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REVIEW

# The Arrival of Anti-CGRP Monoclonal Antibodies in Migraine

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**Abstract**
Remarkable advancements have been made in the field of migraine pathophysiology and pharmacotherapy over the past decade. Understanding the molecular mechanism of calcitonin gene-related peptide (CGRP) has led to the discovery of a novel class of drugs, CGRP functional blocking monoclonal antibodies (mAbs), for migraine prevention. CGRP is a neuropeptide inherently involved in migraine physiology where its receptors are found dispersed throughout the central and peripheral nervous systems. CGRP-targeted mAbs are effective in the preventive treatment of both chronic and episodic migraine. The advantages of mAbs over oral migraine preventives are numerous. Favorable attributes of the mAbs include high affinity and selectivity for CGRP molecular targets, long-circulating plasma half-lives, and limited risk for nonspecific hepatic and renal toxicity. This pharmacological profile leads to fewer off-target (side) effects and drug-drug interactions rendering mAbs an attractive alternative to traditional small molecule therapies, especially for the preventive treatment of migraine. MAbs display minimal drug interaction thus are excellent for patients prescribed with multiple medications. However, the long-term safety of CGRP blockade is incompletely known, and CGRP mAbs use should be avoided during pregnancy. CGRP mAbs represent a radical shift in preventing chronic and episodic migraine.

**Keywords** Monoclonal antibody · CGRP · Calcitonin gene-related peptide · Migraine · Neurogenic inflammation · Trigeminovascular system

## Introduction

Abnormal activation of the trigeminovascular system causes not only vasodilation and neurogenic inflammation but also peripheral and central pain sensitization in migraine. The discovery of calcitonin gene-related peptide (CGRP) has led to the development of a novel class of therapeutic modality, CGRP-targeted monoclonal antibodies (mAbs). CGRP is a 37-amino acid neuropeptide found in the peripheral and central nervous systems. This molecule is considered a critical neuropeptide involved in the migraine pain pathway within the trigeminovascular system. CGRP mAbs antagonize CGRP's functions on the trigeminal nerve and cerebral vasculature [1]. In this chapter, we discuss the role of CGRP in migraine and the development of CGRP mAbs in the successful treatment of migraine.

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There are four CGRP-targeted mAbs currently approved by the Food and Drug Administration (FDA) for the prevention of migraine. CGRP mAbs have become a cornerstone of treatment for patients with migraine resistant to traditional preventive therapies. MAb therapies provide headache relief and exhibit excellent tolerability profiles leading to much-improved treatment adherence among migraine patients. It is worth noting that currently, there is no sufficient safety data for use in pregnant or nursing women, or patients < 18 years old [2].

## Epidemiology of Migraine

Migraine affects over a billion people worldwide and is the second-highest cause of years lived with disability [3]. Migraine attacks last between 4 and 72 h, with characteristics that include unilaterality, aggravation by exercise, pulsatory nature, association with nausea, and/or photophobia and phonophobia. Migraine is grouped by its attack frequency into episodic migraine (EM; < 15 monthly headache days) and chronic migraine (CM; ≥ 15

monthly headache days). EM affects approximately 12% of the Western adult population, while CM affects approximately 1% of the adult population [4]. The decision to start preventive treatments depends on the headache duration and frequency of attacks, level of disability, and co-morbid conditions. The American Headache Society (AHS) guidelines recommend starting preventive treatment if: the patient has > 3 headache days per month with severe disability, > 4 headache days per month with mild disability, or > 6 headache days per month with no disability. If a patient demonstrates an inability to tolerate a 6-week trial of at least two classes of preventive medications or a 6-month trial of onabotulinumtoxinA, a CGRP-targeted mAb may be used. Previously established options for CM prevention include botulinum toxin, antidepressants, antiepileptics, antihypertensives.

