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Loss of Melanoregulin (MREG) Enhances Cathepsin-D Secretion by the Retinal Pigment Epithelium

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Abstract

Abstract Cathepsin-D (Cat-D) is a major proteolytic enzyme in phagocytic cells. In the retinal pigment epithelium (RPE), it is responsible for the daily degradation of photoreceptor outer segments (POSs) to maintain retinal homeostasis. Melanoregulin (MREG)-mediated loss of phagocytic capacity has been linked to diminished intracellular Cat-D activity. Here, we demonstrate that loss of MREG enhances the secretion of intermediate Cat-D (48 kDa), resulting in a net enhancement of extracellular Cat-D activity. These results suggest that MREG is required to maintain Cat-D homeostasis in the RPE and likely plays a protective role in retinal health. In this regard, in the Mreg $^{dsu/dsu}$ mouse, we observe increased basal laminin. Loss of the Mreg ^{dsu} allele is not lethal and therefore leads to slow age-dependent changes in the RPE. Thus, we propose that this model will allow us to study potential dysregulatory functions of Cat-D in retinal disease. Copyright © Cambridge University Press, 2013.

Keywords

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CGRP-Targeted Therapy for Episodic and Chronic Cluster Headache

Shu-Ting Chen[1] · Jr-Wei Wu[2,3]

Abstract

Purpose of Review Chronic cluster headache (CH) substantially affects patients' quality of life, and treatment remains challenging. The current article reviewed controlled studies for new treatment options targeting calcitonin gene–related peptide (CGRP) or its receptors in CH and discussed the current gaps and future directions for the treatment of chronic CH.

Recent Findings Two anti-CGRP monoclonal antibodies (i.e., galcanezumab and fremanezumab) completed randomized-control trials for efficacy for the preventive treatment of episodic and chronic CH. Galcanezumab was effective for preventing episodic CH but not chronic CH. Fremanezumab was ineffective in preventing episodic and chronic CH. Studies for other anti-CGRP monoclonal antibodies and CGRP antagonists are still pending for results.

Summary There are no randomized controlled trials for CGRP-targeted therapies that showed efficacy for chronic CH prevention. The different responses to galcanezumab between episodic and chronic CH may be due to the study design, i.e., the allowance of concomitant preventive therapies in the chronic CH study but not in the episodic CH study. Another reason for the discrepancies is the different roles and sensitivity of CGRP in chronic CH.

Keywords Cluster headache · Calcitonin gene–related peptide · Chronic cluster headache · Gepant · Monoclonal antibody

Introduction

Cluster headache (CH) is one of the most unbearable pain disorders worldwide, and is associated with several psychiatric comorbidities with increased suicidality, which causes significant impairment in patients' quality of life. The prevalence of CH is 1/1000 in the general population, and the male-to-female ratio is approximately 2.5:1 [1•]. The classical presentation is strictly unilateral pain in the first division of the trigeminal nerve, associated cranial

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autonomic features, and a sense of restlessness that lasts for 15 to 180 min, with a frequency between 1/day and 8/day [1•, 2]. The cranial autonomic symptoms of CH include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead and facial sweating, miosis, and ptosis [3]. One important feature of CH is "cluster bouts," which are attacks that occur more frequently during specific seasons or months within the year and typically last 4 to 12 weeks [2, 4]. According to the third edition of the International Classification of Headache Disorders (ICHD-3), CH is divided into episodic and chronic forms. Chronic CH has a short remission period (< 3 months) within a year, and some patients do not even experience a remission period [3]. Chronic CH accounts for approximately 15–20% of all CH cases in Western populations [5, 6], and a lower prevalence (0 ~ 5%) was observed in the Asian population [7–9]. The treatment of CH is divided into acute abortive treatment, transitional treatment, and preventive therapies [10]. Acute treatment includes sumatriptan (subcutaneous injection or nasal spray), high-flow oxygen via a non-rebreather mask, and non-invasive vagus nerve stimulation (only for acute episodic CH). Prednisolone is the most common transitional treatment [11]. Options for preventive treatment include verapamil, topiramate, lithium, and melatonin [10].

Some chronic CH patients are refractory to current options of preventive treatments, and "refractory chronic CH" is a challenge in headache medicine [12]. The introduction of calcitonin gene–related peptide (CGRP)-targeted therapies, including anti-CGRP monoclonal antibodies (anti-CGRP mAbs) and CGRP antagonists (gepants), changed the real-world practice of migraine treatment [13, 14]. The current review provides the most updated knowledge on the role of CGRP-targeted therapies in chronic and episodic CH.

