Effect of Calcitonin Gene-Related Peptide Receptor Antagonists on Migraine Treatment: A Meta-Analysis

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Abstract

Background: The pathophysiology of migraine has been researched incessantly, and it has been suggested that calcitonin gene-related peptide (CGRP) is associated with migraine attacks. CGRP receptor blockers are attracting attention for migraine prevention and treatment of acute episodes, and CGRP receptor antagonists have been shown to be effective in treating acute migraine headaches. This meta-analysis aimed to assess the effect of available CGRP receptor antagonists, focusing on their therapeutic doses for acute migraine treatment.

Methods: We performed a systematic search of MEDLINE (from inception to March 2021) and EMBASE (from inception to March 2021) for English publications using the keywords “migraine” and “Calcitonin gene-related peptide,” limited to human studies.

Results: Five studies that focused on examining the effects of CGRP receptor antagonists on acute migraine treatment met the eligibility criteria for this meta-analysis. The pooled analysis demonstrated that the CGRP receptor antagonist improved freedom from pain (OR=2.066, 95% confidence interval [CI] 1.766–2.418, I²=0%), absence of bothersome symptoms (OR=1.606, 95% CI=1.408–1.830, I²=0%), pain relief (OR=1.791, 95% CI=1.598–2.008, I²=0%), and freedom from nausea (OR=1.361, 95% CI=1.196–1.548, I²=0%), significantly more than the placebo.

Conclusions: CGRP receptor antagonists are effective for acute migraine treatment and are expected to be used clinically as emerging therapeutic agents.

Background

Migraine is one of the prevalent disorders worldwide according to the 2010 Global Burden of Disease study [1]. Migraine is characterized by unilateral throbbing and moderate to severe headache accompanied by nausea, vomiting, photophobia, and phonophobia. Severe headache symptoms and associated symptoms, including nausea and vomiting, lead to disability in migraineurs and affect public health. Although the pathophysiology of migraine is not fully understood, knowledge has gradually evolved. The activation of the trigeminovascular pathway is regarded as an important process in the development of migraine pain [2–4]. Calcitonin gene-related peptide (CGRP) is considered an important neuropeptide that initiates activation of the trigeminovascular pathway [2]. CGRP levels are elevated in the external jugular vein during migraine attacks, and CGRP levels are decreased after the use of sumatriptan for the acute treatment of migraine [5, 6].

CGRP, which is a neuropeptide containing 37 amino acids, was discovered in 1982 [7, 8]. In humans, two isoforms exist: α and βCGRP. αCGRP is the principal form found in the central and peripheral nervous systems, while βCGRP is most abundantly found in the enteric nervous system [9]. The association between migraine pathophysiology and CGRP has been researched for decades, and CGRP receptor antagonists have been developed as acute treatment drugs for at least 10 years [5, 10, 11]. However, some CGRP receptor antagonists have been discontinued or delayed in clinical trials as a treatment for
acute migraine because of liver toxicity (telcagepant, BI44370TA, MK3207) and low oral bioavailability (olcegepant) [12–14]. Two recent oral CGRP receptor antagonists (ubrogepant and rimegepant) have been approved by the US Food and Drug Administration, and one intranasal CGRP receptor antagonist (zavegepant, BHA-3000) has shown positive preliminary data [15–17]. The development and use of triptans represented an unprecedented revolution in 1991, which was the first successful attempt at mechanism-driven migraine treatment [18]. Considering the history of the development of acute treatments for migraine, approximately 30 years after triptan was introduced and available, new mechanism-driven drugs were approved and began to be used. In the future, CGRP receptor antagonists will continue to attract attention as an acute treatment for migraine by headache specialists [19]. Due to this interest, several meta-analyses on CGRP receptor antagonists have been published. However, previous meta-analyses have limitations that include the effects of CGRP receptor antagonists that were discontinued or delayed in clinical trials due to hepatotoxicity or drug characteristics. Therefore, in the present study, a meta-analysis of the effects of the treatment of acute migraine was performed by focusing on the therapeutic doses of CGRP receptor antagonists that are available in the clinical setting or that are actively being developed, except for CGRP antagonists whose development has been discontinued or delayed.

**Methods**

**Data Search and Study Selection**

We performed systematic searches of the MEDLINE (from inception to January 27, 2021) and EMBASE (from inception to January 27, 2021) databases for publications in English using the terms “migraine” and “calcitonin gene-related peptide.” All searches were limited to human studies. All primary studies examining the effects of CGRP in patients with migraines were conducted. Review articles, abstracts, and editorials were excluded, and duplicate data were removed. When more than one study was published from the same institution, only the report with the highest number of patients relevant to this study was included. Two authors independently searched the databases, screened potential studies, and reviewed the data. Discrepancies were resolved by consensus.

