Atogepant for the prevention of episodic migraine in adults

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Abstract
Objective: Atogepant is a newly approved medication for the prevention of migraine. This review aims to discuss the efficacy, safety, cost, and place in therapy of atogepant.
Methods: The authors performed a systematic search for sources, including articles, abstracts, and poster presentations. Queried databases were the National Institute of Health, US National Library of Medicine Clinical Trials, PubMed, European PMC, and the Cochrane Library. Search terms included atogepant, QULIPTA™, AGN-241689, MK-803, and N02CD07. Full-text, English language, randomized-controlled trials from 1 February 2012 to 1 February 2022 were included in the review. Additional relevant prescribing information, abstracts, and articles identified through the search were considered for inclusion in this review. A total of 193 database entries were evaluated for inclusion in this narrative review. Three articles representing two randomized controlled trials were reviewed.
Results and conclusions: Atogepant, a small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist, is a daily oral treatment for migraine prevention. In placebo-controlled clinical trials, atogepant decreased mean monthly migraine days (MMD) over 12 weeks in patients with episodic migraine. Major treatment-related adverse effects include nausea and constipation. Long-term placebo-controlled efficacy and safety studies, chronic migraine studies, and studies in patients that failed more than two classes of preventive therapies are still pending. Atogepant represents one of many novel therapies for the prevention of migraine. To date, no head-to-head comparisons of atogepant versus other agents indicated for migraine prevention have been published. Atogepant offers patients an alternative therapy to injectable or infusion monoclonal antibody treatments and offers an alternative to non-specific migraine medications that are associated with poor tolerability. Due to its high cost and narrower therapeutic indications, atogepant may be reserved for a small subset of migraineurs who prefer oral therapy.

Keywords
Atogepant, calcitonin gene-related peptide (CGRP) receptor antagonist, migraine, episodic headache

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Introduction

Despite a boom in recent years of acute and preventive treatment options for headache and migraine, migraine continues to levy a costly and debilitating tax on its sufferers.¹⁻³ When surveyed, 15% of Americans (9.7% of males and 20.7% of females) reported a migraine in the past 3 months.¹⁻² Migraine remains a top global cause of disability-adjusted life years and leads to significant direct and indirect costs to society.³ In 2019, migraine and headache resulted in over 46 million years lived with disability, of which migraineurs were responsible for 88.2%.³ Migraines are most common during a person’s most productive years (18–44 years old).¹⁻² Those socially and economically disadvantaged experience more migraines, with women experiencing migraine at twice the rate as men.¹⁻²,⁴ Recent advances in migraine therapy attempt to improve life for episodic and chronic migraineurs by combating the associated pain and disability.
Before the injectable calcitonin gene-related peptide (CGRP) monoclonal antibodies entered the market, the standard-of-care medications for migraine prevention were nonspecific with use limited by adherence concerns, drug and disease interactions, and adverse effect profiles. The CGRP medications introduced a new pathway to target migraines specifically. The small-molecule CGRP receptor antagonists, known as the gepants, are approved for the treatment of migraine. The Food and Drug Administration (FDA) approved atogepant, a CGRP receptor antagonist, in September 2021. Atogepant offers an oral, daily option for episodic migraine prevention. This review will discuss atogepant’s efficacy, safety, and cost and dissect its potential place in therapy.

**Pharmacology and pharmacokinetics**

Atogepant is a small-molecule CGRP receptor antagonist. Discovered in 1982, CGRP has α and β forms. αCGRP, a 37-amino acid peptide, located primarily in the peripheral and central nervous system is predominantly located in the spinal C and Aδ of sensory ganglia, whereas βCGRP is mostly expressed in the enteric nervous system. The activity of CGRP in the enteric nervous system is theorized to elicit constipation and other gastrointestinal side effects with CGRP antagonism. CGRP antagonism. CGRP is released during migraine attacks from the trigeminovascular system. It acts as a potent vasodilator and activates the release of pro-inflammatory cytokines and nitric oxide from ganglionic glial cells. Furthermore, CGRP causes persistent pro-inflammatory sensitization of trigeminal nociceptors via mast cell degranulation. Of note, this known mechanism is one of several potential pathways for migraine pain.