## CGRP Pathogenesis in Migraine

The pathogenesis of migraine involves the activation of the trigeminovascular system. Stimulation of the trigeminovascular nociceptive system in migraine causes neurogenic inflammation resulting in both peripheral and central pain sensitization [5]. This involves an array of neuropeptides, including CGRP and substance P. CGRP, which is involved in neurogenic neuroinflammation and released by activating trigeminal nociceptive afferents, is the most relevant neuropeptide in migraine pathogenesis. While known as a potent arterial vasodilator, CGRP's mechanism of action is multifactorial including activation of Aδ fibers and satellite glial cells within the trigeminovascular nociceptive system. Nevertheless, disrupting this sensitization process by blocking the CGRP function appears clinically appropriate in migraine [6].

CGRP is postulated to sensitize migraine signaling pathways within the trigeminovascular system based on human migraine models [7]. Two isoforms of CGRP have been described, α-CGRP and β-CGRP; α-CGRP, which is found throughout the body, is abundantly expressed in the trigeminal system. It is primarily expressed in sensory C-fibers from the trigeminal ganglion (TG) [8, 9]. In TG, these neurons interconnect with the surrounding satellite glial cells. TG neurons join in the trigeminal nucleus caudalis in the brainstem with afferents from the cervical spinal cord, which then project to pain processing centers. The higher nociceptive centers include the cingulate cortex, brainstem, insula, caudate, and thalamus [10]. When subjects with migraine were infused with CGRP, most developed migraine-like attacks [11]. These infusions only evoke delayed migraine-like attacks in most subjects with migraine, but not healthy in control subjects [12].

## CGRP-Targeting mAbs in Migraine

### Formulation

CGRP-targeted mAb therapies were specifically developed for migraine. This is a break from tradition, as most migraine preventive medications were originally developed for other indications then used for migraine. There are currently four mAbs formulations used for migraine prophylaxis. Three of these mAbs target the CGRP ligand (eptinezumab, fremanezumab, and galcanezumab) and are humanized antibodies. Erenumab, in contrast, is a fully human mAb that targets the canonical CGRP receptor. Although showing slight variation in target binding affinity, these four drugs have demonstrated similar efficacy, tolerability, and limited adverse effects (AEs) [13]. Table 1 displays the dosing and frequencies of administrations for the four CGRP mAbs currently available.

Compared to gepants, which are small-molecule CGRP antagonists, mAbs have a much higher target specificity, longer circulating half-life, and lower drug-drug interactions. With poor oral bioavailability due to gastric degradation, mAbs are administered parenterally (intravenous or subcutaneous). MAbs are metabolized via the reticuloendothelial system (RES), target-mediated elimination, and nonspecific pinocytosis. Pinocytosis is a relatively unspecific fluid-phase endocytosis by endothelial cells lining the blood vessels. Due to the large surface area of endothelial cells in the body (> 1,000 $m^2$), the process efficiently eliminates IgG molecules from the body. Because the intracellular uptake via pinocytosis does not differentiate which proteins in the surrounding of a cell are taken up for degradation, a protective mechanism for IgG molecules is necessary to maintain their concentrations in the plasma to support their physiologic function and to provide long-term immunity. This salvage pathway is provided by neonatal Fc receptor (FcRn) that allows IgGs to be recycled back to circulation via FcRN [14]. Its long circulatory half-life allows for monthly or even quarterly dosing. Convenient administration and high tolerability greatly

**Table 1** CGRP-targeting monoclonal antibodies

| Name | IgG | Route | CGRP target | Frequency | Dose |
|---|---|---|---|---|---|
| Eptinezumab | $IgG_1$ | IV | Ligand | Quarterly | 100 mg<br>300 mg |
| Erenumab | $IgG_2$ | SC | Receptor | Monthly | 70 mg<br>140 mg |
| Fremanezumab | $IgG_2$ | SC | Ligand | Monthly<br>Quarterly | 225 mg<br>675 mg |
| Galcanezumab | $IgG_4$ | SC | Ligand | Monthly | 120mg[a] |

*IgG* immunoglobulin G, *IV* intravenous, *SC* subcutaneous

[a]Start with 240 mg loading

improve treatment adherence. Although CGRP mAbs are generally well tolerated, no simple method is currently available for quick removal if a severe AE occurs. Since all trials excluded patients with *BMI* > 40, age > 70 years, pregnancy or breastfeeding, the realistic AE profiles in susceptible populations remain to be answered.