CGRP and Cluster Headache

The pathophysiology underlying CH includes peripheral and central structures. The *peripheral structures* include the trigeminal nerve model, and the *central structures* include the hypothalamus and other pain-related structures [1•]. One unique feature of CH is the circadian and circannual clustering of attacks, which suggests that the endogenous biological clock is associated with the timing of bouts and attacks of CH. Several functional neuroimaging studies have shown that the hypothalamus plays an important role in CH [15–17]. However, functional and structural neuroimaging studies showed alternations of the pain modulatory system in CH patients [18–20]. Dynamic functional differences have been observed between bout and out-of-bout periods in CH patients [19]. These research findings suggest that CH is more likely to be caused by network dysfunction rather than a single structural lesion.

The trigeminal nerve system is the main peripheral structure involved in the pathophysiology of CH. Two important features of CH, activation of the first branch of the ophthalmic trigeminal nerve and cranial autonomic symptoms, are linked to the trigeminal nerve system and trigeminal-autonomic reflex [1•, 21]. The trigeminal nerve model supported by some peripherally acting treatments, such as triptans ($5HT_{1B}$ and $5HT_{1D}$ agonists), effectively relieve CH attacks without evidence of crossing the brain-blood barrier [22, 23]. Some neuropeptides are linked to the development of CH, including CGRP, pituitary adenylate cyclase-activating peptide (PACAP), and vasoactive intestinal peptide (VIP; a marker of parasympathetic neuronal activation) [1•]. Several clinical studies showed a close relationship between CH and these neuropeptides. The most direct evidence is the elevation of these neuropeptides during CH attacks. For example, elevation of CGRP and VIP levels from serum samples collected at the external jugular vein was observed during CH attacks [24, 25]. The elevation of CGRP levels had been observed in tear fluid outside of acute attacks in in-bout episodic CH and chronic CH patients [26]. Another neuropeptide, PACAP-38, also plays an important role in the pathophysiology of CH. Elevation of PACAP-38 from the cubital fossa blood sample was found during CH attacks [27]. The increased CGRP level

during acute attacks normalized after sumatriptan and oxygen administration, which are effective treatment options for CH attacks [28]. However, amelioration of elevated PACAP-38 during acute attacks by triptans had been only proved in migraine, and no studies in CH had yet been published [29, 30].

The infusion of these neuropeptides helped further examine their roles in CH generation. One recent elegant study showed that CGRP infusion induced CH attack in patients during the active phase of episodic CH and chronic CH [31•], which indicates that the link between CGRP and CH may be generalized to chronic CH patients, not only episodic CH. However, CGRP infusion less commonly triggered CH attacks in chronic (50%) than episodic CH patients (89%) [31•], which suggests that the role of CGRP is different in chronic CH. Another study supported this hypothesis and showed that episodic CH in remission had a higher CGRP level than chronic CH [32]. These studies on CGRP suggest basic pathophysiological differences between episodic and chronic CH. However, a recent study found that CH attack induction via infusion of PACAP-38 and VIP was lower than expected [33], and the induced attacks were not accompanied by an elevation of CGRP [34]. Therefore, PACAP-38 or its PAC1 receptor blockade might be a promising target for CH treatments but still warrants further investigation.

Galcanezumab

Galcanezumab is a 90% humanized IgG4 monoclonal antibody that targets CGRP peptides. It is effective in the prevention of episodic and chronic migraine, and treatment-resistant episodic and chronic migraine patients [35–37]. Galcanezumab is also the only CGRP mAb approved by the Federal Drug Administration (FDA) for episodic CH prevention. Notably, the dose for migraine prevention is different than CH prevention.

One phase 3, multi-center, double-blind randomized placebo-controlled trial (NCT02397473, CGAL study) analyzed galcanezumab (subcutaneous injection of 300 mg/month for two months) for the preventive treatment of episodic CH ($n = 106$) [38•]. The study found that galcanezumab met its primary endpoint and effectively reduced CH attack frequency across weeks 1 to 3 compared to placebo (-8.7 attacks/week vs. -5.2 attacks/week, $p = 0.036$). The key secondary end-point was a $\geq 50\%$ reduction in the weekly frequency of CH attacks, and 71% of the galcanezumab group achieved this end-point compared to 53% in the placebo group ($p = 0.046$). Other secondary end-points included the weekly frequency of CH attacks, $\geq 30\%$ reduction in the weekly frequency of CH attacks, and condition very much or much better. Among them, the active treatment group had a higher reduction in the weekly frequency of

CH attacks in week 2. Also, the active treatment group had a higher probability report 'condition very much or much better' at week 4, but not week 8. In this study, several endpoints were reported in eight weekly epochs. There is a trend that the difference between the galcanezumab group and placebo is more prominent in the initial weekly epochs than in the later weeks.

