Recent advances in targeting calcitonin gene-related peptide for the treatment of menstrual migraine
A narrative review
Yan Jiang, MMed*, Zhen-Lun Huang, BMed

Abstract
Menstrual migraine (MM) has a longer duration and higher drug resistance than non-perimenstrual migraine. Calcitonin gene-related peptide (CGRP) and CGRP receptors are expressed in the peripheral and central nervous systems throughout the trigeminovascular system. The CGRP/CGRP receptor axis plays an important role in sensory physiology and pharmacology. CGRP receptor antagonists and anti-CGRP monoclonal antibodies (mAbs) have shown consistent efficacy and tolerability in the prevention of chronic or episodic migraine and are now approved for clinical use. However, few studies have reported the use of these drugs in MM, and no specific treatment for MM has been approved. This review aimed to shed light on the recent advances in targeting calcitonin gene-related peptides for the treatment of menstrual migraines in PubMed. In this review, we first discuss the axis of the CGRP/CGRP receptor. We then discuss the role of CGRP receptor antagonists and anti-CGRP mAbs in MM treatment. Finally, we discuss the role of the combination of anti-CGRP mAbs and CGRP receptor antagonists in migraine treatment and the drugs that inhibit CGRP release. Altogether, the anti-CGRP mAbs or CGRP receptor antagonists showed good efficacy and safety in the treatment of MM.

Abbreviations: AM = Adrenomedullin, AMY = Amylin, CGRP = Calcitonin gene related peptide, CGRP-RAs = CGRP receptor antagonists, CLR = CT receptor-like receptor, CT = Calcitonin, CTR = CT receptor, DILI = drug-induced liver injury, GPCR = G-protein coupled receptors, mAbs = monoclonal antibodies, MM = menstrual migraine, RAMP1 = transmembraneprotein 1.

Keywords: calcitonin gene-related peptide, CGRP receptors, menstrual migraine, treatment

1. Introduction
Menstrual migraine (MM) has a longer duration and higher drug resistance than non-perimenstrual migraine. Patients with MM who do not respond to acute treatment may be suitable for either short-term or long-term preventive treatments.[1] The drugs for short-term prevention of MM include triptans, cyclooxygenase-2 inhibitors, estrogen supplementation, and nonsteroidal anti-inflammatory drugs, which may delay rather than prevent attacks.[1] Topiramate can be used for the long-term prevention of MM, which can reduce the frequency but not the duration or severity of perimenstrual attacks.[2] It is contraindicated for hormonal contraceptives containing estrogens because of its limited effectiveness and increased risk of stroke.[3-5] It is also contraindicated for women with migraine with or without aura, who are smokers and/or aged 35 or older treated with exogenous estrogens.[6,7] So nonhormonal and long-term preventive treatments should be explored for MM.

Calcitonin gene-related peptide (CGRP) and CGRP receptors are expressed in the peripheral and central nervous systems throughout the trigeminovascular system. The CGRP/CGRP receptor axis plays an important role in sensory physiology and pharmacology. CGRP receptor antagonists and anti-CGRP monoclonal antibodies (mAbs) have shown consistent efficacy and tolerability in the prevention of chronic or episodic migraine and are now approved for clinical use.[8-10] However, only a few studies have reported the use of these drugs in MM. Currently, no specific treatment for MM has been approved to date. Therefore, recent advances in targeting calcitonin gene-related
peptides for the treatment of menstrual migraines were reviewed. In this review, we first discuss the axis of the CGRP/CGRP receptor. We then discuss the role of CGRP receptor antagonists and anti-CGRP mAbs in MM treatment. Finally, we discuss the role of the combination of anti-CGRP mAbs and CGRP receptor antagonists in migraine treatment and the drugs that inhibit CGRP release. This study did not involve the patients' private information, so this review did not require ethical approval.

