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Evaluating and comparing the safety and efficacy of rimegepant versus lasmiditan in aborting acute migraine headaches in the adult migraineur

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Abstract

Migraine headaches are one of the most common causes of primary headaches and one of the leading causes of disability worldwide. While the mechanism of migraines are not entirely understood, they can result in significant disability (DynaMed, 2023). Dihydroergotamine was introduced for migraine treatment in the 1920s and in the 1990s triptans were introduced and have been the mainstay of acute migraine treatment since their introduction (Solomon et al., 2008). In recent years, there have been several developments in the acute treatment and prophylaxis of migraine headaches. CGRP receptor antagonists and 5-HT1F receptor agonists have been researched, developed, and approved by the FDA for acute migraine treatment.

The purpose of this literature review was to compare the efficacy and safety of rimegepant, a CGRP receptor antagonist and lasmiditan, a 5HT1F receptor antagonist in the treatment of acute migraine attacks. This comparison was accomplished by a thorough review of scientific articles available through various resources such as PubMed, Clinical Key and CINAHL Complete. The results from 12 clinic trials that were reviewed indicated that rimegepant and lasmiditan are both superior to placebo in aborting an acute migraine in addition to eliminating most bothersome associated symptoms. Rimegepant and lasmiditan were also proved to be safe in the tested populations although each pharmacological intervention does carry its own set of potential side effects. There have been no direct studies comparing both drugs or comparing the drugs to triptans, however several meta-analyses showed triptans to still be superior in aborting acute migraine headaches.

Keywords: migraine disorders/drug therapy, double-blind method, calcitonin gene related peptide receptor antagonists/therapeutic use, 5-HT1F receptor agonists adult, oral administration, lasmiditan, rimegepant, safety, and triptan

Introduction

An analysis of the 2016 Global Burden of Disease study estimated that 45.1 million years were lived with a disability due to migraines across the globe. Migraines were found to be the second most disabling condition, following low back pain. According to DynaMed (2023), migraines typically affect middle aged adults with onset typically in late childhood or early adolescence, affecting women two to three times more than men. The estimated cumulative lifetime incidence is 43% in women and 18% in men with a 15% prevalence in the United States and an 11.6% prevalence worldwide. This is an estimated 40 million people (about twice the population of New York) in the U.S. and 1.02 billion people worldwide. Migraine headaches continue to be a significant health and financial burden on people across the world.

The pathophysiology of migraine headaches is still not fully understood, but there have significant advances in understanding aspects of migraine headaches in the past several decades. Discovery of new proinflammatory mediators and vasoactive neuropeptides have become the focus of abortive and preventive migraine therapy (Curter, 2022). The focus of this literature review was to review the safety and efficacy of two new agents that specifically target recent discoveries in the pathophysiology of migraines.

Statement of the Problem

Migraine continues to be one of the most disabling medical conditions worldwide. The current standard of care for acute abortive therapy has a failure rate of 30-40% in patients and has many associated side effects and risks (Leroux et al., 2020). Many other medications used for prevention and abortive therapy in migraines were not specifically developed for migraine headaches. As our understanding of migraine pathophysiology has evolved, we have begun to develop new pharmacological therapies targeting various neurotransmitters and chemicals in hopes to develop more effective and safer therapy for the acute treatment of migraine headaches.

Research Question

What is the safety and efficacy of rimegepant and lasmiditan to placebo in aborting an acute migraine and how do these medications compare to one another?

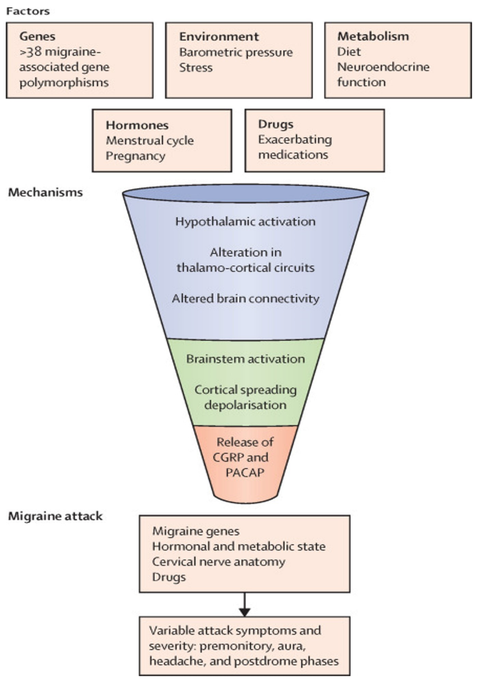
Literature Review

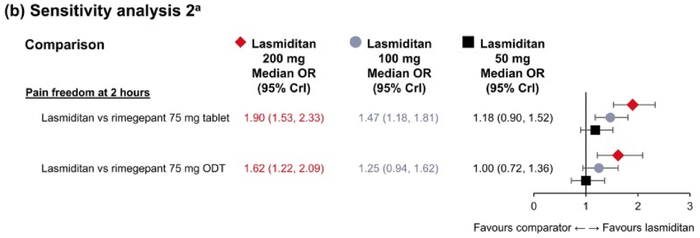
Safety and efficacy of rimegepant vs placebo

