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REVIEW ARTICLE

Update on gepants for the treatment of chronic migraine

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Abstract

Chronic migraine (CM) is a profoundly debilitating condition that has detrimental clinical and social outcomes. Over the past two decades, novel small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists, known as gepants, and CGRP monoclonal antibodies (mAbs) have been developed, ushering in a new era of migraine-specific treatment. In this review, we discuss the literature investigating the role of gepants for the treatment of CM. Numerous completed and ongoing clinical studies have conclusively demonstrated the safety, tolerability, and efficacy of several gepants for the acute treatment of migraine. However, preventive trials involving gepants have focused on patients with episodic migraine, with atogepant being the only gepant approved for CM prevention by the US Food and Drug Administration at the time of writing. Although some preliminary positive results have been reported, further research is still required to achieve additional advancements in the future. In summary, the effectiveness of gepants for treating individuals with CM are highly expected. This review highlights the development and current progress of gepants for the treatment of CM, focusing both on their role as acute abortive agents and preventive measures and on their concomitant use with other antimigraine medications, such as CGRP mAbs or triptans.

Keywords: Calcitonin gene-related peptides; CGRP receptor antagonist; Gepants; Chronic migraine

1. INTRODUCTION

1.1. Migraine

Migraine is the most common disorder of the central nervous system, imposing a tremendous disease burden on patients, their families, and healthcare systems.[1] Effective management of migraine is currently hindered by insufficient treatments and educational resources. According to a study conducted in 2021, less than half of the individuals who meet the criteria for migraine receive the minimally appropriate acute and preventive pharmacological treatment.[2] In addition, traditional acute treatments, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), caffeinated analgesic combinations, and nonopioid analgesics, may not be universally effective in treating all types of migraine.[3] Similarly, conventional preventive treatments, including antihypertensive agents, antiepileptic medications, antidepressants, and onabotulinumtoxin A, are not specifically designed for migraine, and their mechanisms for migraine prevention remain inadequately elucidated.[4] Consequently, the limited treatment options available contribute to the progressive transition of migraine toward a chronic state.[5]

According to the Third Edition of the International Classification of Headache Disorders, migraine is divided into episodic migraine (EM) and chronic migraine (CM).[6] CM is defined as the presence of a headache for at least 15 days per month, with migraine features for at least 8 days, persisting for 3 consecutive months.[7] CM has a prevalence of 1% to 2% among the general population and affects approximately 8% of patients with migraine.[8] Each year, EM transitions into CM in approximately 3% of patients.[9] Compared with EM, CM has a fourfold stronger effect on the healthcare system and patients' quality of life.[10] Advanced age, female sex, low educational status, and overuse of acute migraine medication have been identified as risk factors for migraine chronification.[11]

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1.2. Pathophysiology of migraine

Overall, the pathophysiology of migraine is complex and multifactorial and is still not fully understood in many aspects. According to current understanding and scientific research, trigeminovascular system activation with vasodilatation and neuroinflammation is regarded as the primary mechanism for migraine.[12] This activation also affects brainstem regions, with second-order neurons projecting into areas such as the dorsolateral pons and periaqueductal gray, which play different roles in migraine.[13] In addition to this effect of the trigeminovascular system on brainstem regions, its activation further affects the hypothalamus, thalamus, and cortex, resulting in the unique features of migraine.[12]

CM has different mechanisms and presentations comparing with those of EM.[14] Multiple studies have indicated a strong correlation between structural and functional changes in specific brain regions associated with pain sensitization and top-down pain modulation.[15,16] Various mechanisms involving molecules such as calcitonin gene-related peptides (CGRPs), serotonin, and pituitary adenylate cyclase-activating polypeptides, have also been identified.[17,18] Among the risk factors associated with the progression of pain chronification are baseline headache frequency, medication overuse, insufficient headache relief or prophylaxis, stressful events, and comorbid pain. Inappropriate or insufficient medical treatment is regarded as one of the main factors contributing to central sensitization and the subsequent development of CM.[19]