### Mechanism of Action

The mAbs mechanism of action depends on their target and distribution. Typically, mAbs do not penetrate the blood–brain barrier, but have access to the dura mater and sensory ganglia (e.g., trigeminal, sphenopalatine, vagus) [15]. These locations may be the sites of action. CGRP mAbs block CGRP's function and alter the downstream signaling pathway. In vitro, while galcanezumab and erenumab bind to their targets reversibly, fremanezumab and eptinezumab engage the CGRP ligand with greater affinity [13, 16]. CGRP mAbs have been shown to inhibit neurogenic vasodilatation without affecting heart rate or arterial blood pressure in rats [17] CGRP blockade are supposed to spark no effect in the absence of CGRP.[18] CGRP mAbs selectively inhibit the responsiveness of Aδ -fibers but not C-fibers in a rat model of cortical spreading depression [19]. More details are available by Yuan et al. and Edvinsson et al. [2, 20].

## Clinical Evidence for CGRP Monoclonal Antibody in Migraine

### Eptinezumab

Eptinezumab (Vyepti; Lundbeck A/S, Copenhagen, Denmark) is a humanized $IgG_1$ mAb, and is the only CGRP-targeted mAb administered intravenously in doses of 100 mg or 300 mg (quarterly) [21]. It attains 100% bioavailability at the conclusion of the infusion with a half-life of 27 days [22].

Table 2 summarizes eptinezumab-related randomized controlled trials (RCTs). Early phase II trials demonstrated that eptinezumab appeared effective [23, 24]. In PROMISE-1, a phase III RCT assessing eptinezumab against placebo in subjects with EM, after 12 weeks, eptinezumab as a 30 mg, 100 mg, and 300 mg was more effective than placebo in reducing mean monthly migraine days (MMD) [25]. Similarly, in PROMISE-2, after 12 weeks, CM subjects receiving eptinezumab 100 mg and 300 mg reported a MMD of −7.7 and −8.2, respectively (both $p < 0.0001$) compared to placebo, which was −5.6 [26]. The most common reported side effect was nasopharyngitis. Both trials had high placebo response rates, which was attributed to the IV administration route and expectations given the novel nature of the compound. Recently, eptinezumab was assessed as a migraine abortive, and was found to be more effective than placebo for time to headache and MBS freedom [27].

**Table 2** Summary of eptinezumab RCTs

| Study | Phase | Migraine/*N* | Study period | Primary outcome |
|---|---|---|---|---|
| NCT01772524 Dodick et al. (2014) [23] | II | EM<br>*N* = 174 | 3 months | placebo: −4.6<br>1000 mg: −5.6 ($p = 0.03$) |
| NCT02275117 Dodick et al. (2019) [24] | II | CM<br>*N* = 616 | 3 months | ≥ 75% migraine responder rate:<br>placebo: 20.7%<br>10 mg: 33.3% ($p = 0.033$)<br>30 mg, 100 mg, 1000 mg (all NS) |
| NCT02559895 Ashina et al. (2020) (PROMISE-1) [25] | III | EM<br>*N* = 888 | 3 months | placebo: −3.2<br>30 mg: −4.0 ($p = 0.0046$)<br>100 mg: −3.9 ($p = 0.0182$)<br>300 mg: −4.3 ($p = 0.0001$) |
| NCT02974153 Lipton et al. (2020) (PROMISE-2) [26] | III | CM<br>*N* = 1072 | 12 weeks | placebo: −5.6<br>100 mg: −7.7 ($p < 0.0001$)<br>300 mg: −8.2 ($p < 0.0001$) |
| NCT04152083 Winner et al. (2021) (RELIEF) [27] | III | CM<br>*N* = 480 | Acute treatment | Time to pain freedom:<br>placebo: 9 h<br>100 mg: 4 h ($p < 0.001$)<br>Time to absence of MBS:<br>placebo: 3 h<br>100 mg: 2 h ($p < 0.001$) |

All eptinezumab treatments were given intravenously. Primary outcome was MMD reduction for all studies except RELIEF and Dodick et al. (2019) [24]
*EM* episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day, *NS* non-significant

Several ongoing studies assessing eptinezumab in pediatric populations (NCT04537429, NCT04965675) are still being collected [28].

