Journal Club
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Title: Atogepant for the Preventive Treatment of Migraine

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Source: *New England Journal of Medicine*, 2021 Aug 19;385(8):695-706

Background: Headaches are something that more than likely everyone will experience at some point in their lifetime. While some may consider migraines a bad headache, they are really a complex neurological condition that are often debilitating for patients who experience them. A 2018 systemic review determined that the overall prevalence of migraines in the United States was 15.3% (95% CI [14.75-15.85]), with women having a higher prevalence then men (20.7%, 95% CI [19.84-21.56] versus 9.7%, 95% CI [9.05-10.35] respectively).[2] For several years, preventative therapy has revolved around several classes of medications with varying efficacy. In recent years a new class of medications called calcitonin gene-related peptide antagonists (CGRP) have emerged as a new way to prevent migraine attacks. This class of medications is unique in that medications are available in both injectable and oral formulations each with their own risks. Atogepant is an oral CGRP antagonist seeking to add to the growing list of medications available for migraine prevention.

Primary Objective: To determine if there is a statistically significant difference with once daily oral atogepant versus to placebo in preventing migraines in patients with episodic migraines.

Primary Efficacy Measure: Change from baseline in the mean number of migraine days per month (average of month 1, 2, and 3)

Study Design: This was a phase III, multicenter, double-blind, parallel group, randomized, placebo-controlled trial that took place at 128 sites across the United States. Patients began a 4-week screening and baseline period before beginning the 12-week trial period, after which they participated in a 4-week safety follow-up period. Patients were allowed to use triptans, ergot derivatives, opioids, analgesics, NSAIDs, and antiemetic for abortive migraine therapy.

Subjects: 1:1:1:1 randomization produced similar groups that with regards to age, sex, body-mass index, number of migraine days per month in the past three months, and the number of headache days per month in the past three months. The groups did differ slightly in race or ethnic group with the distribution of Asian and Black patients having wider gaps between groups.

Inclusion Criteria:

- Adults aged 18 to 80 years old with:
    - 4 to 14 migraine days per month in the 3 months prior to visit 1

    - 4 to 14 migraine days during the 28-day baseline period according to an electronic diary
- 1-year history of migraine with or without aura diagnosed as specified in the International Classification of Headache Disorders, 3rd edition (ICHD-3), with first migraine onset before 50 years old

Exclusion Criteria:

- Current diagnosis of chronic migraine, new Daily persistent headache, trigeminal autonomic cephalgia, or painful cranial neuropathy as defined by ICHD-3
- Patients averaging 15 or more migraine days per month across the 3 months prior to visit 1 or during the 28-day baseline period
- Patients with inadequate response to more than four oral medications prescribed for the preventative treatment of migraine
    - Two of which had to have different mechanisms of action
- Patients who used opioids or barbiturates on more than 2 days per month, triptans or ergots on 10 or more days per month, or simple analgesic agents on 15 or more days per month in the 3 months prior to visit 1 or during the 28-day baseline period
- Patients who used barbiturates 30 days prior to screening or during the duration of the trial
- Female participants who were pregnant, planning to become pregnant, or lactating

Study Period: This study took place between December 2018 and June 2020 with a 4-week screening and baseline period. Patients then began a 12-week treatment period with a 4-week safety follow-up.

Monitoring: In total, there were 8 visits, 5 of which took place during the treatment period, The protocol was amended based on the SARS-CoV-2 pandemic, after which, the last safety visit was conducted remotely. Patients could also report adverse events between visits via phone calls.

Data Analysis: Analysis of a modified intent-to-treat population was performed with 214 patients assigned to placebo, 214 assigned to atogepant 10 mg, 223 assigned to atogepant 30 mg, and 222 assigned to atogepant 60 mg (873 total). Power was set at 98% with 218 patients per group required to detect a difference of 1.5 migraine days between each of the three treatment groups and placebo. Alpha was set with considerations made for multiplicity by using an alpha level of 0.05 ÷ 3 for each dose.

Data Analyzed	Type of Data	Statistical Test Used	Appropriate/Not Appropriate
Change from baseline in the mean number of migraine days per month (average of month 1, 2, and 3)	Interval	General linear model for repeated measures	Appropriate

Results: Atogepant had a statistically significant difference at all doses in reducing the number of migraines from baseline across the 12-week treatment period versus placebo. This is shown by the upper bound of the 95% confidence interval not crossing the absolute equivalency of 0 and the reported p values less than alpha

	Placebo	Atogepant	Atogepant	Atogepant

	(n=214)	10 mg (n=214)	30 mg (n=223)	60 mg (n=222)
Change from baseline in number of migraine days per month across 12-week treatment period	-2.5 ± 0.2	-3.7 ± 0.2	-3.9 ± 0.2	-4.2 ± 0.2
Difference vs. Placebo (95% CI)		-1.2 (-1.8 to -0.6)	-1.4 (-1.9 to -0.8)	-1.7 (-2.3 to -1.2)
P value		<0.001	<0.001	<0.001

Tolerability: Between the three treatment groups and the placebo group, the rate of any adverse event was similar. Constipation and nausea were more frequently reported in the atogepant groups than the placebo group. Overall, 4 serious adverse events were recorded with 2 in the placebo group and 2 in the atogepant 10 mg group. Of these 4, only 1 event, from the atogepant 10 mg group, was determined to be from atogepant or placebo. No deaths were reported in this trial.

Author's Conclusion: Atogepant 10 mg, 30 mg, and 60 mg is superior to placebo in reducing the number of migraine days per month.

Strengths:

- Power Set
- Treatment was appropriate and accepted
- Length of study was appropriate to show effect
- Inclusion and Exclusion criteria were appropriate
- Blinding was present
- Randomization produced fairly similar groups
- Biostatistical test was appropriate
- Primary outcome is standard and accepted
- Authors' conclusion supported by results

Limitations:

- Power not met
- Mostly White and Female population
- Distribution of Black and Asian patients differed between groups
- Funded by Allergan (prior to acquisition by AbbVie), potential for bias

Level of Evidence: Level II – interventional, controlled, randomized, power set but not met with Major Limitations

Recommendation: I recommend that atogepant be used for the prevention of migraines in patients experiencing 4 to 14 migraine days per month versus no therapy for the following reasons:

- Efficacy
  - Atogepant was shown to have a statistically significant difference in reducing the number of migraine days from baseline versus placebo
- Safety
  - The rates of adverse events were shown to be similar between the atogepant and placebo groups
  - The most reported adverse events in the treatment groups were constipation and nausea
- Cost[3]
  - According the Lexicomp, the cost of one tablet of atogepant 10 mg, 30 mg, and 60 mg is $39.64
    - $3,567.6 for 90
    - Cost savings available
  - According to Lexicomp, the cost of 100 mg/mL of Vyepti (eptinezumab) is $1,838.86
  - Topiramate 25 mg (per each): $7.56
  - Metoprolol tartrate 25 mg (per each): $0.03 - $0.27
- Special Considerations/Populations
  - This study consisted of a mostly white and female population which affects the overall generalizability
  - This product is a good option for patients with migraines who are unable to tolerate or wish to avoid injections
  - Patients who experience less than 4 and more than 14 migraines per month were excluded from this trial so we cannot apply the results of this trial to that population

Grade of Recommendation: A

References:

1) Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. *N Engl J Med*. 2021;385(8):695-706. doi:10.1056/NEJMoa2035908

2) Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache*. 2018;58(4):496-505. doi:10.1111/head.13281

3) Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed November 10, 2021. http://online.lexi.com