1.3. CGRPs and migraine

The discovery of CGRPs and their causative role in migraine attacks has been regarded as a milestone in migraine-specific treatment. In 1982, CGRPs were first discovered through their expression in the central nervous system of rats, with a suggestive hormonal effect.[20] In 1988, studies involving cat models revealed an increase in substance P-like and CGRP-like immunoreactivity following the activation of the nociceptive afferent system in the cranial region, thus providing insight into the putative role of CGRPs in the pathophysiology of migraine.[21] Subsequent studies have also indicated that the concentration of CGRPs increases in the external jugular vein during migraine attacks,[21,22] rather than in blood drawn from the cubital fossa, and that the infusion of CGRPs induces migraine attacks in patients with migraine.[23]

CGRPs are involved in both the peripheral and central pathways. Compared with prostaglandins or other vasodilators, such as acetylcholine, CGRPs exhibit a much stronger vasodilatory property. This characteristic and its associated inflammatory events within the dura and trigeminal ganglion induce and amplify migraine.[24,25] Both CGRPs and their receptors are widely expressed in the central nervous system, especially in the trigeminovascular system and brainstem, where they are linked to a decline in the descending inhibitory mechanism and pain transmission to other organs. CGRPs are also strongly associated with CM, with previous studies showing higher serum levels of CGRPs among patients with CM compared with patients with EM or no headache.[12,19]

These findings have established the vital role of CGRPs in the pathophysiology of migraine. To achieve effective acute or preventative treatment, CGRP antagonists acting on CGRP receptors or ligands have been developed. These antagonists can be divided into monoclonal antibodies (mAbs) and non-peptide small molecules, also known as gepants. In this review, we focused on studies investigating the safety and efficacy of gepants in CM treatment.

1.4. Gepants and their mechanism of action

Gepants are small-molecule CGRP receptor antagonists. They function by binding to CGRP receptors and blocking the interaction between CGRPs and their receptors. This process prevents the activation of these receptors and the subsequent cascade of biochemical events, which promote the release of inflammatory mediators, dilate blood vessels, and increase the sensitivity of pain-sensing nerve fibers. These events contribute to headache and other symptoms of migraine.[24] Gepants have a molecular weight of <1 kDa, which is much smaller than that of mAbs (approximately 150 kDa) targeting CGRPs or their receptors.[26] In addition, they do not consistently cross the blood–brain barrier (BBB).[24] In primates, the cerebrospinal fluid to plasma ratio of telcagepant, the first oral gepant, is approximately 1.4%, suggesting minimal BBB penetration. Therefore, under physiological conditions, that is, with intact BBB integrity, gepants exert their antimigraine effects outside the BBB.[24] They do not cause vasoconstriction per se, either in cranial or in coronary arteries. Whereas this vasoconstrictive effect is one of the major limitations of triptans as acute treatment of migraine.[27]

As shown in Fig. 1, three generations of gepants are currently available. The development of first generation includes olcegepant, telcagepant, MK3207, and BI44370, which have been discontinued because of their side effects and poor oral accessibility.[28] The second-generation includes ubrogepant, rimegepant,