## Fremanezumab

Fremanezumab (Ajovy; Teva, Petah Tikva, Israel), a humanized $IgG_2$ mAb, is given as subcutaneous injection in doses of 225 mg (monthly) and 675 mg (quarterly). Fremanezumab has a half-life of 32 days, and a mean $T_{max}$ of 7 days and 5 days for 225 mg and 675 mg dosages, respectively [29].

Table 3 summarizes fremanezumab related RCTs. In a phase II RCT assessing fremanezumab in patients with high-frequency EM (8–14 headache days of which at least 8 were migraine days), subjects receiving fremanezumab 225 mg and 675 mg reported MMD reductions of −6.27 and 6.09, respectively, compared to − 3.46 in the placebo group ($p < 0.0001$ for both dosages) [30]. The most common AEs were injection site reaction or pain (3–9%), nausea (1%), sinusitis (5%), dizziness (1–5%), and bronchitis (1%) in the treatment groups. HALO studies were phase III RCTs assessing fremanezumab 225 mg and 675 mg against placebo for migraine prevention in both EM and CM patient populations. Both studies found fremanezumab more effective than placebo in reducing MMD ($p < 0.001$ for both dosages) [31, 32]. FOCUS was an RCT assessing fremanezumab 225 mg and 675 mg in patient populations with EM and CM who failed 2 to 4 preventive medications. Fremanezumab was more effective than placebo in reducing MMD, with participants receiving fremanezumab reporting MMD reductions of −4.1 (225 mg) and −3.7 (675 mg) ($p < 0.001$ for both dosages) [33].

## Galcanezumab

Galcanezumab (Emgality; Eli Lilly, Indianapolis, IN) is a humanized $IgG_4$ mAb, and is administered as a monthly subcutaneous injection dose of 120 mg (with an initial loading dose of 240 mg). Galcanezumab has a half-life of 27 days and a mean $T_{max}$ of 5 days [34]. Table 4 summarizes galcanezumab related RCTs. Two phase II RCTs reported galcanezumab more effective than placebo [35, 36]. In EVOLVE-1 and -2, phase III RCTs on galcanezumab for the prevention of EM, EVOLVE-1 recruited 858 patients and EVOLVE-2 recruited 915. Patients who received galcanezumab 120 mg reported a MMD reduction of −4.7 and −4.3 in EVOLVE-1 and -2 respectively, and patients who received galcanezumab 240 mg reported a MMD reduction of −4.6 and −4.2 in EVOLVE-1 and -2, respectively. Patients who received placebo reported an MMD of − 2.3 and −2.7 in EVOLVE-1 and -2, respectively ($p < 0.001$ for all treatment groups) [37, 38]. REGAIN, a phase III RCT assessing galcanezumab for the treatment of CM, reported galcanezumab 120 mg and 240 mg reduced MMD of −4.8 and −4.6, respectively, compared to −2.8 in the placebo group ($p < 0.001$ for both dosages) [39]. A subsequent post hoc analysis found galcanezumab also effective in treating patients with medication overuse headache [40]. CONQUER was a phase III RCT assessing galcanezumab 120 mg in patients with EM or CM who failed multiple preventive treatments. Patients receiving galcanezumab 120 mg reported a MMD reduction of −4.1 compared to −1.0 in the placebo group ($p < 0.0001$) [41]. When differentiating by EM and CM, participants receiving galcanezumab reported a MMD reduction −2.88 and −5.90, respectively.

