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

Jiyoung Kim (✉ bijoiukim78@gmail.com)

Pusan National University School of Medicine <https://orcid.org/0000-0001-7592-2921>

Kyoungjune Pak

Pusan National University Hospital

Gha-Hyun Lee

Pusan National University Hospital

Jae Wook Cho

Pusan National University Yangsan Hospital

Hyun-Woo kim

Pusan National University Yangsan Hospital

Research article

Keywords: migraine, calcitonin gene-related peptide, gepants, acute treatment

Posted Date: June 11th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-603934/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

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, $I^2=0\%$), absence of bothersome symptoms (OR=1.606, 95% CI=1.408–1.830, $I^2=0\%$), pain relief (OR=1.791, 95% CI=1.598–2.008, $I^2=0\%$), and freedom from nausea (OR=1.361, 95% CI=1.196–1.548, $I^2=0\%$), 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 β CGRP. α CGRP is the principal form found in the central and peripheral nervous systems, while β CGRP 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.

Table 1
Characteristics of the included studies

CGRP receptor antagonist	Author	Dose (mg)	Year of publication	Total number of patients	
				with treatment	with placebo
Ubrogepant	Dodick et al. [22]	50/100	2019	423/448	456
	Voss et al. [25]	50/100	2016	106/102	113
Rimegepant	Marcus et al. [24]	75	2014	86	203
	Croop et al. [11]	75	2019	669	682
	Lipton et al. [23]	75	2019	537	535
CGRP, calcitonin gene-related peptide					

CGRP Receptor Antagonist in Migraines

With both ubrogepant (50 and 100 mg) and rimegepant (75 mg), the pooled analysis showed that CGRP receptor antagonists were effective in freedom from pain (OR = 2.066, 95% confidence interval [CI] 1.766–2.418, $I^2 = 0\%$), absence of bothersome symptoms (OR = 1.606, 95% CI = 1.408–1.830, $I^2 = 0\%$), pain relief (OR = 1.791, 95% CI = 1.598–2.008, $I^2 = 0\%$), and freedom from nausea (OR = 1.361, 95% CI = 1.196–1.548, $I^2 = 0\%$) (Fig. 2)

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 =

1.365–2.681, $I^2 = 0\%$), 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
Subgroup analyses according to the therapeutic dose of CGRP receptor antagonists

CGRP receptor antagonist	Dose (mg)	Endpoint	No. of studies	OR	95% CI of OR	Heterogeneity, I ² (%)
	100	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
		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 2hr	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-HT_{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-HT_{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 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

Acknowledgements

Not applicable.

Author contributions

Conceptualization: Jiyoung Kim. Kyoungjune Pak

Writing the original draft: Jiyoung Kim, Gha-Hyun Lee, Kyoungjune Pak

Writing the review and editing: Jiyoung Kim, Gha-Hyun Lee, Jae Wook Cho, Hyun-Woo Kim, and Kyoungjune Pak

Funding

There are no sources of funding to declare

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

Author details

¹Department of Nuclear Medicine and BioMedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea, ²Department of Neurology and BioMedical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea ³Department of Neurology, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea.

References

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380(9859):2197–2223
2. Dodick DW (2018) A Phase-by-Phase Review of Migraine Pathophysiology. *Headache* 58(Suppl 1):4–16
3. Charles A (2018) The pathophysiology of migraine: implications for clinical management. *Lancet Neurol* 17(2):174–182