Marcus et al., 2014: Double blind, randomized, placebo controlled, single dose, dose ranging trial
- 812 participants, randomized to a rimegepant group of 10mg, 25mg, 75mg, 150mg, 300mg, 600mg, sumatriptan 100mg or placebo
- Participants achieving pain freedom at two hours post dose
  - Sumatriptan (p<0.001), 75mg (p<0.002), 150mg (p<0.001), and 300mg (p<0.002) groups reported to be superior to placebo with statistical significance
- Nausea most common adverse effect reported, approximately 1-4% across ALL groups

Lipton et al., 2019: Multicenter, double blind, phase 3 trial
- Participants completing trial in each group: rimegepant (538) vs placebo (542)
- Rimegepant 75 mg superior to placebo in providing freedom from pain at two hours post dose (19.6% vs 12%, p<0.001)
- Rimegepant superior to placebo in freedom from MBS at two hours post dose (37.6% vs 25.2%, p<0.001)
- Participants reporting an adverse evet
  - Nausea: rimegepant 1.8% vs placebo 1.1%

Croop et al., 2019: Double-blind, randomized, multicenter, phase 3 trial
- Participants completing acute phase in each group: rimegepant (679) vs placebo (689)
- Rimegepant 75 mg superior to placebo in providing freedom from pain at two hours post dose (21.2% vs 10.9%, p<0.0001)
- Rimegepant superior to placebo in freedom from MBS at two hours post dose (35.1% vs 26.8%, p<0.0009)
- Participants reporting adverse event
  - Nausea: rimegepant 2% vs placebo 1%





Safety and efficacy of lasmiditan vs placebo

Farkkila et al., 2012: Phase 2 randomized, placebo-controlled, parallel-group, dose ranging study
- 512 participants randomly assigned in following groups (# who completed study)
  - Placebo (81), 50mg (79), 100mg (81), 200mg (69), 400mg (68)
- Participants reporting freedom from pain at two hours post dose
  - Lasmiditan 200mg (p=0.032) and 400mg (p=0.0007) superior to placebo with statistical significance, all other doses were superior however not statistically significant
- Adverse events reported
  - Dizziness, paresthesia and fatigue were some of the most common adverse events reported and significantly higher in lasmiditan groups

Goadsby et al., 2019: Phase 3 randomized, placebo-controlled, double blinded
- Participants in each group
  - 200mg (528), 100mg (532), 50mg (556), placebo (540)
- Participants reporting freedom from pain at two hours post does
  - Lasmiditan 200 mg and 100 mg superior to placebo (p<0.001), 50 mg superior to placebo (p=0.003)
- Participants reporting freedom from most bothersome symptom to hours post dose
  - Lasmiditan 200 mg and 100 mg superior to placebo (p<0.001), 50 mg superior to placebo (p=0.009)
- Adverse events reported
  - Dizziness, paresthesia and fatigue were some of the most common adverse events reported and significantly higher in lasmiditan groups

Ashina et al., 2021: Randomized, controlled trial over four migraine attacks, multicenter phase 3
- Participants completing trial in each group: control (443), 100mg (408), 200mg (398)
- Participants reporting freedom from pain at two hours post dose
  - Lasmiditan 200mg and 100mg superior to placebo (p<0.001)
- Participants reporting freedom from most bothersome symptom at two hours post dose
  - Lasmiditan 200mg and 100mg superior to placebo (p<0.01 and p<0.001)
- Adverse events reported
  - Dizziness, paresthesia and fatigue were some of the most common adverse events reported and significantly higher in lasmiditan groups

Discussion

Rimegepant
- Rimegepant (when compared to placebo) has been shown to be statistically superior in providing freedom from pain at the two-hour mark. This was demonstrated through several trials with significant sample sizes
- Rimegepant 75 mg was shown to be statistically superior in providing freedom from most bothersome symptoms when compared to placebo
- Rimegepant demonstrated safety in short term, long term (up to 12 months) and repeated use when compared to placebo. Nausea and gastrointestinal upset were the most common side effects with reports in approximately 2-3% of the sample population. There were no serious cardiovascular events reported during any of the clinical trials where rimegepant was the main study medication
- Rimegepant was not shown to be the most effective oral agent in migraine abortion but was still superior to placebo in a meta-analysis
- There has been data to suggest that repeated use of rimegepant correlates with a decrease in monthly migraine days without an increase in rimegepant use or decreased effectiveness
- Rimegepant has been recently approved (May of 2021) for the use in migraine prevention, expanding upon the clinical use of its ability to reduce monthly migraines with limited side effects.
- Further studies are needed to evaluate the long-term effect of CGRP blockade, safety in those with established cardiovascular co-morbidities, efficacy, and safety in the elderly (over 65) and pediatric populations (less than 18) and direct comparisons to other acute migraine treatment medications