There were no deaths or other serious adverse events in this study. Patients in the galcanezumab group experienced a higher percentage of ≥ 1 adverse events (43% vs. 33%). The most common adverse events included injection-site pain, nasopharyngitis, injection-site swelling, and pyrexia, but only injection-site pain was significantly higher in the galcanezumab group [38•]. A post hoc subgroup analysis was performed to analyze the treatment response to galcanezumab in patients with episodic CH who had a known history of preventive treatment failures [39]. Among the 106 patients in the prior randomized control study, 15 patients (6 placebo and 9 galcanezumab groups) reported a prior history of preventive failures, mostly verapamil. Galcanezumab had a greater mean reduction in weekly CH attack frequency across weeks 1 to 3 in patients with a history of failed preventives (8.2 vs. 2.4, least-squares mean difference 5.8 [95% CI 2.0–13.6]). Patients with a history of verapamil failure also had a greater mean reduction in weekly CH attack frequency across weeks 1 to 3 (10.1 vs. 1.6, least-squares mean difference 8.5 [95% CI 0.4–16.7]). This small subgroup analysis suggests that galcanezumab is also helpful in episodic CH patients who are not responsive to other preventive treatments [39].

Another phase 3, double-blind, randomized, placebo-controlled trial analyzed the efficacy and safety of galcanezumab (subcutaneous injection of 300 mg/month for three months) for the preventive treatment of chronic CH [40•]. However, this study did not meet its primary endpoint to effectively reduce CH attack frequency across weeks 1 to 12 compared with placebo (− 5.4 attacks/week galcanezumab vs. − 4.6 attacks/week placebo, $p = 0.334$). This study also failed to meet the key secondary endpoint; 32.6% of chronic CH patients in the galcanezumab group and 27.1% within the placebo group achieved a ≥ 50% reduction in weekly attack frequency from baseline across weeks 1 to 12 ($p = 0.170$). Other secondary end-points included the weekly frequency of CH attacks, ≥ 30% reduction in the weekly frequency of CH attacks, and Patient Global Impression of Improvement (PGI-I). At weeks 1–2, the galcanezumab group had a significantly greater mean change from baseline in the weekly frequency of CH attacks (− 4.0 attacks/week vs. − 1.8 attacks/week, $p = 0.006$) and a higher percentage achieved ≥ 30% reduction in the weekly frequency of CH attacks (35.2% vs. 23.0, $p = 0.037$). Other secondary efficacy endpoints did not show a significant difference. There were no differences between the galcanezumab and placebo groups that achieved

sustained response (16.2% galcanezumab vs. 17.5% placebo, $p = 0.946$) [40•]. During the study period, no deaths were reported, but two galcanezumab-treated patients and three placebo-treated patients reported serious adverse events. The galcanezumab-treated group had higher treatment-emergent adverse events (71.8% galcanezumab vs. 62.5% placebo). Commonly reported adverse events included injection-site pain, nasopharyngitis, injection-site erythema, and nausea. Among the adverse events, injection-site erythema and nausea were significantly higher in the galcanezumab-treated group [40•]. One post hoc analysis found no difference in the concomitant acute treatments between the galcanezumab and placebo groups in chronic CH patients [41].

Fremanezumab

Fremanezumab is a fully humanized IgG2 monoclonal antibody that selectively targets CGRP. It is effective in the prevention of episodic and chronic migraine, and treatment-resistant migraine episodic and chronic migraine patients [42–44]. The dosing schedule of fremanezumab in trials for CH prevention was not identical to migraine prevention.

Two phase 3, double-blind, randomized, placebo-controlled trials were launched to analyze the efficacy and safety of fremanezumab for preventing episodic and chronic CH. The episodic CH prevention study (NCT02945046) compared two treatment arms (high dose: fremanezumab 900/225/225 mg and low dose: fremanezumab 675 mg/placebo/placebo) and a placebo arm. The dosing schedule of the fremanezumab 900/225/225 mg group was 1-h intravenous fremanezumab 900 mg infusion plus subcutaneous placebo at week 0, followed by subcutaneous fremanezumab 225 mg at week 4 and week 8. The dosing schedule of the fremanezumab 675 mg/placebo/placebo group was subcutaneous fremanezumab 675 mg plus a 1-h intravenous placebo infusion at week 0, followed by subcutaneous placebo injections at week 4 and week 8. According to the results presented at the 2019 International Headache Conference ($n = 169$), neither the high- nor low-dose fremanezumab groups met the primary endpoint, i.e., changes from baseline in the weekly average number of CH attacks during the 4-week period (fremanezumab high dose: − 7.6 vs. fremanezumab low dose: − 5.8 vs. placebo: − 5.7, $p ≥ 0.1$) [45•, 46]. Compared with the fremanezumab high-dose and placebo groups, there were significant decreases in acute medication use during the 12-week period and weekly over the first 8 weeks ($p < 0.05$, not multiplicity adjusted) [46]. The episodic CH prevention study was discontinued after the interim analysis demonstrated futility, but there were no safety concerns during the study period [13].