Though CGRP was first theorized to play a role in the pathophysiology of migraine in the 1980s, only in recent years have medications targeting the CGRP pathway via the CGRP ligand (eptinezumab, fremanezumab, and galcanezumab) or receptor (ubrogepant, rimegepant, atogepant, erenumab) have been approved. The medications targeting the CGRP pathway are often divided into small-molecule receptor antagonists known as the gepants (ubrogepant, rimegepant, and atogepant) and large-molecule antibodies (erenumab, eptinezumab, fremanezumab, and galcanezumab). Ubrogepant is indicated for acute migraine alone, while rimegepant is indicated for the prevention and acute treatment of migraine. CGRP large-molecule antibodies are used in the prevention of migraine. These agents require parental administration at a frequency of monthly to every 3 months.

Atogepant is approved for dosing at 10, 30, or 60 mg daily. When given with a high fat meal, the absorption of atogepant was not deemed significantly altered and can be taken with or without food according to the package insert. Atogepant is primarily metabolized by CYP3A4. Pharmacokinetic studies of healthy patients, the area under the curve (AUC) was increased 2.2-fold and the Cmax was increased 5.5-fold when given with itraconazole, a strong CYP3A4 inhibitor. The package insert suggests a reduced dose of atogepant 10 mg daily when given with a strong CYP3A4 inhibitor. When given with steady-state rifampin, a CYP3A4 inducer with repeat administration, atogepant plasma AUC and Cmax decreased by 60% and 30%, respectively. When co-administered with moderate or strong CYP3A4 inducers, atogepant doses of 30 or 60 mg daily are suggested. Atogepant is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein, organic anion transporter proteins (OATP) 1B1, OATP1B3, and organic anion transporter (OAT) 1. Co-administration of a single dose of rifampin, an OATP inhibitor, resulted in a significant increase in exposure (AUC increased 2.9 fold and Cmax increased 2.2 fold) in healthy adults. Atogepant 10 mg or 30 60 mg daily should be avoided with strong OATP inhibitors.

Atogepant is not expected to have clinically relevant drug interactions with sumatriptan, acetaminophen, naproxen, or estradiol/levonorgestrel.

Atogepant is absorbed rapidly with peak concentrations at 1 to 2 h. The half-life of atogepant is 11 h. Atogepant is excreted primarily in the feces (89%) and to a lesser extent in the urine (8%). In the feces, 42% of atogepant was excreted unchanged. Even though renal excretion plays a minor role in the elimination of atogepant, patients with creatinine clearances of less than 30 mL/min or end-stage renal disease were not included in studies. Consequently, the lowest effective dose, 10 mg, is recommended in this population. In a phase I trial studying the single-dose pharmacokinetics of atogepant in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment, higher concentrations of atogepant were seen in those with liver disease compared to healthy subjects leading to concerns of accumulation in this population. Therefore, atogepant should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). There is inadequate data on the risk of atogepant in pregnant women as the major studies excluded pregnant women and required adequate forms of birth control. In regards to breastfeeding women, atogepant’s effects on breastfed infants or maternal milk production have not been studied. In rat studies, lactating females had two-fold higher concentrations of atogepant in maternal milk compared to maternal plasma. Risk to infant development versus clinical benefit should be weighed. Unlike the triptans used in abortive therapy, in a study of isolated human middle meningeal, cerebral, and coronary arteries, atogepant was not associated with coronary vasoconstriction.

**Methods**

To complete this narrative review, the authors performed a systematic search for sources, including articles, abstracts, and poster presentations, published or presented from 1 February 2012 to 1 February 2022. The authors searched the National Institute of Health, US National Library of Medicine
Clinical Trials, PubMed, European PMC, and Cochrane Library databases for atogepant, QULIPTA™, AGN-241689, MK-803, and N02CD07. Entries that included lovastatin (also investigative name MK-803) were excluded. Additional relevant articles were found through the reference list of these queried articles. English language, full-text, randomized controlled trials were included in the narrative. Additional articles, abstracts, and pending studies were included only if the findings were relevant according to the authors. The authors’ search yielded 193 entries, with only three full-text articles representing two randomized-controlled trials included in the review.

