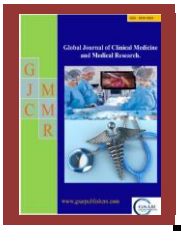

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Silencing the Storm: Rimegepant and the CGRP Pathway in Migraine

By

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Abstract

Migraine is a disabling neurological disorder that significantly affects individuals during their most productive years. Traditional therapies for acute and preventive migraine management are often limited by poor tolerability and contraindications, especially in patients with cardiovascular comorbidities. Rimegepant, a novel calcitonin gene-related peptide (CGRP) receptor antagonist, offers a targeted and well-tolerated option for the acute treatment of migraine. It is approved for use in adults with or without aura and is particularly useful in patients who cannot take triptans due to adverse effects or cardiovascular risk. Clinical trials and meta-analyses have demonstrated that rimegepant is highly effective in alleviating symptoms. Within just two hours of administration, patients experience significant relief, including freedom from pain and resolution of their most distressing symptoms. Unlike triptans, rimegepant does not cause vasoconstriction, making it safer for broader populations. It also avoids issues associated with medication overuse headache and does not exhibit hepatotoxicity. Pharmacokinetically, it has favorable bioavailability and minimal drug interaction potential. Despite these advantages, high costs and limited long-term safety data, especially regarding immune modulation and infection risk with chronic CGRP blockade, warrants caution. Current evidence positions rimegepant as a valuable addition to the migraine treatment landscape, especially in patients with intermediate migraine frequency or contraindications to conventional therapy. Future research should focus on long-term safety, comparative effectiveness, and broader population data to fully establish its therapeutic role and significance.

Keywords: *Rimegepant, Migraine, Headache, CGRP receptor antagonist*

Introduction

Primary headache disorders are chronic conditions that persist throughout life, significantly affecting not only the individuals who suffer from them but also their families, workplaces, and society as a whole. Headaches contribute to widespread disability and economic burden globally.[1] Migraine is a complex neurological condition with multiple symptoms and phases, and in some cases, it may become progressive. It has a considerable negative impact on patients' quality of life. Female sex hormones are known to influence migraine occurrence, and while CGRP (calcitonin gene-related peptide) transmission is known to trigger migraine in some individuals, it remains unclear whether this mechanism affects both sexes equally. Women tend to experience more severe, persistent, and comorbid forms of migraine and also have a higher prevalence compared to men.[2]

Migraine is characterized by recurring episodes of one-sided, pulsating head pain. It is often accompanied by light and sound sensitivity, nausea, and vomiting, migraine is a highly disabling neurological condition. It can lead to work absences and even unemployment. As of 2019, migraine was the most prevalent disabling headache disorder globally, with an age-

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standardized prevalence rate of 14.1%. The condition is most common during peak working years, typically between the ages of 25 and 55 years.[3]

CGRP, the most powerful vasodilator in the human body, is a key player in trigeminovascular pathways involved in migraine. Medications that block CGRP are the first preventive treatments specifically designed for migraine and have side effect profiles comparable to placebo.[4] Migraine attacks can cause substantial disability, severely affecting quality of life and reducing productivity. For treatment to be effective, good tolerability is crucial to maintain patient adherence. However, traditional oral preventive medications for migraine often suffer from poor patient compliance due to their low tolerability and frequent side effects.

Recently, new migraine-specific preventive therapies that target the calcitonin gene-related peptide (CGRP) pathway have been developed to address these limitations.[5] Pfizer recently acquired Nurtec, an emerging medication that has been gaining recognition in the field of migraine management. Known generically as rimegepant, it is part of a newer class of drugs called calcitonin gene-related peptide (CGRP) receptor antagonists. While traditional treatments such as triptans (e.g., sumatriptan) remain widely used for acute migraine relief, gepants like Nurtec offer strong efficacy in quickly alleviating migraine attacks. Nurtec is specifically approved for the acute treatment of migraines in adults, making it a valuable addition to the range of therapies aimed at providing prompt symptom relief.[6]