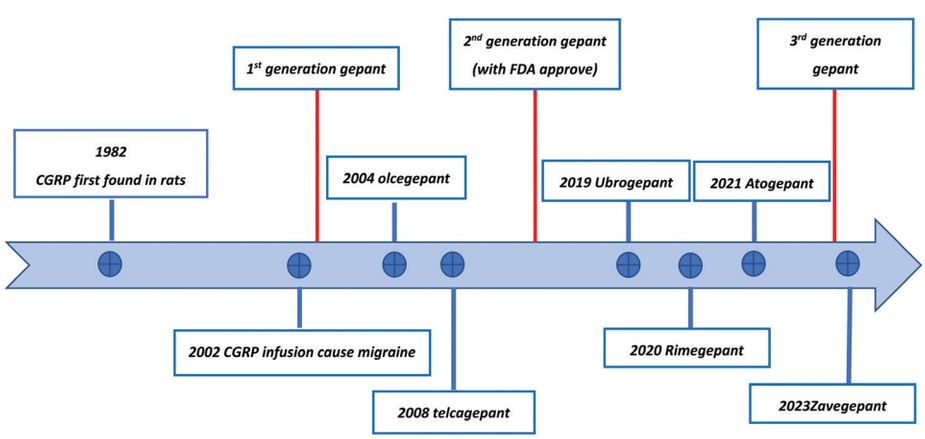

Fig. 1 History of gepant development. CGRP = calcitonin gene related peptide; FDA = Food and Drug Administration.

and atogepant, which have demonstrated efficacy in the acute treatment of migraine and were approved by the US Food and Drug Administration (FDA) between 2019 and 2021.[29–31] Some second-generation gepants have also been approved for use in migraine prevention.[32,33] The third-generation currently includes only zavegepant, whose nasal form has been approved by the FDA for the acute treatment of migraine. Clinical trials involving an oral form of zavegepant for the prevention of migraine are currently underway.[34] Besides, gepants should be taken after the failure of using triptans in acute treatment of migraine according to current guidelines.[3] Several clinical trials had provided evidence of efficacy on gepants as preventive treatment for EM or CM, however, there was no suggestions of gepants as preventive treatment in current guidelines yet.[35,36]

Table 1 lists the current indications of each gepant.

2. HISTORY OF GEPANT DEVELOPMENT

2.1. Olcegepant (BIBN-4096)

Olcegepant, available in intravenous form only, is the first gepant to be studied since 2004. In an international, multicenter, double-blind, randomized controlled clinical trial, olcegepant exerted a clear effect on migraine, with a response rate of 66% and a pain-free rate of 44% at 2 hours.[37] However, olcegepant has no oral bioavailability and the development has therefore been discontinued, and it is currently used primarily for experimental purposes only (Fig. 1).

2.2. Telcagepant (MK-0974), MK3207, and BI44370

Since 2008, telcagepant has undergone several trials as the first oral form of gepants. Overall, it demonstrated a promising effect on acute treatment of migraine, with a response rate of approximately 25% to 55%.[38] It also demonstrated a clear effect vs placebo on phonophobia and photophobia.[39] However, in some studies, it demonstrated innegligible adverse effects (AEs). The development was finally discontinued because of elevated level of alanine aminotransferases, indicating liver toxicity.[40] Thus, the development of Telcagepant, MK3207, and BI44370 has been discontinued according to Hy's law, which refers to drug-induced liver toxicity with severely elevated liver enzymes.[28]

2.3. Ubrogepant

Ubrogepant was the first gepant approved by the FDA for the acute treatment of migraine.[30] In 2019, ubrogepant underwent two phase III double-blind, single-attack trials, namely ACHIEVE-I and ACHIEVE-II.[41] The results indicated that, compared with placebo, ubrogepant had a clearer effect on migraine pain at doses of 25, 50, and 100 mg. However, at a dose of 25 mg, it had no obvious effect on photophobia, phonophobia, or nausea. After multiple phase III trials and studies were conducted, ubrogepant was approved by the FDA for the acute treatment of migraine attacks at doses of 50 and 100 mg.[30]

Some aspects must be considered when ubrogepant is used.[34] First, the peak plasma concentration (T_{max}) of ubrogepant is reached after 0.7 to 1.5 hours, and hence, a second dose cannot be administered except after at least 2 hours. Second, the dosage of ubrogepant should be adjusted in patients with severe renal or hepatic failure. Ubrogepant should also be avoided in patients with end-stage renal disease. Third, no studies have investigated the safety of administering ubrogepant more than eight times monthly or the effect in patients with CM or medication overuse headache (MOH). The majority of ACHIEVE-I and II trials have excluded patients with CM or MOH. Only one real-world study involving 92 patients with CM among a total of 106 patients with migraine has demonstrated a complete headache-free rate of 19.0%, with a headache relief rate of 47.6% among more than 75% of the patients.[42] Fourth, no studies have investigated the role of ubrogepant in migraine prevention, presumably because of its relatively short half-life and high rate of AEs compared with other gepants.

