2022

Is rimegepant an effective treatment for acute migraine pain in adults?

Hanson S. Wright
Philadelphia College of Osteopathic Medicine

Is rimegepant an effective treatment for acute migraine pain in adults?

Hanson S. Wright, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Suwanee, Georgia

November 27, 2021

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Is rimegepant an effective treatment for acute migraine pain in adults?"

STUDY DESIGN: A systematic review of three, peer-reviewed randomized placebo-controlled trials (RCT's).

DATA SOURCES: All studies were obtained from PubMed and were published in English in peer-reviewed journals between 2014-2019. The articles were selected based on their relevance to the clinical question posed in the objective and their inclusion of patient oriented outcomes.

OUTCOMES MEASURED: The main outcome being assessed in all articles was freedom from pain. The absence/presence of pain was self-reported by patients two hours post rimegepant/placebo dose in all trials.

RESULTS: All RCT's found rimegepant to be superior in eliminating migraine pain compared to the placebo group. Croop et al. (2019) found that 21.2% of patients treated with rimegepant had freedom from pain 2 hours postdose while only 10.9% of patients treated with the placebo achieved freedom of pain 2 hours postdose. The study was statistically significant (p-value < 0.0001) and had a large treatment effect based on a calculated NNT of 10. Lipton et al. (2019) found that 19.6% of patients treated with rimegepant had freedom from pain 2 hours postdose while only 12.0% of patients treated with the placebo achieved freedom from pain 2 hours postdose. The study was statistically significant (p-value < 0.001) and had a large treatment effect based on a calculated NNT of 13. Marcus et al. (2014) found that 31.4% of patients treated with rimegepant had freedom from pain 2 hours postdose while only 15.3% of patients treated with the placebo achieved freedom from pain 2 hours postdose. The study was statistically significant (p-value ≤ 0.002) and had a large treatment effect based on a calculated NNT of 7.

CONCLUSIONS: All three studies found rimegepant to be more effective at eliminating acute migraine pain of moderate to severe intensity compared to the placebo. Statistically significant p-values as well as large treatment effects were found in each study. Future research should be conducted looking at safety among individuals with cardiovascular disease.

KEYWORDS: rimegepant, migraine treatment

INTRODUCTION

Migraine headaches are a chronic neurologic disorder characterized by recurrent moderate to severe unilateral throbbing pain, often associated with nausea, vomiting, photophobia, and phonophobia. They can be distinguished from other types of headaches based on their severity, laterality, and associated symptoms (nausea, vomiting, photophobia, phonophobia). Migraine headaches are often separated into two categories, with an aura or without an aura. An aura is sensory anomaly that precedes a migraine headache and can include but is not limited to visual, auditory, sensory, speech, and/or motor disturbances.

Migraine headaches are commonly seen throughout the world, often presenting in many different clinical settings. An estimated 1.04 billion individuals worldwide experienced a migraine headache in 2016.[1] In the US alone, 39 million individuals are affected by migraine headaches, with 28 million being female.[2] With migraines being among the most common neurologic disorders affecting the US population, the financial burden can be substantial. In the United States, the economic burden of migraine headaches is approximately $78 billion annually.[2] With migraine headaches accounting for 800,000 emergency department visits annually,[3] substantial amounts of medical resources are being allocated to the treatment of migraines. Finding an effective treatment for migraine headaches can not only decrease the economic burden of migraine management, but also allow allocation of medical resources to other areas of need.

The pathophysiology of migraine headaches isn't fully understood, but it is believed to be the result of neuronal dysfunction related to the trigeminal nerve.[4] Dysfunction in the trigeminal nerve results in the release of vasoactive neuropeptides which leads to sensitization and neurogenic inflammation resulting in a migraine.[4] One of the major vasoactive neuropeptides

believed to contribute to the development of a migraine headache is calcitonin gene-related peptide (CGRP).

Traditionally, therapy for migraine headaches has involved rest, IV fluids, antiemetics, simple analgesics (NSAIDS, aspirin, acetaminophen), ergotamines, and triptans, which are 5-$HT_{1b/1d}$ receptor agonists. These established methods of acute migraine treatment mentioned have been proven to have some success in the treatment of acute migraines. However, triptans and ergotamines are both contraindicated in patients with cardiovascular disease. Also, current therapies may not be effective or tolerable for all patients. Since rimegepant is a CGRP antagonist, it has a different mechanism of action compared to any current therapies for acute migraine attacks, including triptans and ergotamines. Therefore, rimegepant could be an effective treatment option for acute migraine pain, especially in individuals where current therapies have proven to be ineffective, poorly tolerated, or contraindicated.

