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Review Article

A short review on atogepant: recently approved first oral calcitonin gene-related peptide receptor antagonist

Akash Agnihotri, M. Kanimozhi, Subhash Samanta*, Manjunath Bidarolli, Shailendra Handu

Department of Pharmacology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

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***Correspondence:**
Dr. Subhash Samanta,
Email: drsubhashsamanta@gmail.com

ABSTRACT

Migraine is the second leading cause of disability in terms of 'years lived with disability' and it affects globally about 12% of the general population. Currently available preventive therapies are not specific to migraine. After the discovery of calcitonin gene-related peptide's (CGRP's) role in migraine pathophysiology, CGRP receptor antagonist drugs were developed specifically for migraine. Atogepant is the only oral, selective, potent, second-generation CGRP receptor antagonist approved in September 2021 by Food and Drug Administration (FDA) for prophylaxis of episodic migraines and chronic migraines. It acts by blocking the α-CGRP receptor present on the vascular smooth muscle cell membrane of cranial arteries. It has the added advantage of oral administration, less hepatotoxicity, minimal drug–drug interactions (DDIs) with better efficacy, safety, and tolerability profile compared to the other CGRP receptor antagonists. This present review summarizes the physicochemical properties, pharmacokinetics-pharmacodynamics (PK-PD) parameters, uses, and drug-food interactions with the help of available current evidence.

Keywords: Migraine, Atogepant, CGRP antagonist

INTRODUCTION

Migraine is a complex neurological disorder characterised by episodic headache associated with gastrointestinal (GI) symptoms, autonomic disturbances and other neurological symptoms.[1] Migraine affects globally about 12% of the general population.[2] Migraine with severe intensity interferes with patient's day to day activities and has negative impacts on their quality of life.[3] There is a steady rise in global age-standardised years lived with disability due to migraine since 1990 and higher point prevalence has been reported among females.[4] Migraine is the second leading cause of disability in terms of years lived with disability.[5] Migraine headache is often confused with tension headache and most of them are underdiagnosed and undertreated. The lack of a genetic or biological basis for migraine makes diagnosis difficult. Preventive treatment for migraine is used by very few individuals because of lack in proper diagnostic methods.[6]

In last decade, numerous efforts had been laid to understand the pathophysiology of migraine and it has been found that there is increased levels of calcitonin gene-related peptide (CGRP) in cerebral circulation during migraine attacks, proving CGRP's pivotal role in the pathophysiology of migraine and has become potential novel target for migraine treatment and prevention.[7] Therefore, drugs acting on CGRP pathway might provide significant beneficial effects in preventing and treating migraine. Though many preventive drugs like beta blockers (propranolol and timolol), antidepressants (amitriptyline and nortriptyline), calcium-channel blocker's (CCB) (flunarizine), and antiepileptics (sodium valproate and topiramate) are already in practice, none of them are specific to migraine alone and has poor tolerability which lead to their increasing failure in migraine prevention.[8] CGRP receptor antagonists and anti-CGRP and anti-CGRP receptor monoclonals being specific for migraine has provided promising results in

clinical practice.[5] Monoclonal antibodies must be administered by parenteral route (subcutaneous or intravenous injection) and have a long half-life.[9] In 2018, Food and Drug Administration (FDA) has approved CGRP receptor antagonist class of drugs for treatment and prevention of migraine.[6] Ubrogepant and rimegepant are used to abort acute attacks of migraine but they are also given by parenteral route.[10] Atogepant is the newer drug in this class with the added advantage of being administered by oral route has been recently approved by FDA on 28 September 2021 for prophylaxis of episodic migraines.

PHYSICAL AND CHEMICAL PROPERTIES OF ATOGEPANT

Atogepant differs chemically from other oral CGRP receptor antagonists, such as telcagepant and MK-3207, which were withdrawn from the market due to drug-induced liver injury (DILI).[11-13]

The chemical name of atogepant is (3'S)-N-[(3S,5S,6R)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluoro phenyl)piperidin-3-yl]-2'-oxo-1',2',5,7-tetrahydrospiro [cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide, and it has the structural formula as shown in Figure 1.

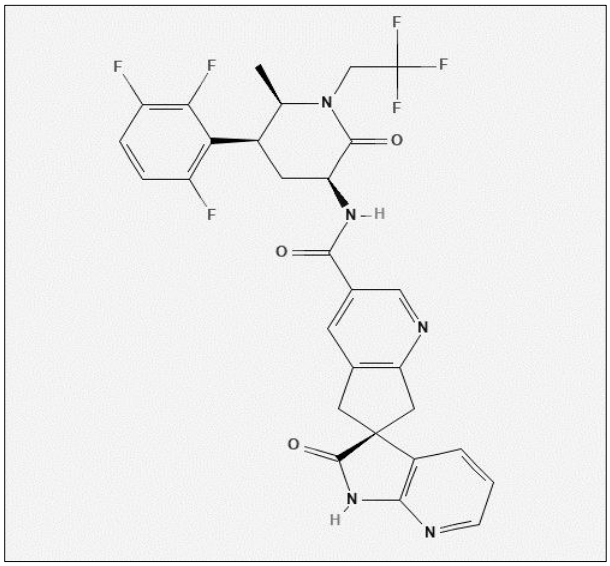

Figure 1: Chemical structure of atogepant.[10]

Type of molecule

Atogepant is a small molecule.