**Table 3** Summary of fremanezumab RCTs

| Study | Phase | Migraine/*N* | Study period | Primary outcome |
|---|---|---|---|---|
| NCT02025556<br>Bigal et al. (2015) [30] | II | HFEM<br>*N* = 297 | 3 months | placebo: −3.46<br>225 mg: −6.27 ($p < 0.001$)<br>675 mg: −6.09 ($p < 0.001$) |
| NCT02621931 Silberstein et al. (2017) (HALO-CM) [31] | III | CM<br>*N* = 1130 | 3 months | placebo: −2.5<br>225 mg: −4.6 ($p < 0.001$)<br>675 mg: −4.3 ($p < 0.001$) |
| NCT02629861 Dodick et al. (2018) (HALO-EM) [32] | III | EM<br>*N* = 875 | 3 months | placebo: −2.2<br>225 mg: −3.7 ($p < 0.001$)<br>675 mg: −3.4 ($p < 0.001$) |
| NCT03308968<br>Ferrai et al. (2019) (FOCUS) [33] | III | EM, CM<br>*N* = 838 | 3 months | placebo: −0.6<br>225 mg: −4.1 ($p < 0.001$)<br>675 mg: −3.7 ($p < 0.001$) |

All studies required ≤ 2 classes of failed preventive treatments. Primary outcome was MMD reduction for all studies. Fremanezumab 225 mg dosages were given monthly, 675 mg dosages were given every 3 months

*EM* episodic migraine, *HFEM* high-frequency episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day

**Table 4** Summary of galcanezumab RCTs

| Study | Phase | Migraine/*N* | Study period | Primary outcome |
|---|---|---|---|---|
| NCT01625988 Dodick et al. (2014) [35] | II | EM<br>*N* = 218 | 3 months | placebo: − 3.0<br>150 mg: − 4.2 ($p = 0.003$ |
| NCT02959177 Sakai et al. (2020) [36] | II | EM<br>*N* = 915 | 6 months | placebo: − 0.59<br>120 mg: − 3.60 (p < 0.001)<br>240 mg: − 3.36 (p < 0.001) |
| NCT02614183 Stauffer et al. (2018) (EVOLVE-1) [37] | III | EM<br>*N* = 858 | 6 months | placebo: − 2.8<br>120 mg: − 4.7 (p < 0.001)<br>240 mg: − 4.6 (p < 0.001) |
| NCT02614196 Skljarevski et al. (2018) (EVOLVE-2) [38] | III | EM<br>*N* = 915 | 6 months | placebo: − 2.3<br>120 mg: − 4.3 (p < 0.001)<br>240 mg: − 4.2 (p < 0.001) |
| NCT02614261 Detke et al. (2018) (REGAIN) [39] | III | CM<br>*N* = 1113 | 3 months | MHD reduction<br>placebo: − 2.7<br>120 mg: − 4.8 (p < 0.001)<br>240 mg: − 4.6 (p < 0.001) |
| NCT03559257 Mulleners et al. (2020) (CONQUER) [41] | III | EM, CM<br>*N* = 462 | 3 months | placebo: − 1.0<br>120 mg: − 4.1 ($p < 0.0001$) |

All studies required ≤ 2 classes of failed preventive treatments except REGAIN (≤ 3 classes) and CONQUER [2–4 classes]. Primary outcome was MMD reduction for all studies except REGAIN

*EM* episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day, *MHD* mean monthly headache day