The chronic CH prevention study (NCT02964338) compared two treatment arms (high dose: fremanezumab 900/225/225 mg and low dose: fremanezumab 675 mg/225 mg/225 mg) and

a placebo arm. The dosing schedule of the fremanezumab 900/225/225 mg group was 1-h intravenous fremanezumab 900 mg infusion plus subcutaneous placebo at week 0, followed by subcutaneous fremanezumab 225 mg at week 4 and week 8. The dosing schedule of the fremanezumab 675 mg/225 mg/225 mg group was subcutaneous fremanezumab 675 mg plus a 1-h intravenous placebo infusion at week 0, followed by subcutaneous fremanezumab 225 mg injections at week 4 and week 8. The primary endpoint was different from the episodic CH study, which was mean changes from baseline in the overall monthly average number of CH attacks within 12 weeks. However, this study was discontinued after the interim analysis showed no effectiveness [13]. Therefore, current evidence does not support the use of fremanezumab in episodic or chronic CH prevention.

Erenumab

Erenumab is a fully human IgG2 monoclonal antibody that competitively inhibits the CGRP receptor. It is the first anti-CGRP mAb, and it is effective in preventing episodic and chronic migraine [39, 47, 48]. The dose of erenumab in ongoing CH prevention studies differs from the dose for migraine prevention.

One double-blind, randomized, placebo-controlled trial is analyzing the efficacy and safety of erenumab for chronic CH prevention (NCT04970355, CHERUB01 study), but there is no ongoing study analyzing its efficacy in episodic CH. The dosing schedule of this study was subcutaneous injection of 280 mg erenumab as a loading dose at week 0, followed by 140 mg erenumab at week 4. Their primary endpoint was a reduction in weekly CH attack frequency between baseline and weeks 5–6 (days 29–42, average for 7 days).

There have been no published randomized controlled studies on the efficacy of erenumab in CH prevention. However, one case report (1 chronic CH), and one case series (migraine patients with comorbid CH; 4 chronic CH and 1 episodic CH) showed that off-label use of erenumab (70 or 140 mg) may be helpful in chronic CH patients [49, 50]. One observation from these case series is that patients who received a higher dose (i.e., 140 mg) with a longer duration (at least three months) tended to be more responsive to erenumab treatment.

Eptinezumab

Eptinezumab is a fully humanized IgG1 monoclonal antibody that targets CGRP peptides. It is delivered by intravenous administration and showed efficacy in preventing episodic and chronic migraine [51, 52]. Notably, one

randomized placebo-controlled trial found that eptinezumab shortened the time of headache resolution in acute migraine attacks, which suggests a rapid onset of action [52].

One double-blind, randomized, placebo-controlled trial is analyzing the efficacy and safety of eptinezumab for episodic CH prevention (NCT04688775, ALLEVIATE study). The precise dosing schedules are not shown on clinicaltrials. gov, and the primary endpoint was change from baseline in the number of weekly CH attacks over weeks 1–2. Another open-label, fixed-dose multiple administration study on chronic CH prevention (NCT05064397, CHRONICLE study) analyzed the safety and tolerance of eptinezumab within 56 weeks. Changes in attack frequencies and conversion from chronic to episodic CH were secondary endpoints. There have been no published randomized controlled studies on the efficacy of eptinezumab in CH prevention.

Studies That Included Different anti-CGRP mAbs

A small, retrospective case series ($n = 22$) analyzed the efficacy of CGRP (or its receptor) monoclonal antibodies in preventing chronic CH. Most patients (73%) in this case series received galcanezumab (mostly 240 mg per month), and other patients received 70 or 140 mg of erenumab [53]. The baseline number of attacks was 23.3/week and significantly decreased by 9.2 attacks/week in the first month of anti-CGRP mAb treatment. A total of 55% of chronic CH patients achieved a 50% reduction, and 36% achieved a 75% reduction in attack frequency [53]. These real-world data suggest that the off-label use of anti-CGRP mAb may be helpful in chronic CH.

Gepants

Gepants are small molecule CGRP receptor antagonists that are different from large monoclonal antibodies [54]. Ubrogepant and rimegepant have been approved for acute migraine treatment [14, 55–57]. Rimegepant and atogepant could be used for migraine prevention [58, 59]. The gepants are administered orally, but published trials only examined their efficacies in acute and preventive treatment for migraine. One small open-label pilot study was recently registered on clinicaltrials.gov and analyzed the efficacy of rimegepant in CH prevention. The dose of rimegepant in the CH trial (150 mg) is larger than migraine treatments (75 mg for migraine acute and preventive treatments) [56, 58].

Discussion

Based on our review, two anti-CGRP mAbs, galcanezumab and fremanezumab, underwent randomized control trials for efficacy for episodic and chronic CH prevention. Only galcanezumab was effective in preventing episodic CH, but the trial for chronic CH did not meet its endpoint. Trials for fremanezumab for episodic and chronic CH prevention were discontinued after interim analyses showed a lack of clinical benefit (Table 1). Small case reports and case series showed that erenumab may be effective in preventing chronic CH. Two possible reasons may account for the discrepancies between these studies, study designs and underlying pathophysiology.