Molecular formula

It consists of the molecular formula $C_{29}H_{23}F_6N_5O_3$.

Molecular weight

The molecular weight of atogepant is 603.5 g/mol.

WHO-anatomical therapeutic classification code for atogepant is N02CD07.

Atogepant is a white to off-white powder. It is freely soluble in ethanol, soluble in methanol, sparingly soluble in acetone, slightly soluble in acetonitrile, and practically insoluble in water. The inactive ingredients include colloidal silicon dioxide, croscarmellose sodium, mannitol, microcrystalline cellulose, polyvinylpyrrolidone vinyl acetate copolymer, sodium chloride, sodium stearyl fumarate, and vitamin E polyethylene glycol succinate.

MECHANISM OF ACTION

CGRP is a 37 amino acid neuropeptide present both in central and peripheral nervous system, acts as potent vasodilator and neurotransmitter in nervous system. There are two isoforms of CGRP-α and -β. α-CGRP is present in peripheral nervous and central nervous system and β-CGRP present in enteric nervous system. α-CGRP plays major role in the pathophysiology of migraine and it is primarily released from trigeminal ganglion to act on the canonical CGRP receptors present on vascular smooth muscle cell surface of cranial arteries**.** CGRP receptors has two subunits: G-protein coupled calcitonin receptor like receptor (CLR) subunit activity modifying protein-1 (RAMP-1) subunit.[14]

Atogepant by binding at the interface between CLR and RAMP-1 subunits of α-CGRP receptor in a competitive manner, blocks the vasodilation in meningeal arteries caused by binding of α-CGRP with its receptor.[10] Atogepant does not cause any vasoconstriction and has no effect on CGRP receptors present in coronary arteries (Figure 2).

PHARMACOKINETIC PARAMETERS

Atogepant is an orally administered drug with the mean C_{max} of 589 ng/ml and mean apparent volume of distribution of 292 l. Atogepant is rapidly absorbed with mean T_{max} of 1-2 hours and $t_{½}$ of approximately 11 hours & clearance of 19 l/hour and has no significant hepatic accumulation with daily regular dosing. It is highly protein bound drug (95.3%) and primarily metabolized in liver and its metabolism is predominantly controlled by CYP3A4 and a little by CYP2D6. Atogepant and its glucuronide conjugate metabolite are the most common circulating molecules (M23) in plasma. Final elimination of drug occurs via biliary secretion.[15]

Safety profile

Telcagepant is the first CGRP receptor antagonist developed for migraine however it was withdrawn due to its fatal hepatotoxicity. Atogepant has been proven safer drug without any hepatotoxicity in a phase 1 trial with healthy people, who were given supra-therapeutic dose of atogepant (170 mg) for 28 days. In this trial, individuals who has taken atogepant have not shown any abnormal

increase in serum alanine transaminase (alt) levels.[13] The treatment emergent adverse events (TEAEs) reported in another phase 2b/3 trial is nausea, constipation, oropharyngeal pain, and mild rhinorrhoea. All TEAEs were milder in intensity and there were no discontinuation of therapy or serious adverse events or death due to this therapy.[5] As atogepant has no effect on coronary CGRP receptors, it is considered as safer anti-migraine drug to be used in patients with increased cardiovascular diseases risk, where triptans are contraindicated.[10]

