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"Atogepant: A Novel Therapeutic Agent in the Management of Migraine"

Dr. Garlapati Usha Kiran* Maareedu Mahesh[1] ,Loya Pavan kumar[1], Kankanala Uma Satya manikanta[1],Gollamudi Nehemiah[1], Guntru pavan kumar[1]

*Corresponding author:Professor, HOD Department of Pharmacology, NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru district.

[1] IV B PHARMACY STUDENT , NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru district.

ABSTRACT :

Migraine is a common neurological condition that can really take a toll on people's quality of life and productivity around the globe. It's marked by recurring headaches that often come with nausea, sensitivity to light, and sensitivity to sound. Traditional preventive treatments, like beta-blockers and antiepileptics, often fall short in terms of effectiveness and tolerability, which is why there's a need for new options. Enter atogepant, an oral calcitonin gene-related peptide (CGRP) receptor antagonist that's making waves in the world of migraine prevention. It got the green light from the FDA in 2021, followed by approvals from Health Canada and the EMA, making it the first oral CGRP antagonist specifically designed for preventing migraines. Atogepant is quickly absorbed, spreads widely in the body, and is mainly broken down by CYP3A4, boasting a half-life of about 11 hours, which allows for once-daily dosing. It works by blocking CGRP-induced vasodilation and neurogenic inflammation, helping to cut down on the frequency and intensity of migraines. Clinical trials have shown it effectively reduces the number of migraine days each month, with some common side effects like constipation, nausea, and fatigue. All in all, atogepant offers a safe, effective, and convenient oral solution, marking a big step forward in personalized migraine management.

KEYWORDS:

Migraine, Atogepant, CGRP receptor antagonist, Episodic migraine prevention, Pathophysio logy, Pharmacokinetics, Neurogenic inflammation, Adverse effects, Drug interactions, Personalized migraine therapy

INTRODUCTION

Migraine is a complicated neurological condition that often seems to run in families. It's marked by episodes of moderate to severe headaches, usually felt on one side of the head, and is often accompanied by nausea and increased sensitivity to light and sound. The term "migraine" actually originates from the Greek word hemikrania, which was later adapted into Latin as hemigranea. Interestingly, the French version of the word is what we commonly use today. Migraine is one of the top causes of disability and lost productivity, significantly impacting a person's daily life and overall well-being. These episodes can be quite complex, lasting anywhere from a few hours to several days. In fact, around 75% of migraine cases are classified as migraine without aura, making it the most common type[(1]When it comes to migraines, people often experience moderate to severe headaches that are usually one-sided and feel

pulsating or throbbing. These headaches can intensify with movement. Interestingly, about one-third of patients report having holocranial headaches.

The individual episodes are marked by a nearly constant loss of appetite, with 80% experiencing nausea, 40% to 50% dealing with vomiting, 60% suffering from light sensitivity, 50% having noise sensitivity, and 10% showing hypersensitivity to certain smells. Additionally, up to 82% of patients report symptoms related to the activation of the parasympathetic system, with mild eye watering being the most common.

One-sided headaches can actually switch sides during an episode or even between different attacks. According to the International Headache Society (IHS), an attack typically lasts anywhere from four to seventy-two hours. For younger individuals, these attacks tend to be shorter and may primarily cause severe nausea, vomiting, and dizziness rather than a headache. More often than not, the pain is experienced on both sides of the head[(2)].

TYPES OF MIGRAINE:

Migraines come in several forms. The most prevalent types of migraines are:

- Migraine with aura (classic migraine). Migraine without aura (common migraine).
- An aura is a phase of the migraine before head pain begins.

Other types of migraines include:

- Migraines in children (abdominal migraine).
- Chronic migraine.
- Hemiplegic migraine.
- Menstrual migraine.
- Migraine without headache (silent migraine)

Fig1:Types Of Migraine

- Retinal migraine (ocular migraine).
- Status migrainosus.