There are some barriers and difficulties in the current study design for CH [60]. First, spontaneous remission is part of the natural history of CH and poses great challenges in study design [60, 61]. The onset and duration of cluster bouts may be irregular and variable in some patients. Therefore, patients in the double-blind phase of the study may subside spontaneously due to a natural course and not because of the treatment response. The placebo arm's improvement may combine the placebo response and spontaneous remission. Patients with chronic CH may not have a remission period, or their remission period may shortened compared to episodic CH. Therefore, the difference in trials of galcanezumab (effective in episodic but not chronic CH) is less likely confounded by spontaneous remission. Second, concomitant preventive therapies may have a substantial impact in randomized control trials [61]. Current concomitant preventive therapies are generally accepted in trials for chronic CH due to ethical considerations but are not allowed in studies for episodic CH. In the chronic CH trial of galcanezumab, ≥ 63% were using ≥ 1 preventive drugs, and 49.8% of participants were taking verapamil [40•]. The concomitant use of preventive therapies may explain the failure to meet the primary endpoint in the chronic CH study, but it is not easy to clarify its impact on treatment response. The future selection of chronic CH patients under similar concomitant preventives and providing a stable maintenance dose during the double-blind phase may be a solution for this problem [61]. Third, the effective dose for CH may be different than migraine. The interim analysis of the fremanezumab trial for episodic CH did not meet its primary endpoint but showed a significant reduction in acute medication use in the higher dose group [34]. The effective dose of galcanezumab for preventing episodic CH was higher than the dose for migraine prevention. Therefore, the insufficient dose of anti-CGRP mAbs may explain the negative findings in CH trials.

The results of trials for preventive CH treatments may differ between episodic and chronic CH. For example, anti-CGRP mAb effectively prevented episodic CH but not chronic CH [38•, 40•]. Conversely, controlled studies found that lithium was ineffective in preventing episodic CH but effective in chronic CH [62, 63]. These observations suggest fundamental pathophysiological differences between episodic and chronic CH. This hypothesis was supported by infusion studies, which found that infusion of CGRP less commonly triggered CH attacks in chronic (50%) than episodic CH patients (89%) [31•]. The baseline CGRP level is lower in chronic CH patients than episodic CH patients in remission [32]. The lack of response of anti-CGRP mAbs in chronic CH is consistent with the above physiological studies, which suggests chronic CH is less sensitive to CGRP, and other factors contribute to this chronic pain disorder. One recent study found that chronic CH patients had a higher family history and higher history of traumatic brain injury [64]. A chronorisk study also showed that episodic CH tended to follow circadian rhythmicity, but chronic CH was dominated by ultradian oscillations [65]. Neuroimaging studies found certain differences between episodic and chronic CH [66]. Lesser sensitivity to CGRP and differences in central pathways may explain the discrepancies in trial results in the same treatment options [46]. Monoclonal antibodies targeting other neuropeptides (i.e., PACAP-38) or a combination of treatments targeting different pathways warrant further investigation of their roles in chronic CH [67].

Table 1 Completed or discontinued pivotal trials of CGRP-related therapies in CH

Study name	Dosing, patient number, treatment duration, and usage of concomitant preventive therapies	Primary endpoint: reduced CHF (attacks/week)	Key Secondary endpoint (s):	Adverse events
Episodic CH				
Goadsby et al. [38●] CGAL study, NCT02397473	• **Galcanezumab 300 mg SC monthly** (N = 49) • **Placebo** (N = 57) • Study duration: 8 weeks • Concomitant preventive therapies: not allowed	**Weeks 1–3** Galcanezumab group: − 8.7 Placebo group: − 5.2 p = 0.036 [Met]	**≥ 50% reduction of weekly CHF at week 3:** Acute treatment group: 53% Placebo group: 71% p = 0.046 [Met]	Injection-site pain, Naso-pharyngitis, Injection-site swelling, Pyrexia *Only injection-site pain was significantly higher in the galcanezumab group
Lipton et al. [45●] NCT02945046 Presentation in IHC 2019 Terminated after the interim analysis	• **Fremanezumab, high dose** **900 IV/225 mg SC/225 mg SC monthly** (N = 55) • **Fremanezumab, high dose** **675 mg SC/225 mg SC/225 mg SC monthly** (N = 55) • **Placebo arm** (N = 59) • Study duration: 4 weeks • Concomitant preventive therapies: up to 2 other preventives were allowed	**Week 1–4** High dose group: -7.6 Low dose group: − 5.8 Place group: − 5.7 p ≥ 0.1 [Not met]	**Percentage of patients with ≥ 50% reduction in monthly attacks** [Not met, not present the data]	Reported no safety concerns
Chronic CH				
Dodick et al. [40●] NCT02438826	• **Galcanezumab 300 mg SC monthly** (N = 117) • **Placebo** (N = 120) • Study duration: 12 weeks • Concomitant preventive therapies: allowed, included verapamil, lithium, topiramate, valproate, melatonin, and gabapentin	**Weeks 1–12** Galcanezumab group: − 5.4 Placebo group: − 4.6 p = 0.334 [Met]	**≥ 50% reduction of weekly CHF across weekz 1–12:** Galcanezumab group: 32.6% Placebo group: 27.1% p = 0.170 [Not met] **Sustained response through week 12:** Galcanezumab group: 17.5% Placebo group: 16.2% p = 0.946 [Not met]	Injection-site pain, Naso-pharyngitis, Injection-site erythema Nausea *Injection-site erythema and nausea were significantly higher in the galcan-ezumab group
NCT02964338 [13, 61] Not published Terminated after the interim analysis	• **Fremanezumab, high dose** **900 mg IV/225 mg SC/225 mg SC monthly** (N = 87) • **Fremanezumab, high dose** **675 mg SC/225 mg SC/225 mg SC monthly** (N = 88) • **Placebo arm** (N = 84) • Study duration: 8 weeks • Concomitant preventive therapies: up to 2 other preventives were allowed	**Weeks 1–12** [Not met, not present the data]	**≥ 50% reduction of weekly CHF** [Not met, not present the data] **Sustained response through week 12:** [Not met, not present the data]	Not reported