**Table 5** Summary of erenumab RCTs

| Study | Phase | Migraine | Study period/*N* | Primary outcome |
|---|---|---|---|---|
| NCT01952574 Sun et al. (2016) [42] | II | EM<br>*N* = 483 | 3 months | placebo: −2.3<br>70 mg: −3.4 ($p = 0.021$)<br>7 mg and 21 mg (NS) |
| NCT02066415 Tepper et al. (2017) [43] | II | CM<br>*N* = 667 | 3 months | placebo: −4.2<br>70 mg: − 6.6 ($p < 0.0001$)<br>140 mg: −6.6 ($p < 0.0001$) |
| NCT02630459 Sakai et al. (2019) [44] | II | EM<br>*N* = 475 | 4–6 months | placebo: 0.06<br>28 mg: −1.19 ($p = 0.004$)<br>70 mg: −2.25 ($p < 0.001$)<br>140 mg: −1.83 ($p < 0.001$) |
| NCT02456740 Goadsby et al. (2017) (STRIVE) [45] | III | EM<br>*N* = 955 | 4–6 months | placebo: −1.8<br>70 mg: −3.2 ($p < 0.001$)<br>140 mg: −3.7 ($p < 0.001$) |
| NCT02483585 Dodick et al. (2018) (ARISE) [46] | III | EM<br>*N* = 577 | 3 months | placebo: −1.8<br>70 mg: −2.9 ($p < 0.001$) |
| NCT03096834 Reuter et al. (2018) (LIBERTY) [49] | III | EM<br>*N* = 246 | 3 months | 50% responder rate<br>placebo: 14%<br>140 mg: 30% ($p = 0.002$) |
| NCT03812224 Takeshima et al. (2021) [47] | III | EM, CM<br>*N* = 261 | 4–6 months | placebo: −1.98<br>70 mg: −3.60 ($p < .001$) |
| NCT03333109 Wang et al. (2021) EMPOwER [48] | III | EM<br>*N* = 900 | 3 months | placebo: −3.1<br>70 mg: −4.2 ($p = 0.002$)<br>140 mg: −4.8 ($p < 0.001$) |

All studies required ≤ 2 classes of failed preventive treatments except, Tepper et al. (≤ 3 classes), LIBERTY (2–4 classes), and Takeshima et al. (≤ 3 classes). Primary outcome was MMD reduction for all studies except LIBERTY

*EM* episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day, *NS* non-significant

### Erenumab

Erenumab (Aimovig; Amgen, Thousand Oaks, CA), is a fully human $IgG_2$ mAb. It is administered as a subcutaneous injection in doses of 70 mg or 140 mg (monthly). Unlike the other mAbs that target CGRP ligands, erenumab binds specifically to the CGRP receptor. Erenumab has a $T_{max}$ ~6 days, and a half-life of 28 days [34].

Table 5 summarizes erenumab related RCTs. Several phase II RCTs demonstrated erenumab (in dosages of 28 mg, 70 mg, and 140 mg) to be more effective than placebo in reducing MMDs [42–44]. Two pivotal studies, STRIVE and ARISE, demonstrated that erenumab was efficacious and had favorable tolerability and safety profiles. STRIVE was a 6-month phase 3 trial of monthly subcutaneous erenumab 70 mg, 140 mg, vs placebo for EM. Primary endpoints were met for 70 mg and 140 mg vs placebo for reduction in mean migraine days of −3.2 days and −3.7 days vs placebo −1.8 days at weeks 13–24 ($p < 0.001$ for both). There have been safety updates related to hypertension and constipation after erenumab was approved [45]. Constipation was a common AE in clinical trials and rated mild to moderate in severity. Concomitant medication associated with constipation may increase the risk of severe cases. In ARISE, only 1.8% ($n = 5/283$) of participants in the erenumab group discontinued treatment due to AE [46]. ARISE was a 12-week phase III RCT trial of subcutaneous erenumab 70 mg monthly vs placebo in 577 patients with EM (8.3 MMDs at baseline). The primary endpoint was met for reduction in MMDs, with −2.9 days vs −1.8 days ($p < 0.001$) in drug vs placebo groups respectively. Similar findings were demonstrated in two phase III studies performed in Asia, middle east, and Latin America [47, 48]. LIBERTY enrolled patients with EM that failed 2 to 4 preventive treatments. After 12 weeks, 30% of patients receiving erenumab 140 mg reported a 50% or greater reduction of MMD compared to 14% from the placebo group (95% CI 1.4–5.2; $p = 0.002$) [49].