2.4. Rimegepant

Rimegepant was the second gepant approved by the FDA on February 27, 2020, for the acute treatment of migraine. In 2019, three phase III trials, namely NCT03461757, NCT03237845, and NCT03235479, were conducted to examine the efficacy and safety of rimegepant.[43–45] The results indicated that rimegepant had a clear effect on migraine pain at 2 hours, with positive effects on pain relief and other migraine symptoms. However, in these three phase III trials, patients with CM were excluded. Currently, there was only one post hoc analysis involving patients with six or more monthly migraine days (MMDs), including patients with CM, has demonstrated reduced MMDs and increased health-related quality of life associated with the use of rimegepant.[46]

Because of its half-life of 11 hours, regular administration of rimegepant is regarded as an effective preventive treatment for migraine. Croop et al[47] conducted a double-blind, placebo-controlled trial to investigate the efficacy of administering placebo and rimegepant at a dose of 75 mg every other day over a treatment period of 12 weeks. They included patients aged older than 18 years who experienced 4 to 18 migraine attacks of moderate to severe intensity every month for the last 3 months. At the primary endpoint of change, rimegepant demonstrated its superiority to placebo in terms of the mean number of MMDs. The results also indicated that rimegepant was associated with a response rate of over 50%. Given these positive outcomes, rimegepant was approved by the FDA for EM prevention in 2021.[33] Notably, rimegepant has not been specifically tested in patients with CM. In a previous study involving 173 patients with CM among a total of 741 patients (23%), post hoc subgroup analysis revealed no difference in MMDs (a reduction of over 50%) in patients with or without a history of CM. Given the positive effects of rimegepant on EM prevention, further research is required to investigate its therapeutic effect on CM.

2.5. Atogepant

With a similar half-life to that of rimegepant, atogepant was developed to prevent migraine.[34] In a phase III double-blind trial examining, the efficacy of atogepant in migraine prevention, 873 individuals received either placebo or atogepant at doses of 10, 30, and 60 mg daily.[32] The study indicated substantial results both in the number of migraine days from baseline over a 12-week period and in the Activity Impairment in Migraine Diary (AIM-D) scores, except at a dose of 10 mg, with the most common AEs being constipation and nausea. However, in this phase III trial, patients with CM were excluded. Following this trial and other trials on the tolerability and safety of atogepant,[48,49] atogepant was approved by the FDA in September 2021 for the treatment of EM.

To date, there has been only one clinical trial examining the efficacy and safety of atogepant in CM. In 2022, following the success of the pivotal ADVANCE study, a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (the PROGRESS study) was conducted to evaluate the efficacy, safety, and tolerability of atogepant for the prevention of CM.[50] This study included 778 patients with CM evaluated over a treatment period of 12 weeks. Patients were randomized into three parallel groups: a group receiving placebo, a group receiving 30 mg of atogepant twice daily, and a group receiving 60 mg of atogepant once daily. Patients with CM who demonstrated no response to more than four preventative agents (with