**Data Extraction and Statistical Analysis**

Two reviewers extracted relevant information from the publications, including the following: first author, year of publication, country, study design, total number of cases, number of positive outcomes, and dose of CGRP receptor antagonist. The endpoints were evaluated 2 hours after administering CGRP receptor antagonist or placebo for 1) freedom from pain, 2) absence of bothersome symptoms, 3) pain relief, and 4) freedom from nausea. The effect size was odds ratio (OR), defined as the ratio of the odds of endpoints between the CGRP receptor antagonist and placebo. Heterogeneity among studies was assessed using Cochran’s $Q$ and $I^2$ statistics. The Mantel-Haenszel method for calculating the weighted pooled OR was used for the fixed-effect model [20]. The heterogeneity statistic was incorporated to
calculate the summary OR using the random-effects model [21]. Data from each study were analyzed using MedCalc Statistical Software version 14.12.0 (MedCalc Software, Ostend, Belgium).

**Results**

**Study Characteristics**

The electronic search identified 2,885 articles. Non-human studies (n = 850), conference abstracts (n = 1,369), and non-English studies (n = 101) were excluded. In total, 530 studies that did not meet the inclusion criteria based on their titles and abstracts were excluded. After reviewing the full text of the remaining 35 articles, 5 studies were eligible for inclusion in the study [11, 22–25]. Two studies involved the use of ubrogepant [22, 25], and three involved the use of rimegepants [11, 23, 24]. The detailed procedure of inclusion is shown in Fig. 1, and the characteristics of the included studies are summarized in Table 1.

**Ubrogepant**

The effect of ubrogepant was reported in 2 studies with both 50 and 100 mg (22, 25)(Table 2). The pooled analysis showed that ubrogepant 50 mg was effective in freedom from pain (OR = 1.913, 95% CI = 1.668–2.193, I² = 0%) (Fig. 2)
1.365–2.681, $I^2 = 0\%$), pain relief (OR = 1.608, 95% CI = 1.265–2.044, $I^2 = 0\%$), and freedom from nausea (OR = 1.403, 95% CI = 1.091–1.805, $I^2 = 0\%$). The pooled analysis showed that ubrogepant 100 mg was effective in freedom from pain (OR = 2.218, 95% CI = 1.596–3.081, $I^2 = 36.43\%$), pain relief (OR = 1.670, 95% CI = 1.317–2.118, $I^2 = 0\%$), and freedom from nausea (OR = 1.375, 95% CI = 1.073–1.763, $I^2 = 0\%$).

### Table 2

| CGRP receptor antagonist | Dose (mg) | Endpoint | No. of studies | OR  | 95% CI of OR | Heterogeneity, $I^2(\%)$ |
|--------------------------|-----------|----------|----------------|-----|--------------|--------------------------|
|                          |           | pain relief at 2 hr | 2 | 1.608 | 1.265–2.044 | 0 |
|                          |           | freedom from nausea at 2 hr | 2 | 1.403 | 1.091–1.805 | 0 |
| 100                      |           | freedom from pain at 2 hr | 2 | 2.218 | 1.596–3.081 | 36.43 |
|                          |           | pain relief 2 at hr | 2 | 1.670 | 1.317–2.118 | 0 |
|                          |           | freedom from nausea at 2 hr | 2 | 1.375 | 1.073–1.763 | 0 |
| Rimegepant               | 75        | freedom from pain at 2 hr | 3 | 2.068 | 1.674–2.554 | 0 |
|                          |           | absence of the bothersome Sx at 2 hr | 2 | 1.606 | 1.350–1.910 | 12.33 |
|                          |           | pain relief at 2 hr | 3 | 1.930 | 1.653–2.252 | 0 |
|                          |           | freedom from nausea at 2 hr | 3 | 1.330 | 1.101–1.605 | 24.23 |

CGRP, calcitonin gene-related peptide; CI, confidence interval; OR, odds ratio; Sx, symptom; hr, hour

### Rimegepant

The effect of rimegepant was reported in three studies with 75 mg (11, 23, 24) (Table 2). In a pooled analysis, rimegepant was effective in freedom from pain (OR = 2.068, 95% CI = 1.674–2.554, $I^2 = 0\%$), absence of bothersome symptoms (OR = 1.606, 95% CI = 1.350–1.910, $I^2 = 12.33\%$), pain relief (OR = 1.930, 95% CI = 1.653–2.252, $I^2 = 0\%$), and freedom from nausea (OR = 1.330, 95% CI = 1.101–1.605, $I^2 = 24.23\%$).

### Discussion
CGRP is an important neurotransmitter associated with migraine attacks, and recent studies regarding migraine management, including prevention and acute treatment, are targeted at the CGRP receptor pathway. This study investigated the effect of a CGRP receptor antagonist for the acute treatment of migraine attacks by meta-analysis of five randomized controlled trials, including two CGRP receptor antagonists (ubrogepant and rimegepant). We found that small molecular receptor antagonists increased the odds of having pain freedom by 106.6% compared to the placebo. According to the prescribing information, 50 or 100 mg of ubrogepant and 75 mg of rimegepant are being prescribed for acute migraine treatment. The present study demonstrated that 50 and 100 mg of ubrogepant and 75 mg of rimegepant were more effective than the placebo for acute migraine treatment in terms of pain freedom, headache relief, and nausea freedom at 2 hours after treatment. In addition, ubrogepant 50 mg and rimegepant 75 mg proved more effective than placebo regarding the absence of most bothersome symptoms at 2 hours.