Results

Clinical trials

Two major studies have demonstrated the efficacy of atogepant against placebo in the prevention of episodic migraine in adults.26,27 The first of these studies, by Goadsby et al.,26 was a phase Ib/III randomized, placebo-controlled trial conducted in 78 academic and private practice sites.26 This study compared atogepant 10 mg daily, 30 mg daily, 60 mg daily, 30 mg twice daily, and 60 mg twice daily to placebo. Twenty-six patients were randomized so that twice as many patients were in the placebo, 30 mg once daily and 60 mg once daily groups.26 The study included patients aged 18–75 years with a history of migraine with or without aura and at least one year of diagnosis of migraine before the age of 50 years.26 Patients with episodic migraine, defined as 4–14 migraine days/month in the 3 months leading up to the start of the trial and 4–14 migraine days in the 28 day baseline period, were included. Patients were excluded if they had an average of greater than 15 headache days per month, had insufficient response to three medications from at least two drug classes for the prevention of migraine, were pregnant, had new daily persistent headache, or barbiturates or any medications considered effective or effective in preventing migraine during the 30 days prior to visit one and through the duration of the study.26 The primary outcome was the change in monthly migraine days (MMD) from baseline to week 12.26 Migraine data during the 4-week baseline period and during the 12 week study period were collected using electronic diaries.26

Of the 1772 individuals screened, 796 were included in the final analysis.26 Overall, most participants were white (76%), middle-aged (mean (SD) 40.1 (12.2) years), and female (87%).26 The average number of years of living with migraine was 19.4 (12.2) years, and 28% of patients previously used a preventive medication.26 During the four-week screening period, participants self-reported a mean of 7.7 (2.5) migraine days, 8.9 (2.7) headache days, and 6.5 (3.2) acute medication use days.26 Change from baseline in the least-squared means difference (LSMD) MMDs and monthly headache days in the 12 weeks of treatment was confirmed in all treatment groups compared to placebo (Table 1).26 Atogepant 10 mg daily, 30 mg daily, and 60 mg daily failed to show a difference in a greater than 50% reduction in MMD compared to placebo. Atogepant 30 mg twice daily and 60 mg twice daily did significantly decrease MMD by greater than 50% compared to placebo.26 Similarly, the once-daily 10 mg, 30 mg, and 60 mg atogepant failed to decrease acute medication use days compared to placebo significantly.26 Though, the difference in acute medication use days was significantly decreased in the 30 mg twice daily and 60 mg twice daily groups (Table 1).26 The prespecified tertiary analysis of mean MMD at 4 weeks showed significant improvements for all doses compared to placebo (LSMD range −1.2 to −1.8, p ⩽ 0.0018).26

Atogepant had higher rates of discontinuation due to adverse events in the safety population compared to placebo (n=825), atogepant 5% (33/639) versus placebo 3% (5/186).26 The most common treatment-emergent adverse effects (TEAE) included nausea (atogepant 5.7% vs placebo 5%), constipation (4% vs 1%), fatigue (2.1% vs 2%), decreased appetite (2.1% vs 1%), and somnolence (1.7% vs 1%). No serious TEAE were reported in the trial.26 There did not appear to be a dose-related increase in adverse effects. Post-baseline alanine transferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal (ULN) occurred in eight patients in the atogepant group and two patients in the placebo group.26 Of these increases, one of the events in the 10 mg atogepant group and the placebo group were considered possibly related to the drug.26 One event in the atogepant 60 mg was likely related. No participants satisfied Hy’s law.26 One participant had an event of major depression and acetaminophen overdose in the 60 mg once daily group.26 The authors stated there were no reports of suicidal ideation with the intent to act in patients receiving atogepant.26

Although this trial provided valuable insights, there are some limitations.26 Notably, this trial had twice as many patients in the 30 and 60 mg daily groups. This ratio was based on pharmacodynamic assays and the anticipated efficacy of once-daily dosing.26 This could have affected the ability to detect clinical differences between groups in secondary and safety outcomes. No clear dose-response relationship was found in this study for either safety or efficacy.26 In addition, there were no major differences in side effects when comparing groups. This led investigators to use the 10, 30, and 60 mg once daily doses in the phase III ADVANCE trial.27
Table 1. Outcomes in major clinical trials for atogepant in the prevention of episodic migraine.