2. Methods

We searched for relevant articles in PubMed (date: January 1, 2016 to August 31, 2021) using the following terms: “menstrual migraine and calcitonin gene-related peptide” (N = 14), “menstrual migraine and CGRP receptor antagonist” (N = 3), “menstrual headache and calcitonin gene-related peptide” (N = 10), “menstrual headache and CGRP receptor antagonist” (N = 3), “perimenstrual migraine and calcitonin gene-related peptide” (N = 2), and “perimenstrual migraine and CGRP receptor antagonist” (N = 2). A total of 34 articles were retrieved from the database. We carefully reviewed the remaining articles and excluded overlapped same article, not accessible and no clinical case. Then, a total of 3 case reports (3492 patients) were used to analyze. It is not necessary for the approval of institutional review board because this is an evidence-based narrative review.

2.1. The axis of CGRP/CGRP receptor

CGRP is a peptide consist of 37-amino acid. It is one of the members of a peptide family includes CGRP and adrenomedullin (AM), calcitonin (CT), and amylin (AMY). αCGRP and βCGRP are the two forms of CGRP in humans. αCGRP is produced by alternate splicing of the CT gene, and βCGRP has a separate genetic origin. αCGRP is highly expressed in sensory neurons and βCGRP is expressed in the enteric nervous system.

The CGRP receptor is a member of the family B G-protein-coupled receptors (GPCRs). The CGRP receptor includes a single transmembrane protein 1 (RAMP1) and a multimeric complex composed of seven transmembrane GPCRs with CT receptor-like receptor (CLR) domains. RAMPs include RAMP1, RAMP2, and RAMP3. CLR can partner with any one of the RAMPs and produces ligand specificity that interacts with a specific RAMP. CLR with RAMP1 forms a CGRP receptor CLR with RAMP2 or RAMP3 produces adrenomedullin AM1 and AM2 receptors, respectively. RAMPs can also form heteromers with CT receptors (CTRs). The forms of AMY receptors AMY1, AMY2, and AMY3 are CTRs linked to RAMP1, RAMP2, and RAMP3, respectively. RAMP1 residue tryptophan 84.

CGRP and CGRP receptors are expressed in the peripheral and central nervous systems throughout the trigeminovascular system. The CGRP/CGRP receptor axis plays an important role in sensory physiology and pharmacology. CGRP is a potent vasodilator and mediator of pain signal transmission after activation of trigeminal sensory nerve fibers. The concentration of CGRP increased in the external jugular venous blood during a migraine attack compared to that during a non-migraine attack. The CGRP level was reduced with migraine relief by treatment. These findings support the potential role of CGRP in migraine. However, CGRP may prolong activation of trigeminal pathways and cause episodic migraine into chronic migraine, which leads to fewer treatment options. Therefore, blocking the axis of the CGRP/CGRP receptor could be a possible treatment for migraine.

2.2. CGRP receptor antagonists in MM treatment

CGRP receptor antagonists (CGRP-RAs) can block the initial CGRP peptide binding event and subsequent receptor activation by binding to CGRP receptors through a hydrophobic pocket formed by CLR and RAMP 1. In the clinic, olcegepant (BIBN4096BS) as the first CGRP-RA can completely block both CGRP and AMY1 receptors. All the next-generation oral CGRP-RAs including telcagepant (MK-0974), MK-3207, rimegepant (BMS-927711), ubrogepant (MK-1602), and atogepant (AGN-241689) have activity against the AMY1 receptor at therapeutic plasma concentrations. The olcegepant (BIBN4096BS) also has antagonist activity of the CGRP receptor, which is less selective for the CGRP receptor than commonly reported.

The olcegepant (BIBN4096BS) is the first non-peptide CGRP-RA that develops and tests in humans and is effective in the acute treatment of migraine. However, olcegepant can only be used as an acute antimigraine therapeutic and is poorly absorbed after oral administration because of its high molecular weight and high polarity with several H-bond donors, which leads to limited further development. Small-molecule oral CGRP-RAs have been developed and shown to be effective against migraine. These CGRP-RAs included telcagepant (MK-0974, MK-3207, rimegepant (BMS927711), BI-443707A, ubrogepant, and atogepant.