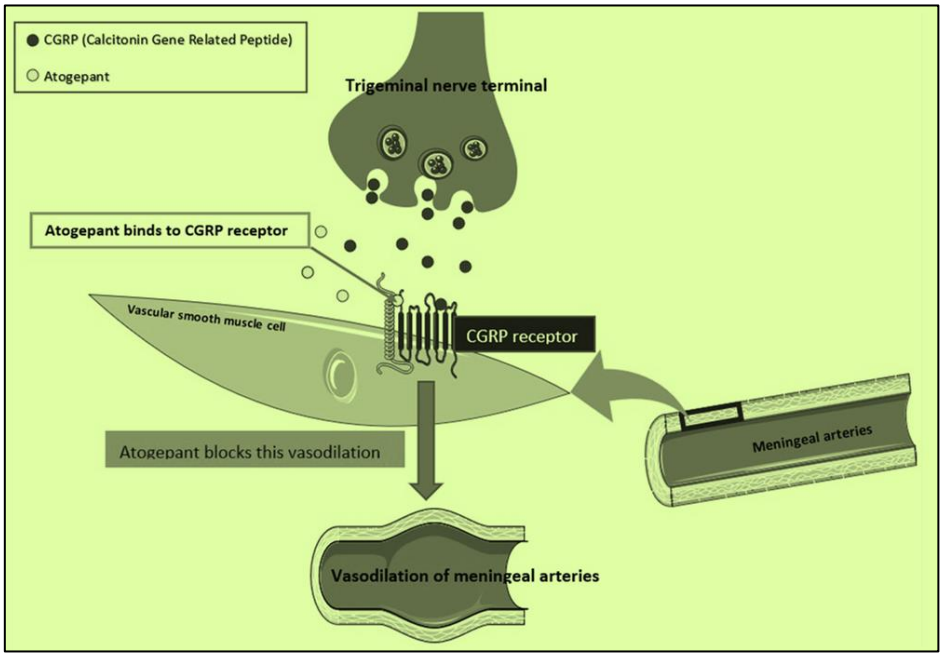

Figure 2: Mechanism of action of atogepant.[10]

EFFICACY

FDA approval was supported by the results of a phase 3 trial. The primary outcome of the pivotal phase 3-multicenter, randomised, double-blind, placebo-controlled, parallel-group ADVANCE trial was change from baseline in mean monthly migraine days over a 12-week treatment period. When compared to placebo, all atogepant dosage groups met the primary endpoint and showed statistically significant ($p<0.001$) reductions in mean monthly migraine days. Over the course of 12 weeks, patients treated with 60 mg of atogepant experienced a 4.2-day reduction from baseline of 7.8.[16]

Pregnancy considerations

In animal reproduction studies, adverse effects were seen after oral administration of atogepant at levels higher than the approved human dose.[16]

Breastfeeding considerations

It is not known if atogepant is present in breast milk.[16]

Clinical trials on atogepant

Summary of various trials conducted on atogepant has been given in Table 1. Phase 1 trial for overall safety, hepatic safety, PK parameters showed that atogepant is safe with almost no heaptic toxicity.[13] Phase 2b/3 trial conducted with various doses of atogepant has also proven its safety, tolerability across various dose ranges and its efficacy in decreasing the mean monthly migraine days.[5] ADVANCE trial – a phase 3 trial with atogepant is the landmark trial that led to FDA approval of atogepant for the prevention of migraine. It is conducted in 910 adult patients with 4-14 migraine days per month over the period of 12 weeks with various doses of atogepant. Safety, tolerability and its efficacy have been confirmed with ADVANCE trial.[16]

Various exploratory trials on atogepant for its interaction with sumatriptan, acetaminophen and naproxen, oral contraceptive pills (OCPs) have also shown that atogepant is safer drug with minimal DDI with these drugs.[18-20] One trial studied the effects of supratherapeutic dose of atogepant on cardiac repolarization also and showed that atogepant has no effect on cardiac repolarization at various time points.[21]

CLINICAL APPLICATIONS

National Institute for Health and Care Excellence (NICE) guidelines recommend the usage of triptans, non-steroidal anti-inflammatory drugs (NSAIDs), and anti-emetics as soon as patient experiences migraine.[17] Triptans are the first line drug for management of acute attack of migraine till date. Other agents like ergot alkaloids, dopamine-D2 antagonists (metoclopramide), and opioids are used only

when triptans are contraindicated or proven inefficient in particular individual.

If headaches occur four or more days per month; if abortive medication is contraindicated and/or inefficient; and if abortive therapies required ten or more days per month every month, preventive pharmacological treatments are tried.[18] Beta blockers, CCBs, anti-epileptics, and anti-depressants are in use for preventive therapy of migraine but they are not specific.

Atogepant is the only oral, selective, potent, second generation CGRP receptor antagonist approved for prophylaxis of episodic migraine and chronic migraine.[15]

Treatment with atogepant has shown significant reduction in the mean monthly migraine days in a phase 2b/3 trial, proving its efficacy for the prophylaxis of migraine.[5]

RECOMMENDED DOSAGE

10 mg/30 mg/60 mg, once daily dose, oral route maximum dose is 60 mg once a day (OD).[5]

Dosing in adult patients with renal impairment

It includes-CrCl ≥30 ml/minute: no dosage adjustment necessary, CrCl <30 ml/minute: 10 mg once daily, and ESRD on dialysis: 10 mg once daily; administer after dialysis, on dialysis days.