4. Erdener SE, Dalkara T (2014) Modelling headache and migraine and its pharmacological manipulation. *Br J Pharmacol* 171(20):4575–4594
5. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 28(2):183–187
6. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 33(1):48–56
7. Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM (1982) Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products. *Nature* 298(5871):240–244
8. Russell FA, King R, Smillie SJ, Kodji X, Brain SD (2014) Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev* 94(4):1099–1142
9. Edvinsson L, Haanes KA, Warfvinge K, Krause DN (2018) CGRP as the target of new migraine therapies - successful translation from bench to clinic. *Nat Rev Neurol* 14(6):338–350
10. Edvinsson L (1985) Functional role of perivascular peptides in the control of cerebral circulation. *Trends Neurosci* 8:126–131
11. Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG et al (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* 394(10200):737–745
12. Xu F, Sun W (2019) Network Meta-Analysis of Calcitonin Gene-Related Peptide Receptor Antagonists for the Acute Treatment of Migraine. *Front Pharmacol* 10:795
13. Ha DK, Kim MJ, Han N, Kwak JH, Baek IH (2021) Comparative Efficacy of Oral Calcitonin-Related Peptide Antagonists for the Treatment of Acute Migraine: Updated Meta-analysis. *Clin Drug Investig* 41(2):119–132
14. Mathew PG, Klein BC. Getting to the Heart of the Matter: Migraine, Triptans, DHE, Ditans CGRP, Antibodies, First/Second-Generation Gepants, and Cardiovascular Risk. *Headache*. 2019;59(8):1421-6
15. Scott LJ. Ubrogapant (2020) First Approval *Drugs* 80(3):323–328
16. Scott LJ. Rimegepant (2020) First Approval *Drugs* 80(7):741–746
17. Moreno-Ajona D, Pérez-Rodríguez A, Goadsby PJ. Small-molecule CGRP receptor antagonists: A new approach to the acute and preventive treatment of migraine. *Medicine in Drug Discovery*. 2020:100053
18. Humphrey PP (2008) The discovery and development of the triptans, a major therapeutic breakthrough. *Headache: The Journal of Head Face Pain* 48(5):685–687
19. Do TP, Guo S, Ashina M (2019) Therapeutic novelties in migraine: new drugs, new hope? *J Headache Pain* 20(1):37
20. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22(4):719–748

21. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* 7(3):177–188
22. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM et al (2019) Ubrogapant for the Treatment of Migraine. *N Engl J Med* 381(23):2230–2241
23. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M et al (2019) Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. *N Engl J Med* 381(2):142–149
24. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ (2014) BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia* 34(2):114–125
25. Voss T, Lipton RB, Dodick DW, Dupre N, Ge JY, Bachman R et al (2016) A phase IIb randomized, double-blind, placebo-controlled trial of ubrogapant for the acute treatment of migraine. *Cephalalgia* 36(9):887–898
26. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ (2001) Oral triptans (serotonin 5-HT_{1B/1D}) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 358(9294):1668–1675
27. Navratilova E, Behraves S, Oyarzo J, Dodick DW, Banerjee P, Porreca F (2020) Ubrogapant does not induce latent sensitization in a preclinical model of medication overuse headache. *Cephalalgia* 40(9):892–902
28. Saengjaroentharn C, Strother LC, Dripps I, Sultan Jabir MR, Pradhan A, Goadsby PJ et al (2020) Differential medication overuse risk of novel anti-migraine therapeutics. *Brain* 143(9):2681–2688
29. Hsu Chen C, Chang CY, Yang MC, Wu JH, Liao CH, Su CP et al (2019) The Impact of Emergency Interventions and Patient Characteristics on the Risk of Heart Failure in Patients with Nontraumatic OHCA. *Emerg Med Int* 2019:6218389
30. Moskowitz MA, Sakas DE, Wei EP, Kano M, Buzzi MG, Ogilvy C et al (1989) Postocclusive cerebral hyperemia is markedly attenuated by chronic trigeminal ganglionectomy. *Am J Physiol* 257(5 Pt 2):H1736–H1739
31. Sakas DE, Moskowitz MA, Wei EP, Kontos HA, Kano M, Ogilvy CS (1989) Trigemino-vascular fibers increase blood flow in cortical gray matter by axon reflex-like mechanisms during acute severe hypertension or seizures. *Proc Natl Acad Sci U S A* 86(4):1401–1405
32. Bigal ME, Walter S, Rapoport AM (2015) Therapeutic antibodies against CGRP or its receptor. *Br J Clin Pharmacol* 79(6):886–895
33. Chaitman BR, Ho AP, Behm MO, Rowe JF, Palcza JS, Laethem T et al (2012) A randomized, placebo-controlled study of the effects of telcagepant on exercise time in patients with stable angina. *Clin Pharmacol Ther* 91(3):459–466
34. DePre C, Antalík L, Starling A, Koren M, Eisele O, Lenz RA et al (2018) A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina. *Headache* 58(5):715–723
35. Rubio-Beltrán E, Duncker D, Villalón C (2018) Is CGRP Receptor Blockade Cardiovascularly Safe? Appropriate Studies Are Needed. *Headache* 58(8):1257–1258

36. Diener HC, Tassorelli C, Dodick DW, Silberstein SD, Lipton RB, Ashina M et al (2019) Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia 39(6):687–710

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