CGRP receptor antagonists can be used in migraineurs who do not sufficiently control acute headaches with triptan or in migraineurs with medication overuse headache (MOH) due to frequent use of acute treatment medication. Triptans are the first-line therapy for acute migraine. However, up to 40% of migraineurs are not responsive to oral triptans [26]. There is insufficient evidence that CGRP receptor antagonists are superior to triptans in terms of efficacy; however, they can be used for those who have not been effectively treated with triptans. Furthermore, CGRP receptor antagonists have been suggested to reduce the risk of developing MOH in animal studies. Ubrogepant and sumatriptan showed efficacy as acute medications for bright light stress and nitric oxide donor-induced cephalic allodynia in a preclinical rat model of MOH, consistent with their clinical efficacy in the acute treatment of migraine. However, unlike sumatriptan, ubrogepant did not result in cutaneous allodynia and latent sensations, which may suggest that ubrogepant is less associated with the development of MOH than sumatriptan [27]. In addition, comparing the risk of MOH between CGRP receptor antagonists (olcegant) and 5-H$_{1F}$ (LY344864) receptor antagonists showed different results. Persistent exposure of mice to the 5-HT$_{1F}$ agonist produced a significant reduction in the hind paw and orofacial mechanical withdrawal thresholds but not olcegant [28]. This result also suggests that CGRP receptor antagonists have a lower risk of developing MOH than 5-H$_{1F}$.

One of the most important potential adverse side effects of CGRP receptor blockade, including CGRP receptor antagonist, CGRP antibody, and CGRP receptor antibody, is a vasoconstrictor effect in cerebral and coronary arteries, whether or not it leads to ischemic events [29]. CGRP has been shown to act as a neuroprotector by increasing blood flow during severe hypertension and cerebral ischemia in animals [30, 31]. Previous research has reported cardiovascular safety issues of CGRP receptor blockades [32]. The development of telcagepant was stopped due to hepatotoxic concerns and was not included in the present study; telcagepant was well tolerated in those with stable angina [33]. A monoclonal antibody against the CGRP receptor (erenumab) demonstrated a cardiovascular safety profile in patients with stable angina. This study suggests that CGRP receptor blockers do not worsen myocardial ischemia [34]. However, there is a debate that this study has limitations in the study design considering the participants,
pharmacokinetics, and pharmacodynamics [35]. The study found that about 78% of participants were male, and it was difficult to reflect the characteristics of migraine, which is more prevalent in women. Participants in the study were those with stable angina, and there were limitations in evaluating the distal section of the coronary bed, in which CGRP highly affects the vasodilator. In addition, the effect of the block of the CGRP receptor on the coronary artery was also evaluated at an early time when considering the pharmacodynamics of erenumab. Although CGRP receptor blockades have recently been approved and can be used for prevention and acute treatment of migraine, cardiovascular adverse side effects have not been disclosed with these drugs, the results for migraineurs regarding the safety of vasoconstriction issues are not sufficient [32].

To the best of our knowledge, this is the first meta-analysis to evaluate only the available CGRP receptor antagonist in a practical clinical setting for acute migraine treatment. However, this study has some limitations. First, a relatively small number of studies were included in the analysis. The International Headache Society has recommended evidence-based guidelines for the quality of clinical trials for the treatment of headache disorders. The evaluation of the most bothersome symptoms is suggested as a co-primary endpoint in the guidelines [36]. However, the results of 100 mg of ubrogepant for the most bothersome symptoms were found in only one article, and a meta-analysis could not be conducted. Second, as studies were restricted to English-language publications, there was language bias. Third, records were searched on only two major databases: MEDLINE and EMBASE.

**Conclusion**

This meta-analysis suggests that small molecular CGRP receptor antagonists are more effective for acute migraine treatment than placebo. Small molecular CGRP receptor antagonists are expected to play an important a role as triptans in the treatment of acute migraine.

**Abbreviations**

CGRP, calcitonin gene-related peptide; OR, odds ratio; CI, confidence interval; MOH, medication overuse headache

**Declarations**

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Not applicable.

**Author contributions**

Conceptualization: Jiyoung Kim. Kyoungjune Pak

Writing the original draft: Jiyoung Kim, Gha-Hyun Lee, Kyoungjune Pak
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Availability of data and materials

Data and materials used for this meta-analytical review can be shared, until 2 years after publication, upon reasonable request to the corresponding author from qualified researchers for purposes of replicating procedures and results.

Ethics approval and consent to participate

Ethical approval was not required as this is a literature-based study.

Consent for publication

Not applicable.

Competing interests

Jiyoung Kim is principal investigator in studies sponsored by Allergan

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Figures

Figure 1

Flowchart of the procedure for identifying eligible studies
Figure 2

Forest plot for the outcome of CGRP receptor antagonists—freedom from pain (A), absence of the bothersome symptom (B), pain relief (C), and freedom from nausea (D) at 2 hours post-dose. The results are expressed as odds ratios and 95% confidence intervals. CGRP, calcitonin gene-related peptide