CHF cluster headache attacks frequency, *SC* subcutaneous injection, *IV* intravenous injection

Conclusions

Randomized-control trials of galcanezumab and fremane-zumab for chronic CH prevention were negative. The effectiveness of galcanezumab and erenumab for chronic CH prevention was reported in case series or small retrospective studies. Studies for other anti-CGRP mAbs and gepants are ongoing. Reasons for the discrepancies in response to anti-CGRP mAbs between episodic and chronic CH include concomitant preventive therapies in chronic CH studies, possible insufficient doses, and lower sensitivity of CGRP in chronic CH.

Compliance with Ethical Standards

Conflict of Interest STC declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. JWW has received honoraria (as a speaker) from Biogen-Idec and Eli Lilly. He has received travel reimbursement and honoraria from American Academy of Neurology, International Headache Society, and Taiwan Headache Society.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1.• May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. Nat Rev Dis Primers. 2018;4:18006. 1. **This article provides a comprehensive review of the clinical presentations, pathophysiology, and treatments for cluster headache.**

2. Schurks M, Kurth T, de Jesus J, Jonjic M, Rosskopf D, Diener HC. Cluster headache: clinical presentation, lifestyle features, and medical treatment. Headache. 2006;46:1246–54.

3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38:1–211.

4. Favier I, Haan J, Ferrari MD. Chronic cluster headache: a review. J Headache Pain. 2005;6:3–9.

5. Donnet A, Lanteri-Minet M, Guegan-Massardier E, Mick G, Fabre N, Géraud G, et al. Chronic cluster headache: a French clinical descriptive study. J Neurol Neurosurg Psychiatry. 2007;78:1354–8.

6. Manzoni GC, Micieli G, Granella F, Tassorelli C, Zanferrari C, Cavallini A. Cluster headache—course over ten years in 189 patients. Cephalalgia. 1991;11:169–74.

7. Ko C-A, Lin G-Y, Ting C-H, Sung Y-F, Lee J-T, Tsai C-K, et al. Clinical features of cluster headache: a hospital-based study in Taiwan. Front Neurol. 2021;12.

8. Lin KH, Wang PJ, Fuh JL, Lu SR, Chung CT, Tsou HK, et al. Cluster headache in the Taiwanese — a clinic-based study. Cephalalgia. 2004;24:631–8.

9. Imai N, Yagi N, Kuroda R, Konishi T, Serizawa M, Kobari M. Clinical profile of cluster headaches in Japan: low prevalence of chronic cluster headache, and uncoupling of sense and behaviour of restlessness. Cephalalgia. 2011;31:628–33.

10. Wei DY, Khalil M, Goadsby PJ. Managing cluster headache. Pract Neurol. 2019;19:521–8.

11. Obermann M, Nägel S, Ose C, Sonuc N, Scherag A, Storch P, et al. Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial. Lancet Neurol. 2021;20:29–37.

12. Mitsikostas DD, Edvinsson L, Jensen RH, Katsarava Z, Lampl C, Negro A, et al. Refractory chronic cluster headache: a consensus statement on clinical definition from the European Headache Federation. J Headache Pain. 2014;15:79.

13. Yuan H, Spare NM, Silberstein SD. Targeting CGRP for the prevention of migraine and cluster headache: a narrative review. Headache. 2019;59(Suppl 2):20–32.

14. Cohen F, Yuan H, Silberstein SD. Calcitonin gene-related peptide (CGRP)-targeted monoclonal antibodies and antagonists in migraine: current evidence and rationale. BioDrugs. 2022.

