain-free 2 hours after taking the first dose, the second dose provided additional benefits (55% compared to 33%). Ubrogepant was also effective in patients who did not respond to triptans [15].

The benefits of ubrogepant (50 or 100 mg) observed in the ACHIEVE studies were maintained in an open-label extension study. Of the 21,454 treated migraine attacks, approximately 24% of attacks experienced pain freedom within 2 hours, and approximately 67% of attacks experienced pain alleviation within 2 hours. Approximately 35% of attacks required a second dose [15].

Rimegepant

Two randomized, placebo-controlled clinical trials have been conducted on the efficacy of rimegepant in the acute treatment of migraine attacks: NCT03237845 (with 1186 participants) and NCT03461757 (with 1811 participants). Both studies compared the effects of oral rimegepant at a dose of 75 mg with placebo and evaluated two primary endpoints 2 hours after the first dose: pain freedom and absence of the most bothersome migraine symptoms [16,17].

In the NCT03237845 clinical trial, the percentage of patients who experienced no pain 2 hours after dose administration was 19.6% in the rimegepant group and 12.0% in the placebo group. The percentage of patients whose most bothersome symptom resolved 2 hours after dosing was 37.6% in the rimegepant group and 25.2% in the placebo group. Secondary endpoint analyses demonstrated that rimegepant provided superior relief to placebo for several migraine symptoms at 2 hours after dosing: more patients reported resolution of photophobia (37% vs. 22%) and phonophobia (37% vs. 27%), and more achieved pain relief (58% vs. 43%). Resolution of nausea was similar in both groups (48% vs. 43%) [16].

According to the NCT03461757 trial, two hours after administration, rimegepant (as an orally disintegrating tablet) was more effective than placebo in terms of absence of pain (21% vs. 11% of patients) and absence of the most bothersome symptoms (35% vs. 27% of patients). Rimegepant also exceeded placebo in terms of early pain relief and maintaining pain relief for up to 48 hours. The only outcome measures in which it did not show superiority were absence of nausea and prevention of pain recurrence [17].

The most frequently reported side effects in both studies were nausea and urinary tract infections [16,17].

Zavegepant

Another randomized, placebo-controlled clinical trial (NCT04571060) evaluated the efficacy of zavegepant 10 mg nasal spray in the treatment of acute migraine attacks. At 2 hours, more participants on zavegepant achieved pain freedom (24% vs 15%) and freedom from their most bothersome symptom (40% vs 31%) than those on placebo. It was also more effective than

placebo in terms of pain relief occurring 15 minutes after administration and lasting up to 48 hours, as well as improvement in functional performance after just 30 minutes. The most common adverse events with zavegepant were: abnormal taste sensation (21% vs. 5%), nasal discomfort (4% vs. 1%), and nausea (3% vs. 1%). As nausea is a frequent symptom during migraine attacks and can make it difficult to swallow oral medications, zavegepant nasal spray offers a significant advantage, making it a promising option for the treatment of acute migraine [18].

Summary

All gepants show comparable efficacy in relieving pain and eliminating the most troublesome symptoms within 2 hours of administration. Their side effects are rare, mild, and do not require discontinuation of treatment. Nausea is the only migraine symptom for which these drugs show limited effectiveness. A summarized efficacy of each gepant based on clinical trials in terms of absence of headache 2 hours after administration is demonstrated in Figure 1.