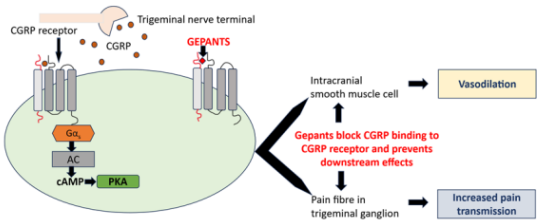

Figure 1: Mechansim of action of rimegepant[7]

Drugs approved in the acute treatment and prevention of migraine.[8–10]

Migraine is a complex neurological disorder characterized by recurrent episodes of moderate to severe headache, often accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. The management of migraine includes both acute treatments aimed at aborting the headache once it begins, and preventive treatment to reduce the frequency and severity of attacks. Acute treatment ranges from commonly used non-steroidal anti-inflammatory drugs (NSAIDs) and triptans to newer classes such as ditans and gepants. Preventive strategies include a variety of medications with varying levels of evidence, including beta-blockers, antiepileptic drugs, antidepressants and monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway. Migraine is often accompanied by nausea and vomiting that can be as distressing and disabling as the pain, hence antiemetics, such as metoclopramide, domperidone, ondansetron and prochlorperazine play a role.

Table 1: Acute treatment of migraine

Drug/classification	Approval	Mechanism of action	Drawbacks
Non-steroidal anti-inflammatory drugs (NSAIDs): acetaminophen (paracetamol)	Acute migraine treatment	Cyclooxygenase inhibitor	Gastrointestinal and renal side effects
Triptans: sumatriptan, eletriptan, rizatriptan, zolmitriptan	Acute migraine treatment (developed in the 1980s)	Serotonin 5-HT 1B/1D receptor agonists: inhibiting the release of vasoactive peptides, promoting vasoconstriction, and inhibiting pain pathways in the brain stem	Contraindicated in individuals with a history of ischemic heart disease, stroke, uncontrolled hypertension, hemiplegic migraine, and peripheral vascular disease
Ditans: lasmiditan	Acute migraine treatment (US FDA (Food and Drug Administration) approval 2019) (if contraindications to triptans due to cardiovascular risk factors) migraine onset occurs in the evenings	Selective 5HT/1F receptor agonist acts on the trigeminal system without causing vasoconstriction (low affinity for 5HT 1B receptors)	dizziness, paraesthesia, somnolence, impairment in driving performance (advised not to drive or perform potentially hazardous activities for at least 8 h post dose)

*Corresponding Author: **Rashmi Chandra**

Gepants: ubrogepant, rimegepant	Acute migraine treatment (Ubrogepant FDA approval December 2019) (Rimegepant FDA approval February 2020) (alternative for patients who cannot take triptans due to cardiovascular disease)	Small molecule CGRP receptor antagonists, does not cause vasoconstriction	Ubrogepant: nausea, somnolence, and dry mouth Rimegepant: nausea and urinary tract infection

Table 2: Preventive treatment of migraine

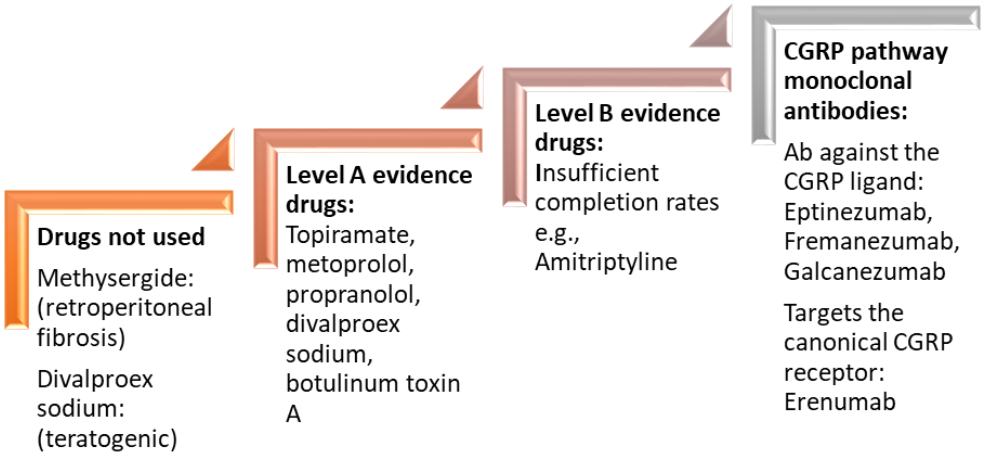

Table 3: Characteristics of Rimegepant[11–15]

