Rimegepant in the Treatment of Migraine Headache: The Importance of Comparator Treatments

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Guest Contributors

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Editor's Note: *You are reading the 76th installment of* Annals of Emergency Medicine *Journal Club. As the Journal Club enters its second decade of publication, we are making a number of changes to the format. The Journal Club format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med.* 2019;381:142-149.

What Question Did This Investigation Aim to Answer?

Is rimegepant, an oral calcitonin gene-related peptide receptor antagonist, a safe and effective treatment for acute migraines?

What Study Design Did the Authors Choose?

Design: Multicenter, double-blind, randomized, phase 3 clinical trial. ClinicalTrials.gov registry number: NCT03237845.

Setting: Outpatient settings (clinics, institutions, and private offices).

Population: Adults presenting with migraine headache, a greater than or equal to 1-year history of migraines with onset before aged 50 years, 2 to 8 migraine attacks of moderate to severe intensity per month, and any headache on less than 15 days per month. Patients with a history of any clinically significant or unstable medical condition were excluded from the study.

Intervention: One 75-mg dose of rimegepant or placebo, received at onset of migraine headache of moderate or severe intensity.

Primary and Secondary Outcomes: Coprimary outcomes of freedom from pain and freedom from patient's most bothersome symptom associated with the migraine 2 hours after intervention. Secondary outcomes included freedom from specific migraine symptoms, use of rescue medications, functional status, and sustained relief from pain.

Sponsors: Biohaven Pharmaceuticals (supplied trial agents, reviewed trial design, collected data, performed data management and analysis, and funded the medical writer who wrote the article).

How Did the Authors Interpret the Results?

Among 1,072 patients included in a modified intention-to-treat analysis, pain relief at 2 hours was 19.6% versus 12.0% for rimegepant and placebo, respectively (absolute difference 7.6%; 95% confidence interval 3.3% to 11.9%). Freedom from bothersome symptoms also favored rimegepant, 37.6% versus 25.2% (absolute difference 12.4%; 95% confidence interval 6.9% to 17.9%). Secondary outcomes in regard to symptom relief favored rimegepant, with similar absolute differences.

The most common adverse events were nausea and urinary tract infection, but these differences did not reach statistical significance. Elevated liver enzyme levels were observed more frequently in the rimegepant cohort, but this difference likewise did not reach statistical significance.

Migraine headaches treated with rimegepant resulted in a higher percentage of patients who were free of pain, bothersome symptoms, or both in comparison with placebo at 2 hours after administration.

How Might This Study Affect Your Clinical Practice in the Emergency Department?

Rimegepant was superior to placebo for the acute treatment of migraine headache. However, these results have minimal influence on clinical practice because there already exist numerous effective treatments. Any role for rimegepant for use in acute migraine in either general

clinical practice or emergency care requires additional prospective study and comparison with standard-of-care alternatives.

DISCUSSION POINTS

1. *The authors compared a novel drug with placebo. Under what circumstances is comparison with a placebo appropriate?*

Randomized controlled trials are widely considered the criterion standard in study design to establish an effect associated with an intervention. By definition, randomized controlled trial design requires that an intervention be compared with a control: an active comparator, no intervention, or placebo. It is widely agreed that comparison with placebo is acceptable when no proven intervention exists.[1,2] Placebo comparison is not acceptable in life-threatening conditions if there is an available treatment that is known to prolong life. However, the use of placebo for comparison in nonlife-threatening conditions, particularly when an accepted treatment exists, is controversial. The argument against the use of placebos in these circumstances is guided by principles set out by the Declaration of Helsinki: "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods." Thus, if an effective treatment exists, it should be prescribed to patients.[3]

Individuals arguing for placebo counter that, even in the presence of effective treatment, placebo control may be necessary when "there are compelling and scientifically sound methodological reasons for its use and the participants in the study will not face additional risks of serious or irreversible harm from exposure to placebo."[4] Even when a widely accepted treatment exists, some individuals argue that informed consent can be used to justify the use of placebo. However, research participants are likely to believe participation in a study will lead to benefit, and this therapeutic misconception may not be resolved simply by informed consent.[5] Patients exposed to a placebo when accepted active treatment exists must not be subjected to additional risks or harms, but in the absence of harm, placebo control would be reasonable.[6] The definition of harm, though, is less clear.

Despite the ethical issues surrounding placebo-controlled studies, there are numerous previous publications that violate the tenets of the Declaration of Helsinki, as well as the ideal of *primum non nocere*. Examples include research into the treatment of onchocerciasis with ivermectin, ondansetron in chemotherapy-induced emesis, angiotensin-converting enzyme inhibitors in congestive heart failure, and antihypertensive agents.[7] If a placebo-controlled approach is used, rationale for this design is necessary. However, Keranen et al found that a minority of randomized controlled trials (35%) actually do this and that the risk of placebo is rarely explained to patients (17%).[4]

There are a number of options with established efficacy for abortive therapy for migraines, including 3 that are considered first line: antidopaminergics, triptans, and nonsteroidal anti-inflammatory drugs.[8,9] Lipton et al stated that up to 66% of patients respond to triptans according to previous work.[10,11] They did not provide justification for the placebo-controlled methodology in the article, which is particularly important in the setting of effective alternative treatment. Although an argument can be made that treating migraines with placebo does not lead to long-term harm, patients with migraines often experience severe, debilitating pain, resulting in an inability to work or perform typical daily activities. The use of a placebo comparison additionally limits clinicians' interpretation of whether the novel drug is superior to standard migraine treatments. One option the authors could have instituted to avoid these issues would have been to offer all patients rescue therapy that could have been used at a certain point after pain onset.

Why Would Researchers Choose to Compare Their Drug With Placebo as Opposed to Standard Therapy?

There are a number of possible explanations for comparing a drug with placebo. The process can be used to establish efficacy and superiority of the new drug over no treatment, and superiority studies are useful in guiding clinician treatment choices. However, a noninferiority design could be used to compare the new drug with established treatment if the new drug had benefits over the previous treatment (eg, ease of use, cost, reduced adverse effects). Some individuals argue that historically, the Food and Drug Administration has withheld drug approval when placebo controls were not used in establishing efficacy. However, these concerns are likely exaggerated.[5,12]

The most obvious reason for using a placebo-controlled methodology is that pharmaceutical companies may believe "it is [in] their interest to compare new drugs with placebo rather than existing therapy, even when better information for patients and physicians would be provided by an active control."[12] Demonstrating superiority to placebo is easier than demonstrating superiority to an effective therapy and is more likely to result in positive findings for the drug and

the pharmaceutical company. This, however, comes at the harm of patients and adds little to our understanding of treatment for the disease. Additionally, it likely leads to increased research and development costs because subsequent studies comparing the new drug with active, accepted treatments would be required before clinicians could use the new drug.

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IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Portal vein thrombosis. This patient had portal vein thrombosis extending to the splenic confluence and superior mesenteric vein, with resultant mesenteric ischemia. She began receiving heparin, and urgent laparotomy demonstrated 60 cm of ischemic small bowel that was successfully resected, with no complications.

Portal vein thrombosis, typically associated with cirrhosis, malignancy, myeloproliferative disease, and coagulation disorders, is a rare complication of oral contraceptive use.[1] The patient had no *JAK2* mutation or myeloprolierative mutations, making oral contraceptive the likely cause of her thrombosis. In experienced hands, ultrasonography is reported to have a sensitivity of 73% to 100% and specificity of 88% to 99% for the detection of portal vein thrombosis.[2,3]

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