Symptoms:

A sharp headache on one side of your head is usually the most common sign of a migraine. The pain tends to be moderate to severe, often throbbing, and it can intensify with movement, making it really tough to get through your daily activities. In some cases, the discomfort might spread to your neck and face or even both sides of your head[(3)].You may experience little changes one or two days prior to a migraine that indicate an impending migraine, such as:

- Constipation.
- Mood changes, from depression to euphoria.
- Food cravings.
- Neck stiffness.
- Increased urination.
- Fluid retention.
- Frequent yawning.

Fig2:Symptoms of Migraine

PATHOPHYSIOLOGY OF MIGRAINE

The way migraine headaches work involves a mix of factors from both the central nervous system (CNS) and the peripheral nervous system, though we still don't have the full picture. In this section, we'll dive into some of the most accepted theories. The old vascular theory, which suggested that auras were due to blood vessel constriction and headaches resulted from their dilation, has fallen out of favor. Nowadays, it's believed that migraines stem from a series of changes happening both inside and outside the skull, triggered by various primary neural issues.

The opening of neuronal pannexin-1 mega channels and the activation of caspase-1 kick off the activation of trigeminal afferents. This leads to the activation of nuclear factor kappa-B (NF-kB), which then triggers the release of proinflammatory mediators. These mediators send inflammatory signals to the trigeminal nerve fibres that wrap around the pia mater vessels. This whole process, through both central and peripheral pathways, results in headaches by igniting inflammation in the pain-sensitive meninges and setting off a series of events in the cortex, meninges, and brainstem. The cerebral depression that leads to the aura,

along with the prolonged activation of trigeminal nociception responsible for headaches, can be traced back to this pathway.

The aura is thought to arise from a process called cortical spreading depression, which activates trigeminal afferents and alters the permeability of the blood-brain barrier through the action of brain matrix metalloproteinases. Neurons from the trigeminal nerve and ganglion at the trigeminal nucleus caudalis gather signals from the upper cervical roots. As these signals make their way up to the thalamus and sensory cortex, their convergence might shed light on why we feel pain that radiates from the front to the back of the head.

The activation of nociceptors, especially in the trigeminal system, triggers neurogenic inflammation, which shows up as symptoms like vasodilation, swelling, and the leakage of plasma proteins. During this process, various substances, including Substance P, calcitonin gene-related peptide (CGRP), and neurokinin, are released. When the trigeminal ganglion gets stimulated, it releases a neuropeptide that impacts blood vessels[4].

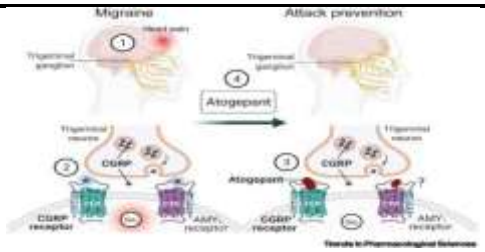

Fig3:Pathophysiology of Migraine

TREATMENT:

To tackle migraine headaches effectively, a well-rounded strategy is essential.The main goals are to ease symptoms, prevent future attacks,and improve the overall quality of life for patients.Typically,effective management combines quick relief options with an understanding of individual needs and specific triggers.

Acute or Abortive Treatments

The main aim of acute treatment is to stop a migraine headache from getting worse, which means getting medical help quickly and often using a high dose of a single medication. For patients dealing with migraine-related gastric stasis, oral medications might not be very ZZ effective. So, for some individuals, especially those who are feeling nauseous or vomiting,

injectable medications could be the better option. Here, we've outlined various treatment possibilities, which you can also find in the treatment planning section.