| Study | Endpoints | Placebo (n = 178) | 10 mg daily (n = 92) | 30 mg daily (n = 182) | 60 mg daily (n = 177) | 30 mg BID (n = 79) | 60 mg BID (n = 87) |
|-------|-----------|-------------------|---------------------|---------------------|---------------------|-------------------|-------------------|
| Goadsby et al.26 | Monthly migraine days | Baseline mean (SD) | 7.8 (2.5) | 7.6 (2.5) | 7.6 (2.4) | 7.7 (2.6) | 7.4 (2.4) | 7.6 (2.6) |
| | | Change from baseline | -2.9 (0.2) | -4.0 (0.3) | -3.8 (0.2) | -3.6 (0.2) | -4.2 (0.4) | -4.1 (0.3) |
| | | LSM (SE) | 0.024 | 0.039 | 0.039 | 0.039 | 0.039 | 0.039 |
| | | LSMD (95% CI) | N/A | -1.2 (-1.9 to -0.4) | -0.9 (-1.6 to -0.3) | -0.7 (-1.4 to -0.1) | -1.4 (-2.2 to -0.6) | -1.3 (-2.1 to -0.5) |
| | | p-value | 0.11 | 0.11 | 0.15 | 0.034 | 0.0097 |
| | | Participants | 72 (40%) | 53 (58%) | 97 (53%) | 92 (52%) | 46 (58%) | 54 (62%) |
| | >= 50% reduction in monthly migraine days | Atogepant vs placebo, OR (95% CI) | N/A | 1.5 (1.0 to 2.3) | 1.5 (1.0 to 2.1) | 1.4 (1.0 to 2.0) | 1.8 (1.2 to 2.9) | 2.0 (1.3 to 3.2) |
| | | p-value | 0.11 | 0.11 | 0.15 | 0.034 | 0.0097 |
| ADVANCE27 | Monthly Migraine Days | Baseline mean (SD) | 7.5 (2.1) | 7.5 (2.6) | 7.9 (2.3) | 7.8 (2.3) | 6.6 (2.3) | 6.4 (2.3) |
| | | LSM (SE) | -2.5 (0.2) | -3.7 (0.2) | -3.9 (0.2) | -3.5 (0.2) | -3.8 (0.3) | -3.6 (0.3) |
| | | LSMD (95% CI) | N/A | -1.2 (-1.8 to -0.6) | -1.4 (-2.0 to -0.9) | -1.1 (-1.7 to -0.5) | -1.4 (-2.1 to -0.6) | -1.2 (-1.9 to -0.5) |
| | | p-value | 0.11 | 0.11 | 0.15 | 0.034 | 0.0097 |
| | | Participants | 62 (29%) | 119 (55.6%) | 131 (58.7%) | 135 (60.8%) | 62 (29%) | 119 (55.6%) |
| | >= 50% reduction in monthly migraine days | Atogepant vs placebo, odds ratio (95% CI) | N/A | 3.1 (2.0 to 4.6) | 3.5 (2.4 to 5.3) | 3.8 (2.6 to 5.7) | 3.1 (2.0 to 4.6) | 3.5 (2.4 to 5.3) |
| | | p-value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