Table 1

List of clinical trials of gepants and outcomes

Name of trial	Gepant	Elimination half-life	State of completion	Year	Patient enrolled	Admin istration	Dose	Target	Migraine type	Study duration	Change in monthly migraine days	2-h pain-free rate	Common side effect (>5%)	Severe side effect rate
NCT03266588	Rimegepant	11 h	Completed	2020	1044	Oral	Rimegepant 75 mg	Acute	EM or CM[a]	52 wk	Rimegepant 75 mg: 2.0		Upper respiratory tract infection, nasopharyngi-tis, or sinusitis	2.6%
NCT03732638	Rimegepant	11 h	Completed	2021	747	Oral	Rimegepant 75 mg every other day, placebo	Preventive	EM or CM[b]	12 wk	Rimegepant: −4.3 ($p = 0.0099$) Placebo: −3.5		Upper respiratory tract infection or nasopharyngitis	Rimegepant: 2% Placebo: 1%
ACHIEVE-I (NCT02828020)	Ubrogepant	5-7 h	Completed	2019	1672	Oral	Ubrogepant 50 or 100 mg, placebo	Acute	EM			Ubrogepant 50 mg: 19.2%, $p = 0.002$	No side effect over 5%	Ubrogepant 50 mg: 0.64% Ubrogepant 100 mg: 0.41% Placebo: 0%
ACHIEVE II (NCT02867709)	Ubrogepant	5-7 h	Completed	2019	1465	Oral	Ubrogepant 25 or 50 mg, placebo	Acute[c]	EM			Ubrogepant 100 mg: 21.2%, $p < 0.001$	No side effect over 5%	Ubrogepant 25 mg: 0.21% Ubrogepant 50 mg: 0% Placebo: 0%
PROGRESS (NCT03855137)	Atogepant	11 h	Completed	2022	778	Oral	Atogepant 30 mg BID or 60 mg QD, placebo	Preventive	CM	12 wk	Atogepant 60 mg QD: −7.27 ($p = 0.0001$) Atogepant 30 mg BID: −7.13 ($p = 0.0009$) Placebo: −4.63		Constipation or nausea	Atogepant 60 mg QD: 2.68% Atogepant 30 mg BID: 1.56% Placebo: 1.18%
NCT04686136	Atogepant	11 h	Not completed yet	2021	596	Oral	Atogepant 60 mg QD	Preventive	EM or CM	156 wk				
NCT05216263	Atogepant With onabotulinumtoxin A (BOTOX)	11 h	Not completed yet	2022	125	Oral	Atogepant 60 mg QD	Preventive	CM	24 wk				
NCT04571060	Zavegepant	6.5 h	Completed	2021	1405	Intra-nasal	Zavegepant 10 mg, placebo	Acute	EM			Zavegepant 10 mg: 24%, $p < 0.0001$ Placebo: 15%	Taste disorders	Zavegepant 10 mg: 0% Placebo: 0%

CM = chronic migraine; EM = episodic migraine.

[a]Inclusion criteria: patient with monthly migraine days ≥6 at baseline.

[b]Inclusion criteria: per subject report, 4-18 migraine attacks of moderate to severe intensity per month within the last 3 mo before the screening visit, 6 or more migraine days during the observation period, not more than 18 headache days during the observation period.

[c]With moderate or severe headache pain.

at least two different mechanisms) were excluded. The results indicated that, compared with the placebo group, the other two groups demonstrated a substantial decrease in the number of migraine days and in the AIM-D and headache impact test scores. In addition, neither of these two groups exhibited a considerable increase in the number of serious AEs. Moreover, in healthy participants, no elevation in alanine aminotransferase was observed, even with a supratherapeutic dose of 170 mg daily for 28 days.[48] Following this phase III trial and other trials, atogepant was approved by the FDA in September 2021 for the treatment of CM.[31] Although atogepant demonstrated a strong capability to prevent CM in the PROGRESS study, difficult-to-treat patients with CM, namely those who did not respond to more than two medications with different mechanisms, were excluded. To alleviate the tremendous health, social, and economic burden of this disorder, further research is required to uncover additional options for treating patients with CM with a poor response to current therapies.

In March 2022, a phase III, multicenter, 24-week, open-label study was initiated to evaluate the safety, tolerability, and efficacy of administering atogepant in combination with onabotulinumtoxin A for the preventive treatment of CM (NCT05216263). The study intended to enroll 125 patients, and the results are not published yet. Another phase III, multicenter, 104-week extension study was initiated to evaluate the long-term tolerability and safety of administering 60 mg of atogepant once daily for the prevention of EM or CM (NCT04686136). Table 2 presents a list of all clinical trials and ongoing studies.