It has been extensively studied on migraine pain mechanisms, potential benefits, and limitations of CGRP modulation in the acute treatment of migraine for telcagepant. The Telcagepant was also used as a headache prophylaxis with MM. Patients with MM were randomized to receive telcagepant or placebo in a 2:1 ratio to evaluate the safety and efficacy of headache prophylaxis. A telcagepant with a dose of 140 mg was used for seven consecutive days peri-menstrually. This study showed that telcagepant cannot reduce the monthly headache frequency. However, it can reduce the number of days of perimenstrual headaches. Approximately 2.5% and 2.7% of patients were discontinued because of adverse events for the telcagent and placebo, respectively.

However, many small molecule CGRP-RAs in registration were halted by safety with unacceptable drug-induced liver injury (DILI). The hepatotoxic effects of telcagepant were not observed with intermittent use for 18 months for the acute treatment of migraine. However, hepatotoxic effects can develop in chronic or when intensive use for migraine prevention or MM. At present, only a few reports have shown CGRP-RAs in the treatment of MM. Therefore, further studies should explore the
role of CGRP-RAs in the treatment of MM. Toxicity should also be studied.

2.3. Anti-CGRP mAbs in MM treatment
Small oral molecules are generally preferred for acute treatment. However, antibodies have some important advantages over small-molecule drugs, especially for chronic treatment because of their long-circulating plasma half-lives (weeks) and low toxicity. The anti-CGRP mAbs as potential migraine therapeutics by early human experimental research could nevertheless induce a migraine attack. However, some studies have shown that anti-CGRP mAbs are effective for treating migraine and CGRP-induced headaches. There are four CGRP mAbs that have been approved by FDA and showed efficacy in the prevention of frequent episodic and chronic migraine. These approved CGRP mAbs included galcanezumab, erenumab, eptinezumab, and fremanezumab in episodic migraine and chronic migraine.[8,9]

Data on the role of anti-CGRP mAbs in MM are rare. Recently, a report compared the difference between menstrual and non-menstrual women with chronic migraine with erenumab treatment. Total of 18 women with 11 erenumab responders and 7 erenumab non-responders were enrolled in this study. A total of 103 menstrual cycles and 2926 days were observed. The results showed that, for responders or non-responders, the proportion of headache days was higher on menstrual days than on premenstrual/non-menstrual days. Similarly, it was higher on menstrual days than on premenstrual or non-menstrual days with erenumab non-responders. Therefore, even when treated with erenumab, migraine is more frequent than outside menstrual days.

Another study on the efficacy and safety of erenumab in the prevention of MM has also been reported. The patients were divided into three groups: placebo, erenumab 70 mg, and erenumab 140 mg. The drugs were administered subcutaneously once monthly for the 6-month. Monthly migraine days were significantly decreased in the erenumab 70 and 140 mg groups than in the placebo group. Similar adverse events were observed in all the groups without cardiovascular events. Therefore, it is safe and effective for the prevention of MM with erenumab. However, more studies should be performed to explore the efficacy and safety of anti-CGRP mAbs in the prevention of MM.

2.4. Combination of anti-CGRP mAbs and CGRP receptor antagonists
Both anti-CGRP mAbs and CGRP receptor antagonists play an important role in the preventive and acute treatment of headache. Treatment of breakthrough attacks during preventive treatments is necessary. Therefore, the use of a combination of anti-CGRP mAbs and CGRP receptor antagonists may result in better outcomes. Recently, two patients with migraine were treated with CGRP receptor antagonists (rimegepant) and anti-CGRP mAbs (erenumab). The results showed that rimegepants are effective for migraine attacks that occur during preventive erenumab therapy. Erenumab is also effective for migraine prevention during the coadministration of rimegepants for acute treatment. Another report showed 13 patients with migraine who simultaneously used rimegepant, erenumab, fremanezumab, or galcanezumab to evaluate the safety and tolerability of the co-administered drugs. The 13 patients were treated combined with 7 erenumab, 4 fremanezumab, and 2 galcanezumab. The results showed that no serious adverse effects were observed. Therefore, the combination of anti-CGRP mAbs and CGRP receptor antagonists is effective and safe.