BID: Twice daily; SD: Standard deviation; LSM: Least-squares means; SE: standard error; LSMD: least squared means difference; CI: confidence interval; some results are also reported as percentages; N/A: Not Applicable; OR: Odds Ratio.
Based on these results, ADVANCE\textsuperscript{27} was a 12 week, double-blind trial that randomized patients in a 1:1:1:1 ratio to placebo or a once-daily dose of oral atogepant at doses of 10, 30, or 60 mg.\textsuperscript{27} Similar to Goadsby et al.,\textsuperscript{26} the trial used a 4-week screening period, 12-week treatment period, and 4-week safety follow-up.\textsuperscript{27} Due to interruptions caused by the coronavirus disease 2019 pandemic, both in person and virtual clinic visits were used to monitor patients and collect data.\textsuperscript{27} Clinical data were recorded via an electronic diary, while quality of life data was collected using the Activity Impairment in Migraine Diary (AIM-D) survey and Migraine Specific Quality of Life Questionnaire (MSQ).\textsuperscript{27} The study enrolled 910 patients across 128 sites throughout the United States.\textsuperscript{27} Of enrolled patients, 873 (95.9%) were included in the final efficacy analysis and 902 (99.1%) were included in the final safety analysis.\textsuperscript{27} The average age was 41.6 (SD 12.2) years old and 88.8% were female (801/902).\textsuperscript{27} Those with at least two separate mechanisms of action.\textsuperscript{27} Also like with the exception of patients with an inadequate response to 3/902), or multiple races (1.1%, 10/902).\textsuperscript{27} These demo- nic groups included were black (13.7%, 124/902), Asian (1.3%, 12/902), American Indian or Alaska Native (0.3%, 3/902), or multiple races (1.1%, 10/902).\textsuperscript{27} These demo- graphics are similar to those of Goadsby et al.\textsuperscript{26} Meanwhile, more patients in ADVANCE (70.3%) reported previous use of preventive migraine medications.\textsuperscript{27} Patients were included if they met the following criteria: adults with episodic migraine, a one-year history of migraine with or without aura, and migraine onset before 50 years of age.\textsuperscript{27} Patients were excluded for the same criteria used in Goadsby et al.\textsuperscript{26} With the exception of patients with an inadequate response to more than four oral medications for migraine prevention with at least two separate mechanisms of action.\textsuperscript{27} Also like Goadsby et al.,\textsuperscript{26} patients were allowed to use triptans, ergot derivatives, opioids, analgesics, NSAIDs, and antiemetic agents for the duration of the study. Patients were, once again, not allowed to use barbiturates or other medications for the prevention of migraine during the 30 days prior to the first visit and during the treatment period.\textsuperscript{27}

The primary outcome was the change in the mean number of MMD during the 12-week treatment compared to the 4-week baseline period.\textsuperscript{27} Each dose resulted in a statistically significant decrease in mean MMD compared to placebo (Table 1).\textsuperscript{27} This study had secondary endpoints related to headache days per month, a 50% reduction from baseline, and medication use for acute migraine attacks, as presented in Table 1.\textsuperscript{27} Notably, the 50% reduction in MMD and acute medication use outcomes were significant in this study.\textsuperscript{27} However, they were not significant for the same daily doses in Goadsby et al.\textsuperscript{26} (Table 1). Quality of life was assessed using the Role Function-Restrictive Domain of the MSQ (range 0–100) and AIM-D (range 0–100) scores.\textsuperscript{27} In the AIM-D, higher scores demonstrate a more severe impact of migraine on daily activities and physical impairment, whereas lower scores on the MSQ demonstrate a more severe impact of migraine on daily activities.\textsuperscript{27} All quality of life endpoints for the treatment groups, except the AIM-D scores when comparing 10 mg atogepant versus placebo, showed statistically significant differences from baseline when referenced to placebo (Table 2). However, the relatively small magnitude of difference in AIM-D scores in the 30 and 60 mg groups may not be clinically significant considering the small magnitude of difference versus placebo (Table 2). In the treatment groups, 14.9%–23.1% of participants experienced an atogepant-related adverse event, resulting in only one serious atogepant-related adverse event of optic neuritis in the 10 mg group.\textsuperscript{27} In the atogepant groups, the most common adverse events were constipation (6.9%–7.7% compared to 0.5% in the placebo group) and nausea (4.4%–6.1% compared to 1.8% in the placebo group).\textsuperscript{27} ADVANCE had similar limitations to the previously mentioned phase 2b/3 trial, such as a lack of long-term efficacy and safety data, analysis limited to episodic migraine, generalizability to a more diverse patient population, and generalizability to patients with other significant coexisting conditions. Of these limitations, the most concerning would be the lack of data on long-term efficacy and safety since atogepant will be taken as an ongoing preventive migraine treatment.