Lasmiditan
- Lasmiditan was shown to be superior to placebo in eliminating acute migraines
- Lasmiditan was shown to be superior in eliminating the most bothersome symptoms associated with migraine
- When compared to placebo, the side effects of lasmiditan were more prominent, especially CNS effects. Lightheadedness, dizziness, paresthesia, and fatigue were the most reported side effects. These side effects appeared to be more intense with higher doses and there were some indications that these side effects lessened over time as the medication was used more.
- There is currently a caution listed under the medication side effects to not drive or operate heavy machinery within eight hours of taking lasmiditan. This could potentially limit or discourage some people from taking this medication.
- Lasmiditan works on a different 5HT receptor, in theory it should not cause some of the chest heaviness or additional cardiovascular complications that have been theorized/experienced with the triptans. Cardiovascular or vasoconstrictive adverse events were not reported in trials where lasmiditan was the primary medication being studied.
- There have been no direct comparisons performed between lasmiditan and any other abortive therapies for migraine, however several meta-analyses have been performed. Lasmiditan was shown to be superior to placebo and CGRP receptor antagonists and some triptans, but overall, still inferior to the triptan class at providing pain freedom at the two-hour mark
- Further studies are needed to evaluate the safety in those with established cardiovascular co-morbidities, efficacy, and safety in the elderly (over 65) and pediatric populations (less than 18), direct comparisons to other acute migraine treatment medications and the safety of long-term use when it comes to CNS suppression and abuse potential.

Applicability to Clinical Practice

The American Headache Society (2021) recommends starting with NSAIDs, acetaminophen, non-opioid analgesics and/or caffeine combination products in the acute treatment of mild to moderate attacks and migraines specific treatments (triptans or ergots) for moderate to severe attacks. Treatment is recommended at onset to ensure effective pain management. In current clinical practice, lasmiditan and rimegepant are not recommended as first line abortive treatments by the American Headache Society. A patient must have a contraindication to using a triptan or have failed two oral triptans before coverage will be approved. These guidelines are important to keep in mind when dealing with patients who present with an initial onset of migraines or are dealing with refractory migraines. Although these medications are new, have been shown to be effective and are safe, they are not always the most cost-effective option for the patient. On the other hand, if there is a patient who has tried several different medications with no improvement or cannot use other first line medications due to side effects or contraindications rimegepant and/or lasmiditan are safe and effective alternatives.

References

Ailani, J., Burch, R. C., & Robbins, M. S. (2021). The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache: The Journal of Head and Face Pain*, *61*(7), 1021–1039. https://doi.org/10.1111/head.14153

Ashina, M., Reuter, U., Smith, T., Krikke-Workel, J., Klise, S. R., Bragg, S., Doty, E. G., Dowsett, S. A., Lin, Q., & Krege, J. H. (2021). Randomized, controlled trial of lasmiditan over four migraine attacks: Findings from the CENTURION study. *Cephalalgia : an international journal of headache*, *41*(3), 294–304. https://doi.org/10.1177/0333102421989232

Croop, R., Goadsby, P. J., Stock, D. A., Conway, C. M., Forshaw, M., Stock, E. G., Coric, V., & Lipton, R. B. (2019). 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 (London, England)*, *394*(10200), 737–745. https://doi-org.ezproxylr.med.und.edu/10.1016/S0140-6736(19)31606-X

DynaMed. Migraine in Adults. EBSCO Information Services. Accessed November 30, 2022. https://www.dynamed.com/condition/migraine-in-adults

Färkkilä, M., Diener, H. C., Géraud, G., Láinez, M., Schoenen, J., Harner, N., Pilgrim, A., Reuter, U., & COL MIG-202 study group (2012). Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *The Lancet. Neurology*, *11*(5), 405–413. https://doi.org/10.1016/S1474-4422(12)70047-9 doi-org.ezproxylr.med.und.edu/10.1177/0333102413500727

Goadsby, P. J., Wietecha, L. A., Dennehy, E. B., Kuca, B., Case, M. G., Aurora, S. K., & Gaul, C. (2019). Phase 3 randomized, placebo-controlled, double-blind study oflasmiditan for acute treatment of migraine (SPARTAN). *Brain : a journal of neurology*, *142*(7), 1894–1904. https://doi.org/10.1093/brain/awz134

Leroux, E., Buchanan, A., Lombard, L. et al. Evaluation of Patients with Insufficient Efficacy and/or Tolerability to Triptans for the Acute Treatment of Migraine: A Systematic Literature Review. Adv Ther 37, 4765–4796 (2020).https://doi.org/10.1007/s12325-020-01494-9

Lipton, R. B., Croop, R., Stock, E. G., Stock, D. A., Morris, B. A., Frost, M., Dubowchik, G. M., Conway, C. M., Coric, V., & Goadsby, P. J. (2019). Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. The New England journal of medicine, 381(2), 142–149. https://doi.org/10.1056/NEJMoa1811090

Marcus, R., Goadsby, P. J., Dodick, D., Stock, D., Manos, G., & Fischer, T. Z. (2014). BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia : an international journal of headache*, *34*(2), 114–125. https://

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