OBJECTIVE

The objective of this systematic review is to determine whether or not "Is rimegepant an effective treatment for acute migraine pain in adults?"

METHODS

Three randomized placebo-controlled trials comparing rimegepant intervention to a placebo in the treatment of acute migraine pain of moderate to severe intensity were found using the key words "migraine treatment" and "rimegepant" via PubMed. Criteria for the articles included in this systematic review were selected by the author of this paper based on their relevance to the question, Is rimegepant an effective treatment for acute migraine pain in adults, as well as their inclusion of patient oriented outcomes (POEMS), specifically freedom from migraine pain. All three articles selected were published in peer-reviewed journals written in

English in the years 2014 and 2019. Exclusion criteria included articles published prior to 2011, non peer-reviewed articles, and articles with secondary study design.

The population criteria used for this review included adults (18 or older) with at least a 1-year history of migraines who were randomly assigned to a treatment group receiving either rimegepant 75 mg or a placebo to treat an acute migraine attack of moderate to severe intensity. The selected articles compared the intervention rimegepant 75 mg to a control group receiving a placebo with the measured outcome of freedom from pain 2 hours post dose. Statistic values reported and used included p-values and NNT. Demographics of each study can be found in Table 1.

OUTCOMES MEASURED

The primary outcome measured in all three RCTs was freedom from pain 2 hours post rimegepant/placebo dose following an acute migraine attack of moderate to severe intensity. Patients were instructed to self-report the absence or presence of pain 2 hours post rimegepant/placebo dose in an electronic diary.

RESULTS

Croop et al.[5] performed a randomized double-blind placebo-controlled trial to determine the efficacy of rimegepant 75 mg versus placebo in the treatment of acute migraine pain of moderate to severe intensity in adults. The trial took place across 69 study locations across the United States between February 27 – August 28, 2018. Participants were required to be 18 years of age or older and have a 1-year history of migraines with or without an aura per the criteria of the 3rd Edition of International Classification of Headache Disorders (beta version).[5] More inclusion and exclusion criteria can be found in Table 1.

A 1:1 ratio was used to randomly assign participants via a web system independently

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/ D	Interventions
Croop[5] (2019)	RCT	1375	Adults ≥18 years old	Patients ≥ 18 y.o. with at least a one year history of migraine w/ or w/o an aura. Migraine onset before age 50; Must be able to distinguish migraine attacks from tension or cluster headache. 2-8 migraine attacks of moderate/severe intensity per month, <15 days per month with headache within the past 3 months. Stable dose of preventive migraine medication at least 3 months before trial entry	History of any clinically significant medical condition, including substance abuse that could interfere with the study or put patients at health risk	24	Rimegepant VS. Placebo
Lipton[6] (2019)	RCT	1086	Adults ≥18 years old	Patients ≥ 18 y.o. with at least a 1 year history of migraine, with onset before 50 y.o.; headache < 15 days per month during previous 3 months. 2-8 migraine attacks of moderate/severe intensity per month. Stable dose of preventive migraine medication at least 3 months before entry to trial	History of any clinically significant medical condition, including substance abuse that could interfere with the study or put patients at risk. Received biologic agents within 90 days Received nonbiologic agents within 30 days	6	Rimegepant VS. Placebo
Marcus[7] (2014)	RCT	320	Adults 18-65 years old	18-65 y.o. w/ ≥ 1 year history of migraine w/ or w/o an aura. Migraine onset before 50 y.o, with migraine duration of 4-72 hours. Headache for < 15 days per month during previous 3 months. 2-7 migraine attacks of moderate/severe intensity per month within 3 months of screening Must be able to distinguish migraine attacks from tension or cluster headache. Stable dose of preventive migraine medication at least 3 months before trial entry.	Patients with history of basilar or hemiplegic migraines; any patients who didn't get relief from migraines from triptans. History of any clinically significant medical condition, including substance abuse as well as any medications that could interfere with the study or put patients at health risk. Pregnant/breastfeeding women or women who didn't use contraceptives	24	Rimegepant VS. Placebo

operated by a research organization not involved with any other aspects of the trial to either rimegepant or placebo. The treatment assignments of rimegepant and placebo were hidden from all participates, investigators, and study staff. Both rimegepant and placebo were matched in flavor, appearance, and presentation. Participants were instructed to sublingually administer a single dose of the study medication assigned to them in the event of a single acute migraine attack of moderate to severe intensity over the 45 day trial period. Participants were instructed to document their symptoms and pain at set timepoints over a 48 hour period post study medication dose in a provided electronic diary. This review specifically focused on the endpoint of freedom from pain at the 2 hours post dose timepoint for each study medication.