One prominent post hoc analysis evaluated the onset, magnitude, and persistence of the therapeutic effect of daily atogepant for the prevention of migraine.\textsuperscript{30} The analysis was completed on 873 patients who received at least one dose of the study drug, had an evaluable baseline period of eDiary data, and had at least one post-baseline period of eDiary data.\textsuperscript{30} Atogepant at all doses showed efficacy in the first 4 week post-baseline treatment period with a LSM change from baseline of −3.1 for 10 mg, −3.4 for 30 mg, and −3.9 for 60 mg, and only −1.6 for placebo (p < 0.001 for all treatment groups).\textsuperscript{30} The second and third 4 week trial periods saw similar results with each study group, signifying the duration of therapeutic effect at a magnitude that slightly increased as duration continued.\textsuperscript{30} The second 4-week mean change from baseline in MMDs was −3.7 for atogepant 10 mg, −3.9 for atogepant 30 mg, −4.2 for atogepant 60 mg, and −2.9 for placebo (p < 0.012 for all groups).\textsuperscript{30} The third 4 week mean change from baseline in MMDs was −4.2 for atogepant 10 mg, −4.3 for atogepant 30 mg, −4.4 for atogepant 60 mg, and −3.0 for placebo (p < 0.0002 for all groups).\textsuperscript{30} Similar trends were observed in the secondary outcomes of moderate-to-severe headache days and mean headache days.\textsuperscript{30} When evaluating the efficacy by week, patients in the placebo group had a −0.3 reduction in MMD compared to baseline, while atogepant 10 mg group had a −0.8 day reduction, 30 mg had a −0.9 day reduction, and 60 mg had a −1.0 day reduction in MMD (p < 0.0001).\textsuperscript{30} Improvement in migraine was seen in the first week. One day after the first dose 14.1% of patients in the 10 mg group, 10.8% in the 30 mg group, and 12.3% in the 60 mg group reported a migraine versus 25.2% in the placebo group (p < 0.0071 for all atogepant groups).\textsuperscript{30} There was no significant difference noted in all doses on each day during the first week of treatment. The
authors concluded efficacy was seen as early as the first day of treatment and maintained throughout 12 weeks.\textsuperscript{30}

Most of the evidence for atogepant’s use is published in 12 week studies of atogepant versus placebo. Two abstracts presented at the 63rd Annual Meeting of the American Headache Society evaluated the efficacy and safety of atogepant 60 mg daily versus oral standard-of-care migraine prevention medications in a 52-week open-label extension trial (NCT03700320).\textsuperscript{31,32} Patients were randomized in a 5:2 ratio of atogepant to standard of care.\textsuperscript{31,32} Investigators only compared the standard of care arm to atogepant as part of the safety analysis.\textsuperscript{31,32} In the efficacy analysis (n = 521), the mean age was 42.5 years, and the majority of patients were female (88.3%) and white (76.8%).\textsuperscript{31} The mean MMD (standard error (SE)) during the four-week baseline period was 7.30 (2.62). The LSM change in MMD at weeks 1 to 4 was −4.04 (95% CI −4.28 to −3.81) and was −4.93 (95% CI −5.20 to −4.66) during weeks 49 to 52.\textsuperscript{31} Adverse events were reported by 67.0% of patients treated with atogepant, though only 18.0% of those adverse events were deemed to be related to the study drug by investigators.\textsuperscript{32} Discontinuation due to adverse events occurred in 5.7% in the atogepant group.\textsuperscript{32} The investigators reported no serious adverse events related to atogepant.\textsuperscript{32} Cases of ALT or AST greater than three times ULN were reported in 2.4% (13/531) of participants in the atogepant group and 3.2% (6/190) in the standard of care group.\textsuperscript{32} No cases of Hy’s Law were reported.\textsuperscript{32} The authors of these abstracts reported an early and sustained response with no long-term side effects.\textsuperscript{31,32} Similar decreases in MMD were reported throughout the study, and no serious adverse events were reported.\textsuperscript{32} The lack of comparators for the efficacy analysis and no reported adverse events in the standard of care group for the safety analysis does limit the internal validity of these findings.\textsuperscript{32} In addition, the abstract did not give any information on what medications were used as standard of care.\textsuperscript{32}