CLASSIFICATION OF MIGRAINE:

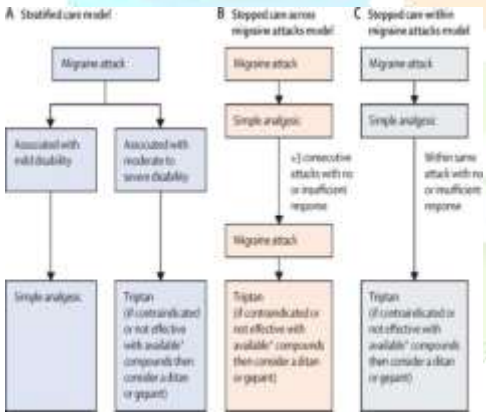

Fig4:Classification Of Drugs for Migraine

DRUG PROFILE

- **Drug Name:** Atogepant
- **Molecular Formula:** $C_{29}H_{23}F_6N_5O_3$
- **Molecular Weight:** 603.170508599
- **Chemical Name:** Aquipta, Qulipta
- **Category:** Migraine

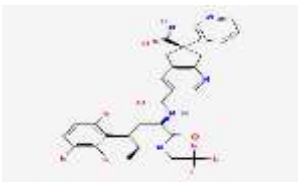

Fig5:Structure of Atogepant

Atogepant, an oral calcitonin gene-related peptide (CGRP) receptor antagonist, is prescribed to help manage episodic migraine headaches. Developed by AbbVie, it received FDA approval in September 2021 under the brand name Qulipta. What sets atogepant apart is that it's the first and only oral CGRP antagonist approved for preventive use in migraines, while two other similar medications, Ubrogepant and Rimegepant, were approved earlier but are only intended for treating migraines once they occur. In

December 2022, Health Canada also gave the green light for atogepant to be used in preventing adult episodic migraines. Then, in August 2023, the EMA followed suit, approving it for the preventive treatment of adult migraines.

Current guidelines recommend using beta-blockers, such as propranolol, or anti-epileptic medications like valproic acid or topiramate for patients seeking preventive treatment for migraines. For those who have had negative experiences with other preventive medications, the "gepants" class.

❖ **Pharmacokinetics:**

If you're dealing with adult episodic migraines, atogepant might be the solution you're looking for this new oral medication works as a small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist, and it can help prevent those painful episodes.

Absorption:

Bioavailability:When taken orally, atogepant is absorbed pretty quickly. The time it takes to reach peak plasma concentration, known as Tmax, is about one to two hours. As for food interactions, you can take it with high-fat meals, whether you eat beforehand or not. **Distribution:**

The volume of distribution (Vd) is approximately 292 L, indicating that the medication is spread out quite extensively throughout the body. Additionally, around 98% of the drug circulating in the bloodstream is probably bound to plasma proteins, based on the data regarding plasma protein binding.

Metabolism:

The primary metabolic pathway for atogepant involves the CYP3A4 enzyme, which plays a crucial role in its metabolism in the liver.

Elimination:

Half-life (t½): ~11 hours, enabling daily dosage.

Drug Interactions:

CYP3A4 inducers and inhibitors can have a big effect on how much atogepant is present in your system. To ensure it works effectively, it's a good idea to steer clear of strong CYP3A4 inducers, such as rifampin, when taking it.

1. **Prevention of Episodic Migraine in Adults:**

Atogepant is primarily used for treating migraines, and it has been shown to significantly reduce the number of migraine days each month. It's particularly beneficial for those who suffer from 4 to 14 migraine days monthly.

2. **Prevention of Chronic Migraine (Investigational/Off-label in some regions):**

Chronic migraine: If you suffer from chronic migraines, you might find that at least eight out of the fifteen headache days each month are actually migraine days. Fortunately, Atogepant has shown promising results in clinical trials, like the progress study, by helping to reduce the number of headaches for those dealing with chronic migraines.