Approved Dose	75 mg
Approved Dosage form	Oral disintegrating tablets (ODT)
Molecular formula	$C_{28}H_{28}F_2N_6O_3$
Mechanism of action	Calcitonin Gene-related Peptide Receptor Antagonist
Indication	Acute treatment of migraine with or without aura in adults with a previous insufficient response to triptans
Clinical trial **Phase IIb** **Phase III** **Phase III** **Phase III**	 NCT01430442 NCT03235479 NCT03237845 NCT03461757

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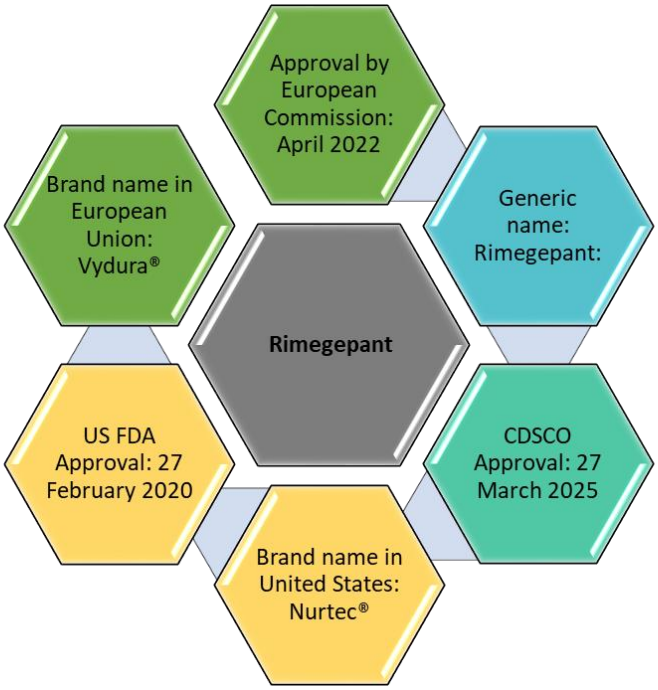

Figure 2: Characteristics of Rimegepant

Table 4: Pharmacokinetics and Pharmacodynamics properties of rimegepant[16]

Pharmacokinetics	Pharmacodynamics
Absolute oral bioavailability ≈64%	CGRP antagonist: at CGRP receptor and structurally related amylin 1 (AMY1) receptor
Administration with high-fat meal: prolongs Tmax; reduced Cmax and reduced AUC (area under curve)	Absence of vasoconstriction
Steady-state volume of distribution of 120 L and is highly (≈ 96%) bound to plasma proteins	No effect on haemodynamic or electrocardiographic parameters No cardiovascular parameter changes
Elimination half-life of ≈11 h Eliminated mostly ≈77% of the dose as unchanged drug	Single therapeutic (75 mg) or supratherapeutic (300 mg) dose: no prolongation of QT interval
Avoid in End stage renal disease and severe hepatic impairment patients	No clinically relevant differences in resting blood pressure

Figure 3: Drug interactions with Rimegepant:

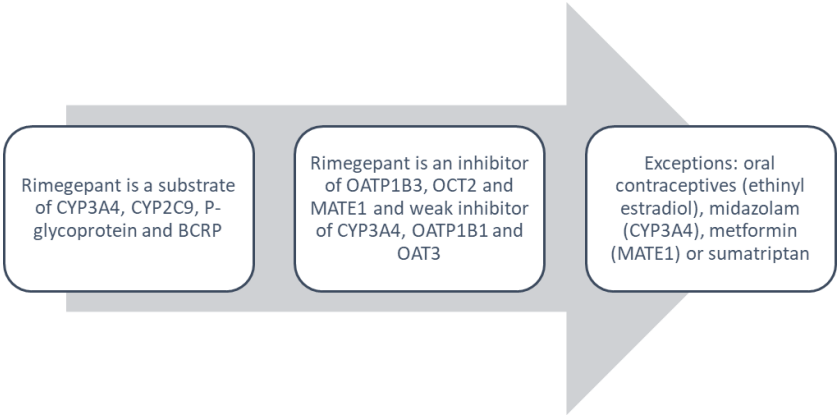

Table 5: Systematic Review and Meta Analysis comparison of Rimegepant with other drugs:

Study with PROSPERO trial registration CRD42022308224 concluded that lasmiditan was the most effective intervention in the treatment of migraine attacks, although it was associated with high degrees of dizziness, nausea and somnolence. Rimegepant showed slightly lower, but similar efficacy rates to lasmiditan.[17]

*Corresponding Author: **Rashmi Chandra**

Study with PROSPERO trial registration CRD42022310579 concluded that medications targeting calcitonin gene-related peptide were effective in preventing migraine compared to placebo. All novel treatments decreased mean monthly migraine and headache days and showed higher responder rates than placebo.[18]
Study with PROSPERO trial registration CRD42022310579 concluded that monoclonal antibodies targeting the calcitonin gene-related peptide pathway and gepants are safe and well tolerated option for migraine prevention.[19]
Study with PROSPERO trial registration CRD42021242145 concluded that pain freedom or pain relief at 2 hours after the dose, lasmiditan, rimegepant and ubrogepant were associated with more relief compared with placebo but lower relief compared with most triptans.[20]
Study with PROSPERO trial registration CRD42024544972 concluded that lasmiditan, rimegepant and ubrogepant are effective for acute treatment of migraine in triptan-insufficient responders; with high-dose lasmiditan showing the highest efficacy for pain control.[21]
Study with PROSPERO trial registration CRD42023467187 concluded that favorable efficacy and tolerability of rimegepant and ubrogepant positioning them as potential candidates for the acute management of migraine also lasmiditan exhibits notable efficacy.[22]
Study with PROSPERO trial registration CRD42024588786 concluded that CGRP has multiple and often potentially opposing effects on the immune system but unlikely to affect most migraine patients. It potentially depends on the type of pathogen and patient's immune status. Increased infection risk in immunocompromised patients or at public health levels.[23]

Clinical Considerations

Rimegepant and other gepants have demonstrated efficacy comparable to triptans in abortive migraine treatment without the associated risk of vasoconstriction or hepatotoxicity seen in older generations. This makes them an appealing alternative for patients unable to tolerate triptans. Nonetheless, due to cost constraints, gepants may not be the first-line treatment option in all settings. Current clinical guidelines and expert consensus can aid physicians in selecting appropriate acute and preventive therapies based on individual patient profiles.

Public Health Perspective

In low-resource environments, emphasis should be placed on affordable and accessible interventions such as lifestyle modifications including regular physical activity, adequate hydration, balanced nutrition, and proper sleep hygiene as initial strategies to mitigate migraine burden. Although these approaches may be less evidence-based compared to pharmacologic interventions, they offer a low cost, holistic method to reduce the frequency and severity of primary headache disorders.

Future directions:

While present data, including small-scale safety studies and case reports, support the use of rimegepant in combination with injectable CGRP monoclonal antibodies, larger, controlled trials are needed to validate its efficacy and safety in broader patient populations. Furthermore, long-term studies are required to better understand the implications of chronic CGRP modulation, especially regarding cardiovascular outcomes and potential unforeseen side effects identified through post-marketing surveillance.

Conclusion:

Rimegepant emerges as a promising option for the acute management of migraine, particularly in patients who have contraindications to triptans or have not responded well to traditional oral preventives. Its favourable safety profile, absence of vasoconstrictive properties and low potential for causing medication overuse headaches make it suitable for patients with cardiovascular comorbidities or those experiencing moderate migraine frequency. However, the modest therapeutic benefits and potential long-term risks associated with CGRP pathway inhibition necessitate cautious use, tailored to appropriately selected individuals.

Conflict of interest: None

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