Current gaps in the literature may be answered in several ongoing and unpublished studies.\textsuperscript{33} At the time of writing this review, published data for atogepant has exclusively been in the episodic migraine population. Multiple studies (NCT04829747, NCT05216263, NCT04437433, NCT03855137, and NCT04686136) have yet to be published or are recruiting and will evaluate atogepant in chronic migraine or combined episodic and chronic migraine populations.\textsuperscript{33} One of these studies (NCT05216263) evaluates atogepant with Onabotulinumtoxin A in chronic migraine. Another study will look at atogepant with ubrogepant in patients with a history of migraine (NCT04818515).\textsuperscript{33} These could provide valuable information regarding combination therapies. Furthermore, one study is assessing long-term (52 week) safety and efficacy of atogepant 60 mg daily in episodic and chronic migraine (NCT04437433). A study evaluating the use of atogepant in patients who have failed preventive therapy (ELEVATE, NCT04740827) with drugs from 2 to 4 different medication classes is also underway. These findings will help guide clinicians in the treatment of resistant patients.\textsuperscript{33}

| Table 2. Quality of life measures in the ADVANCE trial. |
|-------------------------------|-------------------|-----------------|-----------------|-----------------|
| ADVANCE Quality of life measures | Placebo (n = 214) | Atogepant 10 mg (n = 214) | Atogepant 30 mg (n = 223) | Atogepant 60 mg (n = 222) |
| AIM-D | Mean monthly score at baseline (SD) | 15.2 (8.3) | 15.5 (8.9) | 16.9 (8.0) | 15.9 (8.3) |
| | Change from baseline at week 12 (SE) | −6.1 (0.5) | −7.3 (0.5) | −8.6 (0.5) | −9.4 (0.5) |
| | Difference vs placebo (95% CI) | N/A | −1.2 (−2.6 to 0.2) | −2.5 (−3.9 to −1.2) | −3.3 (−4.7 to −2.0) |
| | p value | 0.09 | <0.001 | <0.001 | <0.001 |
| AIM-D score on physical impairment domain | Mean monthly score at baseline (SD) | 11.2 (8.1) | 11.7 (8.5) | 13.0 (8.0) | 11.6 (7.9) |
| | Change from baseline at week 12 (SE) | −4.0 (0.4) | −5.1 (0.4) | −6.0 (0.4) | −6.5 (0.4) |
| | Difference vs placebo (95% CI) | N/A | −1.1 (−2.3 to 0.1) | −2.0 (−3.2 to −0.8) | −2.5 (−3.7 to −1.3) |
| | p value | 0.90 | 0.002 | <0.001 | <0.001 |
| MSQ-9 | Mean monthly score at baseline (SD) | 46.8 (19.7) | 44.9 (21.4) | 44.0 (19.6) | 46.8 (20.4) |
| | Change from baseline at week 12 (SE) | 20.4 (1.6) | 30.3 (1.6) | 30.5 (1.6) | 31.2 (1.6) |
| | Difference vs placebo (95% CI) | N/A | 9.9 (5.4 to 14.4) | 10.1 (5.7 to 14.5) | 10.8 (6.4 to 15.2) |
| | p-value | <0.001 | <0.001 | <0.001 | <0.001 |

AIM-D: Activity Impairment in Migraine-Diary; SD: Standard deviation; SE: Standard Error; CI: Confidence Interval; N/A: Not Applicable; MSQ: Migraine-Specific Quality of Life Questionnaire.
Discussion

Atogepant’s place in therapy will be similar to other CGRP antagonists. In a recent consensus statement, the American Headache Society recommended the use of CGRP monoclonal antibodies in patients with 4–14 migraine days only after a patient had an inadequate response or experienced intolerable adverse effects to two or more of the oral agents with established or possible efficacy for the prevention of migraine. It is therefore notable that patients who failed three or more preventive medications from two or more different classes were excluded from the discussed atogepant studies. Rimegepant for prevention was not included in the consensus statement. It was not yet approved for prevention, but possibly has a similar place in therapy.

While atogepant was effective in clinical trials compared to placebo in decreasing MMD in patients with episodic migraine, there are no head to head trials of atogepant versus other migraine therapies. Prior to the CGRP therapies, preventive therapies for migraines were dominated by non-migraine specific agents like antiepileptics, antidepressants, and cardiovascular medications. Topiramate, divalproex, propranolol, and timolol are approved by the FDA for the prevention of migraines. Other non-specific oral agents such as candesartan, metoprolol, amitriptyline, memantine, and venlafaxine have also shown efficacy in clinical trials. The older, non-CGRP agents are non-specific to migraines and are plagued with adverse events that reduce adherence.