MECHANISM ACTION OF ATOGEPANT

CGRP, CT, amylin (AMY), adrenomedullin (AM1), and adrenomedullin 2 (also known as intermedin; AM2) all belong to the calcitonin (CT) family of peptides. In humans, CGRP exists in two forms:

α-CGRP, which is mainly found in the enteric nervous system, and β-CGRP, which is primarily located in the primary spinal afferent C and Aδfibers of sensory ganglia in both the central and peripheral nervous systems. The calcitonin receptor (CTR) is part of a broader family that includes six heterodimers of transmembrane-bound, class B G-protein-coupled receptors. This family consists of either CTR or calcitonin receptor-like receptor (CLR), along with three variants of receptor activity-modifying protein (RAMP1, RAMP2, and RAMP3), each having different subunit configurations. Additionally, these receptors contain an intracellular membrane protein known as receptor component protein (RCP), which is crucial for Gα coupling. Each RAMP orthologue associated with CTR or CLR contributes to the ligand specificity of the CT peptide family. Since the CGRP and Amylin 1 (AMY1 [CTR/RAMP1]) receptors share the RAMP1 subunit, CGRP can bind to AMY1, activating both receptors in the process. When CGRP attaches to the CGRP receptor on vascular smooth muscle cells, it triggers vasodilatory effects by activating adenylyl cyclase. This activation leads to the production of cyclic adenosine monophosphate (cAMP), which then activates protein kinase A (PKA). Once PKA is activated, potassium is released, causing the vascular smooth muscle to hyperpolarize and dilate, which in turn sensitizes the perivascular nociceptors.

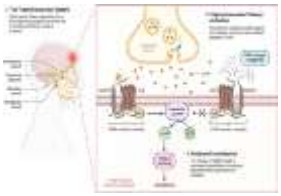

Fig6: Mechanism Action of Atogepant

Atogepant might help ease or even stop migraines by blocking the way CGRP attaches to its receptor. This action could prevent vasodilation, reduce CGRP-triggered neurogenic inflammation, and halt nociceptive transmission, along with other CGRP-related processes that contribute to the development and persistence of a heightened sensitivity. It seems that Atogepant mainly works on the periphery by blocking CGRP receptors outside the blood-brain barrier (BBB), which is supported by its low penetration into the brain and a high apparent volume of distribution (V z /F = 292 L).CGRP-targeting therapies, which struggle to effectively cross the blood-brain barrier, have demonstrated that addressing peripheral factors can help manage central sensitization, ultimately easing or preventing migraine headaches and associated symptoms like light and sound sensitivity[5].

PHARMACOLOGICAL ACTIONS

Atogepant is an oral small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist that is primarily used to prevent migraines in adults.

1. **CGRP Receptor Antagonism:**

   Atogepant works by selectively binding to and blocking the receptor that allows CGRP, a neuropeptide associated with migraines, to attach and activate it. By doing this, it helps reduce both

the frequency and intensity of migraines by countering CGRP's effects, which can cause blood vessels to widen and trigger inflammation in the trigeminal vascular system.

2. **Prevention of Neurogenic Inflammation:**

   CGRP contributes to migraine attacks by promoting neurogenic inflammation. Atogepant helps alleviate this by blocking CGRP receptors, which in turn reduces dural inflammation, prevents mast cell degranulation, and interrupts pain signals in the migraine pathways.

3. **Reduction in Vasodilation:** One of the key features of a migraine is the expansion of blood vessels in the brain and the protective layers around it, which is triggered by CGRP. Atogepant helps by blocking this expansion, ensuring a more stable blood flow and slowing down the onset of migraines.

4. **Central and Peripheral Nervous System Action**

Atogepant might influence trigeminal ganglion neurons, which play a role in the onset and progression of migraines, even though its main action occurs in the periphery.

ADVERSE EFFECTS:

For adults dealing with episodic migraines, atogepant can be a helpful preventive option. It works by blocking the calcitonin gene-related peptide (CGRP) receptor. While atogepant is generally well tolerated, like many medications, it does come with some potential side effects.An outline of frequently reported and potentially dangerous side effects linked to atogepant is provided below:

1. Common Adverse Effects:

The following are the most commonly reported adverse effects that are usually seen during clinical trials:

Constipation:

One of the most frequent side effects, usually mild to moderate.