## Clinical Perspective

Since the approval of CGRP-targeted mAbs in 2018, it has been a widely prescribed and effective migraine preventive medication. The AHS and the European Headache Federation both recommend initiation of CGRP-targeted mAb upon failure of at least 2 standard oral migraine preventives [50, 51]. Overall, it reduces 0.7–2.4 MMD and 0.5–2.5 acute medication use days. The low number-needed-to-treat and high number-needed-to-harm of CGRP-targeted mAbs reflect a favorable benefit-risk profile against other migraine preventive therapies [52]. CGRP receptor blockade may alter the function of amylin leading to constipation, for which the FDA has issued a warning on erenumab regarding possible worsening of constipation. In addition, CGRP plays a role in placental vascular adaptation and decidualization [53]. CGRP is believed to be involved in utero-placental functions, and IgG can cross the placenta [54]. At this moment, we do not have sufficient clinical data to justify its safety for use in pregnant or breastfeeding women.

CGRP is a potent peripheral and cerebral vasodilator, and plays an influential role in mediating regional organ blood flow and vascular resistance [55]. Studies of short-term blockade of CGRP in animal models demonstrated no changes in heart rate, blood pressure, coronary flow, and cardiac output. Phase II and III RCTs of the CGRP-targeted mAbs did not demonstrate any cardiovascular safety concerns [56]. Post-marketing surveillance of erenumab revealed an association of elevated blood pressure [57]; hypertension has since been included as warnings and precautions in the prescribing information for erenumab. No other major cardiac safety issues with CGRP antagonism have been established at the time of writing. However, diminished CGRP activity has been reported to be involved with the pathophysiology of Raynaud's phenomenon (RP) [58]. A retrospective cohort study reported 5.3% of the study population with RP had microvascular complications (e.g., worsening RP, digital ulcerations, and gangrenous necrosis) after initiating treatment with a CGRP-targeted mAb [59]. No statistically significant differences were found in risk factors for RP or with a specific CGRP-targeted mAb. Nevertheless, caution should be considered when prescribing CGRP-targeted mAbs to patients with RP. While cardiovascular conditions are not listed as a contraindication for prescribing CGRP-targeted mAbs and gepants, the potential of CGRP antagonism to accentuate and/or unmask cardiovascular complications, albeit rare, cannot be overlooked. CGRP neutralization may block the protective vasodilatory response in certain disease states [60]. We, therefore, recommend reviewing the risks and benefits before prescribing CGRP-targeted mAbs and gepants in patients with cardiovascular conditions (e.g., hypertension, coronary artery disease, cerebral ischemia, peripheral vascular disorder). In addition to informing patients about cardiovascular risks, providers should monitor patients for changes in vascular perfusion and hemodynamics. Long-term studies examining cardiovascular safety in CGRP antagonism are still warranted.

Due to complementary mechanism of actions, concurrent use of onabotulinumtoxinA and CGRP-targeted mAb seems additive in several real-world studies [61, 62]. Such a dual therapy is considered "probably effective" by the AHS,[50] but may not be covered by insurance companies. Similarly, the benefit of concurrent use of CGRP-targeted mAb and gepants is uncertain; well-designed controlled trials are needed [63]. In addition, switching between CGRP-targeted

mAbs due to lack of efficacy remains to be investigated. A small retrospective cohort demonstrated a small benefit of switching with ≥ 50% responder rate in 12% of patients [64]. It has been our personal experience that a second mAb may be beneficial if the first one fails or has significant AEs.

## Conclusion

Thirty years after the discovery of CGRP, we now have 4 different CGRP-targeted mAb formulations that bind to either CGRP ligands or its canonical receptors. With CGRP being a critical neuropeptide in migraine pathogenesis, CGRP-targeted mAb was specifically developed for migraine treatment. In clinical trials, it reduces MMD and acute medication use days with minimal AEs. It works in subjects who failed multiple preventives or overused acute medications. Dosing convenience and superior tolerability further enhance its compliance. Furthermore, it may augment the therapeutic effect when used in conjunction with other preventive medications of different mechanisms of action. However, there remains no antidote if a serious AEs occurs, and the long-term effects from prolonged blockade of CGRP's protective mechanisms in susceptible populations remain to be explored. These newly arrived CGRP-targeted mAbs are a powerful addition to the headache medicine's armamentarium.

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**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

## Declarations

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