2.5. Drugs inhibits CGRP release
5-HT agonists can suppress CGRP release in preclinical studies. The ergots and 5-HT1B/5-HT1D receptor agonists (triptans) can attenuate elevated levels of CGRP. Pharmacological experiments have shown that triptans inhibit CGRP release through action at prejunctional 5-HT1D receptors. These studies led to the initiation of novel antimigraine drug discovery programs targeting CGRP and its receptor. Therefore, the combination of anti-CGRP mAbs or CGRP receptor antagonists with drugs that inhibit CGRP release may have better outcomes in the treatment of MM.

3. Conclusion
Altogether, the anti-CGRP mAbs or CGRP receptor antagonists showed good efficacy and safety in the treatment of MM. However, a larger number of prospective and multicenter studies are needed to further explore the role of anti-CGRP mAbs or CGRP receptor antagonists in the treatment of MM. In addition, the role of the combination of anti-CGRP mAbs with CGRP receptor antagonists in the treatment of MM is also needed for further research in clinics and on the mechanism underlying the benefits of concomitant use. Finally, the efficacy and safety of the combination of anti-CGRP mAbs or CGRP receptor antagonists with drugs that inhibit CGRP release should be explored in the treatment of MM.

Acknowledgments
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions
All the authors wrote and approved the paper.
Conceptualization: Yan Jiang, Zhen-Lun Huang.
Data curation: Yan Jiang, Zhen-Lun Huang.
Investigation: Yan Jiang, Zhen-Lun Huang.
Writing – original draft: Yan Jiang.
Writing – review & editing: Yan Jiang, Zhen-Lun Huang.

References
[1] Allais G, Chiarle G, Sinigaglia S, et al. Menstrual migraine: a review of current and developing pharmacotherapies for women. Expert Opin Pharmacother 2018;19:123–36.
[2] Allais G, Sanchez del Rio M, Diener HC, et al. Perimenstrual migraines and their response to preventive therapy with topiramate. Cephalalgia 2011;31:152–60.
[3] Sacco S, Merki-Feld GS, Egidius KL, et al. Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and...
the European Society of Contraception and Reproductive Health (ESCRH). J Headache Pain 2018;19:76.

[4] Sacco S, Merki-Feld GS, Egidius KL, et al. Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH). J Headache Pain 2018;19:108.

[5] Ornello R, Canomico M, Merki-Feld GS, et al. low-dose combined hormonal contraceptives, and ischemic stroke in young women: a systematic review and suggestions for future research. Expert Rev Neurother 2020;20:313–7.

[6] ACOG Practice Bulletin No. 206: use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol 2019;133: e128–50.

[7] Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition): on behalf of the European Headache Federation and Lifting the Burden: the Global Campaign against Headache. J Headache Pain 2019;20:57.

[8] Zhu Y, Liu Y, Zhao J, et al. The efficacy and safety of calcitonin gene-related peptide monoclonal antibody for episodic migraine: a meta-analysis. Neurol Sci 2018;39:2097–106.

[9] Deng H, Li GQ, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine: an updated systematic review and meta-analysis. BMC Neurol 2020;20:57.

[10] Hargreaves R, Olesen J. Calcitonin gene-related peptide modulators— the history and renaissance of a new migraine drug class. Headache 2019;59:951–70.

[11] Amara SG, Jonas V, Rosenfeld MG, et al. Alternative RNA processing in calcitonin gene expression generates miRNAs encoding different polypeptide products. Nature 1982;298:240–4.