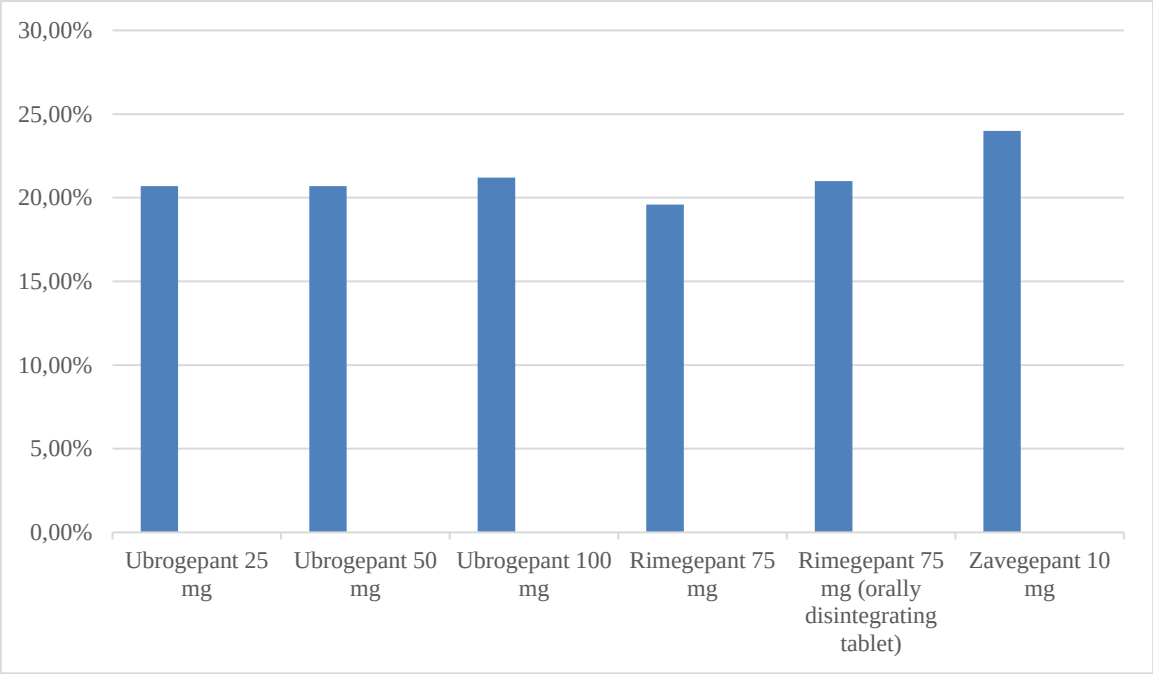

Figure 1. Efficacy of each gepant in terms of absence of headache 2 hours after administration.

Currently, triptans are the first-line medication for the acute treatment of moderate to severe migraine attacks [19]. Their efficacy in terms of absence of headache 2 hours after administration varies from 28 to 37% [20]. Despite their proven efficacy and low cost, triptans are still underused, partly due to contraindications in patients with vascular disease. However, existing evidence suggests that concerns about vasoconstriction associated with the use of

triptans may be exaggerated, highlighting the need for current studies to reassess their cardiovascular safety. Gepants, which do not cause vasoconstriction, are a valuable alternative for patients who cannot use triptans [20]. However, a systematic review and meta-analysis comparing rimegepant and ubrogepant with triptans for the treatment of acute migraine showed that although gepants were more effective than placebo in relieving pain and eliminating pain after 2 hours, their efficacy was generally lower than that of most triptans [21]. For this reason, their relatively low efficacy compared to triptans and higher cost may limit the availability of these drugs, highlighting the need for further cost-effectiveness studies, particularly in patients with insufficient response or intolerance to triptans [20]. To date, two studies were focused exclusively on the effects of ubrogepant and rimegepant in patients who are unable to take triptans due to contraindications, tolerability issues, or insufficient efficacy. In both of these studies, the use of gepants benefited this group of patients in terms of improving headaches and returning to normal functioning [22,23]. This provides a basis for acknowledging gepants as valuable and effective drugs in this patient group, despite their overall lower efficacy compared to triptans.