15. Yang F-C, Chou K-H, Fuh J-L, Lee P-L, Lirng J-F, Lin Y-Y, et al. Altered hypothalamic functional connectivity in cluster headache: a longitudinal resting-state functional MRI study. J Neurol Neurosurg Psychiatry. 2015;86(4):437–45.

16. Schulte LH, Haji AA, May A. Phase dependent hypothalamic activation following trigeminal input in cluster headache. J Headache Pain. 2020;21:30.

17. Barloese MC. Neurobiology and sleep disorders in cluster headache. J Headache Pain. 2015;16:562.

18. Buture A, Boland JW, Dikomitis L, Ahmed F. Update on the pathophysiology of cluster headache: imaging and neuropeptide studies. J Pain Res. 2019;12:269–81.

19. Sprenger T, Ruether KV, Boecker H, Valet M, Berthele A, Pfaffenrath V, et al. Altered metabolism in frontal brain circuits in cluster headache. Cephalalgia. 2007;27:1033–42.

20. Yang FC, Chou KH, Fuh JL, Huang CC, Lirng JF, Lin YY, et al. Altered gray matter volume in the frontal pain modulation network in patients with cluster headache. Pain. 2013;154:801–7.

21. Goadsby PJ. Cluster headache and the trigeminal-autonomic reflex: Driving or being driven? Cephalalgia. 2018;38:1415–7.

22. Plosker GL, McTavish D. Sumatriptan. A reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs. 1994;47:622–651.

23. Edvinsson L, Tfelt-Hansen P. The blood-brain barrier in migraine treatment. Cephalalgia. 2008;28:1245–58.

24. Fanciullacci M, Alessandri M, Figini M, Geppetti P, Michelacci S. Increase in plasma calcitonin gene-related peptide from the extracerebral circulation during nitroglycerin-induced cluster headache attack. Pain. 1995;60:119–23.

25. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. Brain. 1994;117:427–434.

26. Kamm K, Straube A, Ruscheweyh R. Baseline tear fluid CGRP is elevated in active cluster headache patients as long as they have not taken attack abortive medication. Cephalalgia. 2021;41:69–77.

27. Tuka B, Szabó N, Tóth E, Kincses ZT, Párdutz Á, Szok D, et al. Release of PACAP-38 in episodic cluster headache patients — an exploratory study. J Headache Pain. 2016;17:69–69.

28. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. Brain. 1994;117(Pt 3):427–434.

29. Zagami AS, Edvinsson L, Goadsby PJ. Pituitary adenylate cyclase activating polypeptide and migraine. Ann Clin Transl Neurol. 2014;1:1036–40.

30. Ashina H, Guo S, Vollesen ALH, Ashina M. PACAP38 in human models of primary headaches. J Headache Pain. 2017;18:110–110.

31. • Vollesen ALH, Snoer A, Beske RP, Guo S, Hoffmann J, Jensen RH, et al. Effect of infusion of calcitonin gene-related peptide on cluster headache attacks: a randomized clinical trial. JAMA Neurol. 2018;75:1187–1197. **This infusion study found CGRP infusion less commonly triggered CH attacks in chronic (50%) than episodic cluster headache patients (89%), suggesting differences in CGRP sensitivity between episodic and chronic cluster headache patients.**

32. Snoer A, Vollesen ALH, Beske RP, Guo S, Hoffmann J, Fahrenkrug J, et al. Calcitonin-gene related peptide and disease activity in cluster headache. Cephalalgia. 2019;39:575–84.

33. Vollesen ALH, Snoer A, Chaudhry B, Petersen AS, Hagedorn A, Hoffmann J, et al. The effect of pituitary adenylate cyclase-activating peptide-38 and vasoactive intestinal peptide in cluster headache. Cephalalgia. 2020;40:1474–88.

34. Pellesi L, Chaudhry BA, Vollesen ALH, Snoer AH, Baumann K, Skov PS, et al. PACAP38- and VIP-induced cluster headache attacks are not associated with changes of plasma CGRP or markers of mast cell activation. Cephalalgia. 0:03331024211056248.

35. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018;38:1442–54.

36. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018;75:1080–8.

37. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine. The randomized, double-blind, placebo-controlled REGAIN study. 2018;91:e2211–21.

38. • Goadsby PJ, Dodick DW, Leone M, Bardos JN, Oakes TM, Millen BA, et al. Trial of galcanezumab in prevention of episodic cluster headache. N Engl J Med. 2019;381:132–141. **This manuscript demonstrates the efficacy of galcanezumab for the preventive treatment of episodic cluster headache.**

39. Plato B, Andrews JS, Rettiganti M, Tockhorn-Heidenreich A, Bardos J, Wenzel R, et al. Efficacy of galcanezumab in patients with episodic cluster headaches and a history of preventive treatment failure. Cephalalgia Reports. 2021;4:25158163211015656.