2.6. Zavegepant

Zavegepant (BHV-3500/BMS-742413, formerly known as vazegepant) is a third-generation, small-molecule, CGRP receptor antagonist developed for the prevention and acute treatment of EM and CM. In March 2023, zavegepant nasal spray was approved in the United States for the acute treatment of migraine in adults.[51] In a phase III study of zavegepant, 1269 patients with migraine were randomly assigned at a ratio of 1:1 to either a group receiving 10 mg of zavegepant nasal spray or a placebo group. Patients with CM were excluded from the trial. The results indicated that the treatment dose of zavegepant resulted in a clear improvement in the pain-free rate after 2 hours, with the alleviation of other migraine symptoms.[51,52] Zavegepant demonstrated obvious clinical benefits, with pain relief after 15 minutes and a return to normal function after 30 minutes of administration. In both treatment groups, the most common AEs were dysgeusia, nasal discomfort, and nausea, with no signs of hepatotoxicity.

Zavegepant was also developed as a preventive treatment for migraine. An oral form of zavegepant is currently under evaluation in a phase II/III, 12-week, randomized, double-blind, placebo-controlled study (NCT04804033) involving approximately 1440 adults, aiming to evaluate the efficacy of zavegepant for migraine prevention. However, no published studies have investigated the effect of zavegepant on CM prevention. Therefore, further research and report for the ongoing study are required.

2.7. Gepants and mAbs targeting CGRPs

Previous studies have explored the possibility of combining gepants with other medical agents. In a long-term, open-label study investigating the safety in adults with 2 to 14 monthly migraine attacks of moderate to severe pain intensity, a small subgroup of 13 patients, who experiencing 2 to 8 monthly attacks and were taking a stable dose of a CGRP mAb also took rimegepant 75 mg as needed up to once daily for acute treatment for 12 weeks (54% received erenumab [n = 7], 31% received fremanezumab [n = 4], and 15% received galcanezumab [n = 2]). In patients who received anti-CGRP mAbs, no serious AEs or AEs requiring treatment discontinuation were observed.[53]

In the aforementioned study, two patients received erenumab on a monthly basis as a preventive treatment while receiving rimegepant as an acute treatment, and their experiences were documented in a case study report. Patient 1 received rimegepant for 6 months and was subsequently started on 70 mg of erenumab subcutaneously on a monthly basis. Over the subsequent month, she experienced substantial relief, with all acute attacks resolved with rimegepant, thereby eliminating the need for the regular use of ibuprofen and caffeinated analgesics. Patient 2 received rimegepant for 60 days and was subsequently started on 140 mg of erenumab subcutaneously on a monthly basis. While on erenumab, she experienced relief, with all attacks resolved with rimegepant, thereby eliminating the almost daily requirement for ketorolac and diphenhydramine injections. All patients, either on rimegepant alone or on rimegepant combined with erenumab, reported no AEs.[26]

In a phase Ib, randomized, drug–drug interaction study by Jakate et al,[54] no considerable changes were observed in the PK profile of ubrogepant, and no safety concerns were raised when ubrogepant was co-administered with erenumab or galcanezumab. However, no data on the efficacy of these drugs in managing migraine were collected.

2.8. Gepants and triptans

Given the large percentage of patients requiring combined therapy for headache remission, efficacy assessments must be conducted on the concomitant use of triptans and CGRP antagonists. Multiple studies have examined the hemodynamic effects and pharmacokinetic interactions associated with the concomitant use of rimegepant and sumatriptan or atogepant and sumatriptan in healthy adults. For example, in a phase II/III, 12-week, double-blind trial examining the preventive effect

Table 2

Gepants indication

Gepant	Indication	FDA approval	EMA approval
Rimegepant (Nurtec/Vydura)	Acute treatment of migraine	February 27, 2020	February 25, 2022
	Preventative treatment of episodic migraine	May 27, 2021	February 25, 2022
Ubrogepant (Ubrelvy)	Acute treatment of migraine	December 23, 2019	None
Atogepant (Qulipta)	Preventative treatment of episodic migraine	September 28, 2021	August 17, 2023
	Preventative treatment of chronic migraine	September 28, 2021	August 17, 2023
Zavegepant (ZAVZPRET)	Acute treatment of migraine	March 9, 2023	None