Gepants for migraine prophylaxis

Rimegepant

One randomized, placebo-controlled clinical trial (NCT03732638) was conducted to assess the efficacy of oral rimegepant at a dose of 75 mg every other day in migraine prophylaxis. In this study, rimegepant was more effective than placebo in reducing the number of migraine days per month during weeks 9–12. Participants receiving rimegepant reported a reduction of 4.3 days compared to 3.5 days for placebo, and a higher percentage of patients achieved at least a 50% reduction in the number of days with moderate or severe migraine (49% compared to 41%). Over the 3-month treatment period, rimegepant also reduced the total number of migraine days more than placebo (3.6 compared to 2.7 days). There were no significant differences between the groups in the use of rescue medications. Adverse events occurred with similar frequency in both groups. The most common adverse events associated with rimegepant were nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection, and almost all of them were mild or moderate. There were no serious adverse events associated with rimegepant treatment, and the percentage of discontinuations due to adverse events was low in both groups (2% in the rimegepant group, 1% in the placebo group) [24].

Atogepant

Another randomized, placebo-controlled clinical trial (NCT03777059) evaluated the efficacy of oral atogepant (10 mg, 30 mg, or 60 mg) once daily in migraine prophylaxis. Over the 12-week treatment period, atogepant reduced the number of migraine days per month more than placebo: −3.7 (10 mg), −3.9 (30 mg), and −4.2 (60 mg) compared with −2.5 for placebo. An at least 50% reduction in the number of migraine days per month was achieved by 55.6% (10 mg), 58.7% (30 mg), and 60.8% (60 mg) of participants, compared with 29.0% for placebo. Adverse events occurred with similar frequency in the atogepant and placebo groups and were not dose-dependent. The most common adverse events associated with atogepant were constipation (6.9–7.7%), nausea (4.4–6.1%), and upper respiratory tract infections (3.9–5.7%). Serious adverse events were rare. The number of discontinuations due to adverse events was low and similar in both groups [25].

Summary

Based on clinical trial data, both rimegepant and atogepant appear to be safe and effective in preventing migraine. Atogepant shows slightly greater efficacy in reducing the number of migraine days while maintaining a safety profile comparable to that of rimegepant.

Other CGRP-targeted therapies, that are available for the preventive treatment of migraine, include four monoclonal antibodies targeting CGRP, administered parenterally. However, more than half of migraine patients prefer oral treatment over injections due to convenience and needle anxiety. Moreover, rimegepant and atogepant have a relatively short half-life of 11 hours, compared to the approximately one-month half-life of CGRP monoclonal antibodies. This shorter half-life allows doctors to quickly reduce or discontinue exposure to the drug if side effects occur, and may also be beneficial for women of childbearing age, facilitating family planning or discontinuation of the drug during pregnancy [24,25]. In a study utilizing matching-adjusted indirect comparisons, rimegepant demonstrated comparable efficacy to erenumab and galcanezumab (two monoclonal antibodies targeting CGRP) in terms of long-term preventive effects on monthly migraine days and health-related quality of life [26]. Further studies are needed to directly compare the efficacy and safety of different gepants and CGRP monoclonal antibodies. Such studies would aid in determining whether any of these therapies are more effective or have a more favorable safety profile.

Conclusions

Gepants are a class of medications that can be utilized both in the acute treatment of migraine attacks (rimegepant, ubrogepant, zavegepant) and in migraine preventive therapy (rimegepant, atogepant). Rimegepant is the only one of these that has demonstrated efficacy in both indications. Gepants have a favorable safety profile and are administered orally or as a nasal spray. There have been no serious adverse events reported in clinical trials. Unlike triptans, which are first-line drugs for the acute treatment of migraine, gepants can be used in patients with cardiovascular precautions, although they are generally less effective than triptans. They may also be effective in patients who do not respond to triptans, cannot tolerate them, or have contraindications to their use. Compared to CGRP monoclonal antibodies, the only currently approved targeted therapy for migraine prevention, gepants show similar efficacy and safety while offering the convenience of oral administration instead of injections. Further research and ongoing clinical trials are needed to continue evaluating the efficacy and safety of gepants in both acute and preventive migraine treatment and to compare them more precisely with currently available migraine therapies.

Disclossure

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