40. • Dodick DW, Goadsby PJ, Lucas C, Jensen R, Bardos JN, Martinez JM, et al. Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: results from 3-month double-blind treatment. Cephalalgia. 2020;40:935–948. **This paper found that galcanezumab is ineffective for the preventive treatment of chronic cluster headaches.**

41. Lanteri-Minet M, Kalidas K, Oakes TM, Bardos J, Zhou C, Wenzel R, et al. Acute and preventive treatment use in a phase 3 randomized trial of galcanezumab in chronic cluster headache (4023). Neurology. 2020;94:4023.

42. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA. 2018;319:1999–2008.

43. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017;377:2113–22.

44. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet. 2019;394:1030–40.

45. • Lipton RB, Diener HC, Barbanti P, Schiemann J, Barash S, Cohen JM, et al. Efficacy and safety of fremanezumab for the prevention of episodic cluster headache: results of a randomized, double-blind, placebo controlled, phase 3 study. Cephalalgia. 2019;39:358–9. **This abstract from the Internation Headache Congress 2019 showed that fremanezumab is ineffective for the preventive treatment of episodic cluster headache.**

46. Chan C, Goadsby PJ. CGRP pathway monoclonal antibodies for cluster headache. Expert Opin Biol Ther. 2020;20:947–53.

47. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med. 2017;377:2123–32.

48. Wang SJ, Roxas AA Jr, Saravia B, Kim BK, Chowdhury D, Riachi N, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: The EMPOwER study. Cephalalgia. 2021;41:1285–97.

49. Silvestro M, Tessitore A. Scotto di Clemente F, Tedeschi G, Russo A: Erenumab Efficacy on comorbid cluster headache in patients with migraine: a real-world case series. Headache. 2020;60:1187–95.

50. Riederer F, Wenner AM. Erenumab for chronic cluster headache: a case report. Cephalalgia Reports. 2020;3:2515816320947713.

51. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia. 2020;40:241–54.

52. Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology. 2020;94:e1365–77.

53. Ruscheweyh R, Broessner G, Goßrau G, Heinze-Kuhn K, Jürgens TP, Kaltseis K, et al. Effect of calcitonin gene-related peptide (-receptor) antibodies in chronic cluster headache: results from a retrospective case series support individual treatment attempts. Cephalalgia. 2020;40:1574–84.

54. Tepper D. Gepants. Headache: J Head Face Pain. 2020;60:1037–1039.

55. Dodick DW, Lipton RB, Ailani J, Halker Singh RB, Shewale AR, Zhao S, et al. Ubrogepant, an acute treatment for migraine, improved patient-reported functional disability and satisfaction in 2 single-attack phase 3 randomized trials. ACHIEVE I and II Headache. 2020;60:686–700.

56. Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG, et al. 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. 2019;394:737–45.

57. Chiang CC, VanderPluym JH. Ubrogepant in the acute management of migraine: a narrative review. J Pain Res. 2021;14:1185–92.

58. Slomski A. Oral Rimegepant Safe, Effective for migraine prevention. JAMA. 2021;325:713–713.

59. Ailani J, Lipton RB, Goadsby PJ, Guo H, Miceli R, Severt L, et al. Atogepant for the preventive treatment of migraine. N Engl J Med. 2021;385:695–706.

60. Lipton RB, Micieli G, Russell D, Solomon S, Tfelt-Hansen P, Waldenlind E. Guidelines for controlled trials of drugs in cluster headache. Cephalalgia. 1995;15:452–62.

61. Dodick DW, Goadsby PJ, Ashina M, Tassorelli C, Hundemer HP, Bardos JN, et al. Challenges and complexities in designing cluster headache prevention clinical trials: a narrative review. Headache. 2022;62:453–72.

62. Bussone G, Leone M, Peccarisi C, Micieli G, Granella F, Magri M, et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache. 1990;30:411–7.

63. Steiner TJ, Hering R, Couturier EG, Davies PT, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. Cephalalgia. 1997;17:673–5.

64. Barloese MCJ, Beske RP, Petersen AS, Haddock B, Lund N, Jensen RH. Episodic and chronic cluster headache: differences in family history, traumatic head injury, and chronorisk. Headache. 2020;60:515–25.

65. Barloese M, Haddock B, Lund NT, Petersen A, Jensen R. Chronorisk in cluster headache: a tool for individualised therapy? Cephalalgia. 2018;38:2058–67.

66. Naegel S, Holle D, Obermann M. Structural imaging in cluster headache. Curr Pain Headache Rep. 2014;18:415.

67. Rustichelli C, Lo Castro F, Baraldi C, Ferrari A. Targeting pituitary adenylate cyclase-activating polypeptide (PACAP) with monoclonal antibodies in migraine prevention: a brief review. Expert Opin Investig Drugs. 2020;29:1269–75.