Of the 1375 participates randomly assigned to rimegepant or placebo who experienced a qualifying migraine, 21.2% of participants that received rimegepant reported freedom from pain at 2 hours post dose (Table 2).[5] Only 10.9% of participants that received placebo reported freedom from pain at 2 hours post dose (Table 2).[5] The study was statistically significant with a p-value of $p<0.0001$ and had a large treatment effect based on a calculated NNT of 10. Results of this study indicate rimegepant was more effective than placebo at achieving freedom from pain.[5]

Table 2. Comparison of Freedom from Pain of the Study Groups in Croop et al.[5]

	Rimegepant 75 mg Events/patients	**Placebo** Events/patients	
Freedom from Pain at 2 Hours Post Dose	142/669 (21.2%)	74/682 (10.9%)	**p-value** < 0.0001

Lipton et al.[6] performed a similar randomized double-blind placebo-controlled trial to determine the efficacy of rimegepant 75 mg versus placebo in the treatment of acute migraine pain of moderate to severe intensity in adults. The trial took place across 49 study locations

across the United States between July 2017 - January 2018. Participants were required to be 18 years of age or older and have a 1-year history of migraines with or without an aura per the criteria of the 3rd International Classification of Headache Disorders (beta version).[5] More inclusion and exclusion criteria can be found in Table 1.

Similar to Croop et al,[5] a 1:1 ratio was used to randomly assign participants via a web system to the rimegepant treatment group or placebo treatment group. Both rimegepant and placebo were matched in flavor, appearance, and presentation. Participants were instructed to administer a single dose of the study medication assigned to them at the occurrence of a single acute migraine attack of moderate to severe intensity over the 45 day trial period. Participants were instructed to document their symptoms and pain at set timepoints over a 48 hour period post study medication dose in a provided electronic diary. This review specifically focused on the endpoint of freedom from pain at the 2 hours post dose timepoint for each study medication.

Of the 1086 participates randomly assigned to rimegepant or placebo who received the study medication dose, 19.6% of participants that received rimegepant reported freedom from pain at 2 hours post dose (Table 3).[6] Only 12.0% of participants that received placebo reported freedom from pain at 2 hours post dose (Table 3).[6] The study was statistically significant with a p-value < 0.001 and had a large treatment effect based on a calculated NNT of 13. Results of this study indicated rimegepant was more effective than placebo at achieving freedom from pain.[6]

Table 3. Comparison of Freedom from Pain of the Study Groups in Lipton et al.[6]

	Rimegepant 75 mg Events/patients	**Placebo** Events/patients	
Freedom from Pain at 2 Hours Post Dose	105/537 (19.6%)	64/535 (12.0%)	**p-value** < 0.001

Marcus et al.[7] performed a randomized double-blind placebo-controlled trial similar to the two studies mentioned above. However, the Marcus et al.[7] trial differed in that it investigated the efficacy of rimegepant at six different doses (10mg, 25mg, 75mg, 150mg, 300mg, and 600mg) versus placebo versus oral sumatriptan 100 mg in the treatment of acute migraine pain of moderate to severe intensity in adults. The trial took place in the United States between October 2011 – May 2012. Participants were required to be 18-65 years of age and have a 1-year history of migraines with or without an aura. More inclusion and exclusion criteria can be found in Table 1.

A fixed ratio was used to randomly assign participants to the treatment group or placebo group. The treatment group was then further allocated randomly into groups receiving varying doses of rimegepant and sumatriptan 100 mg. Participants were instructed to administer the study medication assigned to them at the occurrence of a single acute migraine attack of moderate to severe intensity over the 45 day trial period. Participants were then instructed to document their symptoms and pain at set timepoints over a 48 hour period post study medication dose in a provided electronic diary. This review specifically focused on the endpoint of freedom from pain at the 2 hours post dose timepoint for rimegepant 75 mg and placebo.

Of the 320 participates randomly assigned to rimegepant 75 mg or placebo who experienced a qualifying migraine, 31.4% of participants that received rimegepant reported freedom from pain at 2 hours post dose (Table 4).[7] Only 15.3% of participants that received the placebo reported freedom from pain at 2 hours post dose (Table 4).[7] The study was statistically significant with a p-value of $p \leq 0.002$ and had a large treatment effect based on a calculated NNT of 7. Results of this study indicate rimegepant 75 mg was more effective than placebo at achieving freedom from pain.[7]

Table 4. Comparison of Freedom from Pain of the Study Groups in Marcus et al.[7]

	Rimegepant 75 mg Events/patients	**Placebo** Events/patients	
Freedom from Pain at 2 Hours Post Dose	27/86 (31.4%)	31/203 (15.3%)	**p-value** ≤ 0.002

DISCUSSION

This systematic review assessed the efficacy of rimegepant as a treatment for acute migraine pain of moderate to severe intensity in adults. All three trials evaluated showed a statistically significant difference between rimegepant and placebo in achieving freedom from pain.[5-7] In each study, rimegepant was significantly better at eliminating migraine pain compared to a placebo.[5-7]

All three studies evaluated in this review randomly assigned patients to treatment groups, concealing participants from assignments while blinding participants, clinicians, and study workers.[5-7] In addition, both treatment groups (rimegepant and placebo) exhibited similar demographics and baseline characteristics including but not limited to sex, ethnicity, race, and frequency of migraine attacks across all three studies. Implementation of these measures added to the validity of each study.