Dosing in adult patients with hepatic impairment

It includes-mild to moderate impairment (child-Pugh class A, B): no dosage adjustment necessary; and severe impairment (Child-Pugh class C): use is not recommended.[16]

Drug-drug interactions with atogepant

Primary headache patients, mostly young adults are exposed to a high level of polypharmacy comparable to that of the elderly. This polypharmacy practice will increase risk of adverse effects and drug-drug interactions (DDIs) as number of medications are used concurrently. DDIs are one of the most common reasons for pharmacologic headache therapy failure. While DDIs can develop through a variety of pathways and causes, the majority of them are caused by changes in the cytochrome P450 pathways.[19]

The drug-drug interactions of those medications are analysed using 2 online software "Drugs.com drug interactions checker" and "UpToDate's Lexicomp® drugs interactions", which are enumerated in the table below (Table 2).[25,26]

Table 1: Summary of clinical trials conducted with atogepant.

Clinical trial phases	Study design and methods	Primary endpoint	Results
Phase 1 trial[13]	Randomized, double-blind, placebo-controlled phase I trial in healthy participants	Safety, tolerability and pharmacokinetics of supratherapeutic dose of atogepant	AE reported in 87% of atogepant group compared to 72.7% in placebo
	Intervention and duration: atogepant 170 mg OD (supratherapeutic dose) for 28 days		No ALT elevation above 1.5 × upper limit of normal in atogepant group
	Conducted on 34 participants of 23-55 years of age		C_{max} – 2 hours and t½ - 11 hours
Phase 2b/3 trial[5]	Double-blinded, randomized (2:1:2:2:1:1) trial	Change from baseline in monthly migraine days	All atogepant group showed significant reduction in monthly migraine days. Atogepant 10 mg OD (p=0·024), 30 mg OD (p=0·039), 60 mg OD (p=0·039), 30 mg BD (p=0·0034), and 60 mg BD (p=0·0031)
	Conducted on 835 adult (18-75 years) migraine patients	Safety, tolerability and efficacy of atogepant in various doses	
	Intervention: placebo or atogepant 10 mg OD or 30 mg OD or 60 mg OD or 30 mg BD or 60 mg BD		TEAE frequency ranged from 18% for 10 mg OD to
	Study duration: 12 weeks		26% for 60 mg BD versus 16% for placebo
Phase 3 trial[16]	Double binded, randomized (1:1:1:1) phase 3 trial Intervention and duration: atogepant 10 mg or 30 mg or 60 mg OD dose for 12 weeks	Change from baseline in the mean number of migraine days per month	Mean differences from placebo in change from baseline were −1.2 days with 10-mg atogepant (95% CI, −1.8 to −0.6), −1.4 days with 30-mg atogepant (95% CI, −1.9 to −0.8) and −1.7 days with 60-mg atogepant (95% CI, −2.3 to −1.2) (p<0.001)
	Conducted on 910 adult patients with 4-14 migraine days per month		

Table 2: Drug-drug interactions (DDIs) with atogepant.

Drug class	Interaction found
Atogepant DDIs with anti-hypertensive drugs	
ACE inhibitors, ARBs, direct renin-inhibitor, β-blockers, α-blockers, diuretics (thiazides, loop, potassium sparing/ aldosterone antagonist), vasodilators	No interaction found
Phenylalkamines: verapamil	Verapamil is moderate CYP3A4 inhibitor may increase the serum concentration of atogepant, severity=minor[a,b]
Dihydropyridines	
Amlodipine	Amlodipine is weak CYP3A4 inhibitor may increase the serum concentration of atogepant, severity=minor[a,b]
Nifedipine	Nifedipine is CYP3A4 inhibitor may increase the plasma concentration of atogepant, severity=minor[b]
Benzothiazepines: diltiazem	Diltiazem is moderate CYP3A4 inhibitor may increase the serum concentration of atogepant, severity=minor[a,b]
Atogepant DDIs with anti-diabetic drugs	
Biguanide, DPP-4 inhibitors, SGLT-2 inhibitor, insulin, GLP-1 agonists, sulfonylureas	No interaction found
Atogepant DDIs with other anti-migraine drugs	
Triptans, ergot alkaloid, NSAIDs, antiemetics	No interaction found

a=Drugs.com drug interactions checker, and b=UpToDate's Lexicomp® drugs interactions

Food interaction

It may be taken with or without food. Co-administration with food does not affect the pharmacokinetics of atogepant to a clinically significant extent.

CONCLUSION

Atogepant an oral, selective CGRP receptor antagonist has shown clinically significant reduction in mean monthly migraine days with better safety profile and has been FDA approved for prophylaxis of chronic migraine. Though there is no hepatotoxicity like other gepants, vigilant post-marketing surveillance is needed. Being specific to pathogenesis involved in migraine, CGRP receptor antagonists might emerge as first line drug in terminating acute attacks as well as for the prophylaxis of migraine.

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