EMA = European Medicines Agency; FDA = Food and Drug Administration.

of rimegepant on migraine, rescue medications such as triptans, NSAIDs, paracetamol up to 1000 mg/d for a maximum of 2 consecutive days (including a fixed combination of 250 mg paracetamol, 250 mg aspirin, and 65 mg caffeine), baclofen, antiemetics, and muscle relaxants were evaluated during the treatment phase. During the trial, patients were allowed to use these rescue medications while maintaining regular doses of the assigned study drug every other day. Sumatriptan was used in both the rimegepant and placebo groups (0.4% vs 1.3%).[47] Overall, the following categories of drugs were allowed: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.[55] In the studies, no hemodynamic or pharmacokinetic interactions were observed between these drugs, thereby indicating their safety and tolerability.

In patients who do not respond to triptans, rimegepant may be effective for the acute treatment of migraine. Post hoc analysis of three phase III treatment trials investigating the use of rimegepant at a dose of 75 mg revealed that the participants had a history of insufficient response to one triptan (n = 910, 25.9%) and two or more triptans (n = 325, 9.3%), with 2272 participants (64.8%) having no history of insufficient response to triptans (current use = 595, 17.0%). Rimegepant was effective at the coprimary endpoints in all subgroups ($p \leq 0.013$). No cardiovascular (CV) contraindications or warnings were reported with respect to rimegepant treatment in acute or preventative settings, and no CV AEs were reported in two open-label extension studies evaluating the long-term safety of rimegepant.[56]

3. CONCLUSIONS AND FUTURE DIRECTIONS

Approximately 40 years since the discovery of CGRPs, gepants, which act as antagonists on CGRP receptors, have demonstrated clear efficacy in the acute treatment and prevention of migraine. Most AEs associated with gepants are gastrointestinal in nature. Ubrogepant, rimegepant, and zavegepant (nasal spray) have been approved by the FDA for the acute treatment of migraine. Atogepant and rimegepant were approved by the FDA in 2021 and have been used for EM prevention. Further research is still required to determine the effects of gepants on CM. So far, prevention trials on gepants have mostly focused on patients with EM, but results on CM have yet been released. At the time of writing, atogepant is the only gepant approved by the FDA for CM prevention. Treatment of CM with gepants is regarded as a new area of focus in the context of CGRP-targeting therapy.

As a promising approach for migraine treatment, gepants have multiple indications with FDA approval. However, only a few studies have focused on CM and MOH. The majority of phase III studies have excluded patients with CM, resulting in limited evidence supporting the efficacy of atogepant in CM prevention. Therefore, further studies are required to investigate the preventive effect of rimegepant, ubrogepant, and zavegepant for the treatment of CM. Further research is also required to evaluate the efficacy of gepants for the acute treatment of CM.

Although no apparent CV AEs have been observed, patients with debilitating CV diseases have been excluded from multiple studies. Therefore, additional data are required to evaluate the safety of gepants among patients with CV diseases, especially in those with CM. Although gepants are not associated with a considerable percentage of AEs within 1 year of administration, long-term AEs should be evaluated because CGRP receptors are disseminated throughout the body. Currently, multiple trials (e.g., NCT05156398, NCT04743141, NCT05707949, NCT04649242, NCT05198245, and NCT05711394) are underway to evaluate the efficacy and safety of gepants in children and pregnant women, specifically for the acute or preventive treatment of EM. However, additional data regarding CM in these two patient populations are still required.

Comparative studies involving other medications within the same class and other therapeutic classes, such as CGRP mAbs and triptans, and studies on the combination of gepants with other medications are required to aid clinical practice. Although substantial progress has been made in the treatment of CM, much work remains.

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