The three studies evaluated were not without limitations. Because each study implemented a single-attack design, consistency of rimegepant's efficacy over multiple attacks couldn't be established. In addition, "worst case" analysis of participants lost to follow-up was not performed in any of the studies. Additionally, Marcus et al.[7] was limited by its small sample size compared to the other two studies. A final limitation worth mentioning involved the author's method of article selection for this systematic review. Because PubMed was the only database

utilized for research, other studies that could have better answered the author's original question may have been excluded.

Both Croop et al.[5] and Lipton et al.[6] found safety and tolerability to be similar between participants treated with rimegepant versus placebo with nausea being the most common adverse effect noted.[5,6] Rimegepant has recently received FDA approval for treating acute migraines as of February 2020.[8] The only known contraindication to rimegepant is hypersensitivity to rimegepant.[9]

CONCLUSION

Based on the results of the three randomized placebo-controlled trials evaluated in this systematic review, rimegepant is an effective treatment for acute migraine pain in adults. All the studies were statistically significant with large treatment effects.

More recent studies involving rimegepant that were not included in this systematic review have evaluated the medication's long-term safety, use as preventive therapy, as well as the its safety in subgroups of individuals where triptans are poorly tolerated or not effective.[10,11] Rimegepant was recently FDA approved for the preventive treatment of migraines in May 2021, making it FDA approved for both acute therapy and preventative therapy.[8] Future research could be expanded to patient populations that include individuals under the age of 18 as well as individuals with cardiovascular disease. With the success of CGRP antagonists, future research could also target other vasoactive neuropeptide pathways as possibilities for new therapies.

References

1. Stovner LJ, Nichols E, Steiner TJ, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: A systematic analysis for the global burden of disease study 2016. *Lancet*. 2018;17(11):954-976. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(18)30322-3/abstract. Accessed Oct 9, 2021. doi: 10.1016/S1474-4422(18)30322-3.

2. Concomitant medical conditions and total cost of care in patients with migraine: A real-world claims analysis. AJMC Website. https://www.ajmc.com/view/total-cost-of-care-in-patients-with-migraine-a-realworld-claims-analysis. Accessed Oct 9, 2021.

3. Minen MT, Loder E, Friedman B. Factors associated with emergency department visits for migraine: An observational study. *Headache*. 2014;54(10):1611-1618. Accessed Oct 16, 2021. doi: 10.1111/head.12461.

4. Aminoff MJ, Douglas VC. Chapter 24: Nervous System Disorders. In: Papadakis MA, McPhee SJ, Rabow MW, eds. *Current Medical Diagnosis & Treatment: 2021*. 60th Ed. New York, NY; McGraw-Hill; 2021. 1005-1007.

5. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: A randomised, phase 3, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10200):737-745. Accessed Jan 6, 2021. doi: 10.1016/S0140-6736(19)31606-X.

6. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *NEJM*. 2019;381(2):142-149. Accessed Jan 6, 2021. doi: 10.1056/NEJMoa1811090.

7. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: A double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*. 2014;34(2):114-125. Accessed Jan 6, 2021. doi: 10.1177/0333102413500727

8. Rimegepant. Biohaven Pharmaceuticals Website. https://www.biohavenpharma.com/science-pipeline/cgrp/rimegepant. Accessed Dec 10, 2021.

9. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212728s006lbl.pdf. Accessed Dec 10, 2021.

10. Croop R, Berman G, Kudrow D, et al. Long-term safety of rimegepant 75 mg for the acute treatment of migraine (study 201) (4829). *Neurology*. 2020;94(15 Supplement):4829. http://n.neurology.org/content/94/15_Supplement/4829.abstract. Accessed Dec 10, 2021.

11. Mullin K, Hutchinson S, Smith T, et al. Long-term safety of rimegepant 75 mg for the acute treatment of migraine in adults with a history of triptan treatment failure (5142). *Neurology*. 2021;96(15 Supplement):5142. http://n.neurology.org/content/96/15_Supplement/5142.abstract. Accessed Dec 10, 2021.