Therefore, it is notable that approximately 85% of patients enrolled in atogepant trials completed all 12 weeks of the trial. This is comparable to the rates of persistence in clinical studies of topiramate (88%) and propranolol (86.2%). Due to the heterogeneity in clinical outcomes, patient populations, and trial length, comparisons of atogepant to these non-specific agents based on magnitude of benefit are difficult to quantify.

Similarly, no clinical trials have directly compared the efficacy between the CGRP monoclonal antibodies, rimegepant, and atogepant. In clinical trials of similar length, including patients with episodic migraine, at treatment doses of each medication, the least square means reduction in MMD compared to placebo for erenumab (−1.0 to −2.3), galcanezumab (−1.1 to −2.0), fremanezumab (−1.3 to −3.0), and eptinezumab (−0.6 to −1.1) were somewhat similar to atogepant (−0.7 to −1.7). The phase IIb/III patients study of rimegepant for prevention included patients with episodic and chronic migraine (4–18 migraines/month). Despite the higher baseline rate of migraines among participants in the rimegepant study (9.9–10.3 MMD) compared to the atogepant studies (7.4–7.9 MMD), rimegepant 75 mg by mouth every other day decreased MMD compared to placebo at a similar rate (LSM decrease in MMD −0.8 days (95% CI (−1.5 to −0.2)) to atogepant.51

Due to their similar efficacy, selection among these agents may depend on patient characteristics. All four FDA-approved monoclonal agents have been studied and approved for chronic migraine and galcanezumab, erenumab, and fremanezumab have data to support their use in patients with a history of treatment resistance. Although atogepant is dosed daily, its onset of efficacy is similar to the monthly and quarterly injectables. Since atogepant does not yet have data for chronic or resistant migraineurs, the monoclonal antibodies will likely be preferred in these patients. Rimegepant received FDA approval to prevent migraine after its initial approval for acute treatment. Although rimegepant has both indications listed in the package insert, no study has evaluated the use of rimegepant concomitantly for both treatment and prevention. The most common adverse effects of the monoclonal antibodies compared to placebo are injection site pain, nausea, and constipation. Constipation and nausea were also observed as adverse effects in the atogepant and rimegepant studies. This is likely due to the effects of CGRP on gastrointestinal motility.

Cost is another consideration that providers should weigh when selecting therapy. Atogepant is available under the brand name QULIPTA (R) with dosage forms of 10, 30, and 60 mg. The wholesale acquisition cost for atogepant is US$39.64 per tablet and US$991 for a 30 days supply at any dose. This is more expensive than the CGRP monoclonal antibodies (range US$523–US$647, average US$629 per month). For prevention, rimegepant is given every other day but comes in a package with 8 oral disintegrating tablets for US$919.28 (~US$1724 per month). At the time of this review, there were similar coupons available from the manufacturers of rimegepant, erenumab, eptinezumab, galcanezumab, and fremanezumab.

Atogepant’s place in therapy will likely be similar to other CGRP agents as a second line to other oral options that are less expensive. Atogepant, rimegepant, and monoclonal antibodies have a potential cost barrier and similar efficacy. Therefore, when deciding between atogepant and monoclonal antibodies, monoclonal antibodies may enable better adherence as monthly or quarterly injections, while atogepant provides a non-injectable option for patients who cannot or will not self-inject. Clinicians might prefer rimegepant as an oral option due to dual indications in acute and preventive treatment of migraine, but it has a high monthly cost. Like other CGRP medications, atogepant is not recommended in patients who are pregnant, or trying to get pregnant, due to the fetal harm concerns in animal studies.

Conclusion

Recently approved by the FDA, atogepant is a daily oral CGRP receptor antagonist for the prevention of episodic migraine. The efficacy of atogepant has not yet been compared to other medications used for the prevention of episodic migraine. Atogepant offers patients an alternative therapy to injectable or infusion monoclonal antibody
treatments and offers an alternative to non-specific migraine medications that are associated with poor tolerability. Atogepant is less expensive than rimegepant every other day but does not have the dual indications for acute and preventive therapy. Due to its high cost and narrower therapeutic indications, atogepant may be reserved for a small subset of migraineurs who prefer oral therapy.

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