Nausea

Reported in a considerable proportion of patients, particularly in the early stages of treatment.

Fatigue or Somnolence

Unusual fatigue or drowsiness may strike some patients.

Urinary tract infection (UTI)

There has been a modest increase in the incidence of UTIs.

2. Gastrointestinal Effects

In addition to nausea and constipation, patients have also reported:

Dry mouth

Dyspepsia (indigestion)

Abdominal pain

These effects are usually manageable and do not require discontinuation of therapy in most cases.

3.Hypersensitivity Reactions: Hypersensitivity reactions such rash itching (pruritus), though uncommon,there may be swelling (angioedema). Any indications of a serious allergic response necessitate stopping the medication and getting medical help right once.

4. Drug-Drug Interactions and Tolerability:

Despite having a good interaction profile, atogepant's plasma levels and consequent negative effects may rise when used with some medications, such as potent CYP3A4 inhibitors[6].

CONTRAINDICATIONS:

Hypersensitivity to any of the formulation's inactive constituents, including atogepant.

Warnings/Precautions

✓ **Hypersensitivity Reactions**

Atogepant has been associated with hypersensitivity reactions, which can include serious issues like anaphylaxis, difficulty breathing, rashes, itching, hives, and swelling of the face. These reactions might show up days after taking the medication.

✓ **Hypertension**

There have been some reports indicating that using atogepant can lead to high blood pressure or worsen existing hypertension after it hits the market. Some patients who were newly diagnosed with hypertension had risk factors that contributed to this increase in blood pressure. While high blood pressure can develop at any time during treatment with atogepant, it was most frequently observed within the first week of starting the medication.

Specific Populations

Pregnancy : The risks associated with atogepant use during pregnancy aren't thoroughly documented. Research on animals suggests that this medication could potentially harm the developing foetus. Studies have indicated that using the drug during pregnancy and breastfeeding, especially at doses higher than those typically used in clinical trials, can negatively impact embryonic and foetal development. Additionally, research indicates that pregnant women who experience migraines might be at a higher risk for conditions like preeclampsia and gestational hypertension.

Lactation : The way atogepant spreads in human milk is still a mystery; however, we do know that it appears in the milk of rats. We're also unsure about how atogepant might influence milk production or affect a breastfed baby. It's important to consider not just the mother's need for atogepant, but also the benefits of breastfeeding for the baby's growth and health, along with any potential risks that the medication or the mother's health condition might pose to the child.

Geriatric Use : In the clinical trials for atogepant, there just weren't enough participants over the age of 65 to really figure out if their reactions differed from those of younger folks. The pharmacokinetic studies didn't reveal any major differences in how atogepant was processed between younger and older adults[7].

CONCLUSION

A groundbreaking oral medication known as atogepant is changing the game for preventing episodic migraines. It belongs to a group of drugs called calcitonin gene-related peptide (CGRP) receptor antagonists, which work by blocking the CGRP pathwayan essential player in the development of migraines. By directly addressing the migraine mechanism, atogepant offers better effectiveness and fewer side effects compared to older migraine treatments that often-lacked specificity and came with significant adverse effects.

When you stack Atogepant against a placebo, the results are pretty impressiveit significantly cuts down the number of migraine days each month, as shown by clinical studiesOverall, Atogepant is generally well tolerated. While serious side effects are rare, some people might experience common issues like fatigue, nausea, or constipation.

It's important to steer clear of potent CYP3A4 inhibitors and to be cautious when using this with patients who have severe liver issues. Since the U.S. FDA gave it the green light in 2021, those dealing with migraines now have more options, especially for those who prefer taking oral medications over injections. Atogepant represents a major step forward in personalized migraine treatment, helping those who suffer from migraines enjoy a better quality of life.

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