[12] Alevizaki M, Shiraishi A, Rassoul FV, et al. The calcitonin-like sequence of the beta CGRP gene. FERB Lett 1986;206:47–52.

[13] Mulderry PK, Gathe MA, Spokes RA, et al. Differential expression of the beta CGRP gene. FEBS Lett 1986;206:47

[14] gingell JJ, simms J, barwell J, et al. Erratum: An allosteric role for alpha-CGRP and beta-CGRP by primary sensory neurons and enteric autonomic neurons of the rat. Neuroscience 1988;25:195–205.

[15] Knight YE, Edvinsson L, Goadsby PJ. Blockade of calcitonin gene-related peptide receptor activity-modifying proteins in de

[16] Ornello R, Frattale I, Caponnetto V, et al. Menstrual headache in women with coexisting medical conditions. Obstet Gynecol 2019;133:

[17] Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine. Cephalalgia 2014;34:114–25.

[18] Diener HC, Barbanti P, Dahlöf C, et al. BI 44370 TA, an oral CGRP receptor antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia 2011;31:573–84.

[19] Voss T, Lippton RB, Dodick DW, et al. A phase IbB randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia 2016;36:887–98.

[20] Bell IM. Calcitonin gene-related peptide receptor antagonists: new therapeutic agents for migraine. J Med Chem 2014;57:7838–58.

[21] Ho TW, Ho AP, Ge YJ, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. Cephalalgia 2016;36:148–61.

[22] Connor KM, Aurora SK, Loeys T, et al. Long-term tolerability of telcagepant for acute treatment of migraine in a randomized trial. Headache 2011;51:73–84.

[23] Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology 2014;83:958–66.

[24] Ashina M, Dodick D, Goodysh PJ, et al. Erenumab (AMG 334) in episodic migraine: interim analysis of an ongoing open-label study. Neurology 2017;89:1237–43.

[25] Ashina M, Tepper S, Brands JL, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia 2018;38:1611–21.

[26] Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:425–34.

[27] Petersen KA, Lassen LH, Birk S, et al. BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. Clin Pharmacol Ther 2005;77:202–13.

[28] Ornello R, Frattale I, Caponnetto V, et al. Menstrual headache in women with chronic migraine treated with erenumab: an observational case series. Brain Sci 2021;11:370.

[29] Pavlovic JM, Paemeleire K, Gobel H, et al. Efficacy and safety of erenumab in women with a history of menstrual migraine. J Headache Pain 2020;21:95.

[30] Mullin K, Kudrow D, Croop R, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. Neurology 2020;94:e2121–5.

[31] Berman G, Croop R, Kudrow D, et al. Safety of rimegepant, an oral CGRP receptor antagonist, Plus CGRP monoclonal antibodies for migraine. Headache 2020;60:1734–42.

[32] Buzzi MG, Carter WB, Shimizu T, et al. Dihydroergotamine and sumatriptan attenuate levels of CGRP in plasma in rat superior sagittal sinus during electrical stimulation of the trigeminal ganglion. Neuropharmacology 1991;30:1193–200.

[33] Goodysh PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 1993;33:48–56.

[34] Knight YE, Edvinsson L, Goodysh PJ. Blockade of calcitonin gene-related peptide release after superior sagittal sinus stimulation in cat: a comparison of avitriptan and CP122,288. Neuropeptides 1999;33:41–6.

[35] Williamson DJ, Hargreaves RJ, Neurogenic inflammation in the context of migraine. Micros Res Tech 2001;53:167–78.

[36] Williamson DJ, Hargreaves RJ, Hill RG, et al. Sumatriptan inhibits neurogenic vasodilation of dural blood vessels in the anaesthetized rat intravital microscope studies. Cephalalgia 1997;17:525–31.

[37] Longmore J, Shaw D, Smith D, et al. Differential distribution of 5HT1D-receptor activity-modifying proteins in de