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CHRONIC DAILY HEADACHE (S-J WANG AND S-P CHEN, SECTION EDITORS)



# Real-World Patient Experience of CGRP-Targeting Therapy for Migraine: a Narrative Review

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## Abstract

**Purpose of Review** To summarize available calcitonin gene-related peptide (CGRP)-targeting therapies for migraine and discuss their use in real-world populations.

**Background** CGRP has long been a topic of interest in migraine pathophysiology, with new therapies targeting CGRP since 2018 for both the preventive and acute treatment of migraine.

**Methods** We searched PubMed using keywords including "migraine," "CGRP," "real-world," "erenumab," "galcanezumab," "fremanezumab," "eptinezumab," "ubrogepant," "rimegepant," and "atogepant." We reviewed all pertinent studies and summarized main findings. We also compiled detailed patient characteristics (e.g., migraine diagnoses, medication overuse, prior treatment failures) and treatment outcome measures, such as 50% responder rates, reduction in migraine days, and adverse event rates in several tables.

**Recent Findings and Summary** Overall, studies reporting real-world patient experiences of CGRP-targeting therapies suggested meaningful effectiveness for migraine treatment with response rates comparable to the numbers reported in clinical trials. Furthermore, studies suggested benefit in patients with multiple prior unsuccessful treatment trials, medication overuse, and complex medical comorbidities. In some studies, adverse event rates have been notably higher than reported in clinical trials. Additional long-term data is needed to further evaluate sustained efficacy, predictors of treatment response, and adverse events.

**Keywords** Real-world studies · CGRP · Monoclonal antibody · CGRP receptor antagonist · Medication overuse · Chronic migraine

## Introduction

Calcitonin gene-related peptide (CGRP) has been a focus of migraine research for decades. The CGRP neuropeptide, released predominantly from sensory nerves, plays a key role in migraine pathophysiology [1]. Both in vitro and in vivo studies have demonstrated increased CGRP levels in triggered and spontaneous migraine attacks, with normalization after the migraine attack is treated [2–7]. In the last several years, multiple acute and preventative migraine therapies have become available that target either the CGRP ligand or its receptor. These include four monoclonal antibodies (mAbs) that target either the CGRP receptor or ligand and several small molecule CGRP receptor antagonists. Early randomized controlled trials showed promising efficacy and safety data for these new medications. However, some clinical trials were performed on selected patients that might not necessarily represent the real-world patient population, and patients were followed for limited periods of time. Subsequent studies have evaluated the efficacy and safety of CGRP-targeted therapies in broader patient populations, including patients with chronic migraine (CM), patients with medication overuse (MO), and patients with multiple prior unsuccessful treatment trials. Because some of these studies were longer in duration than the original clinical trials, they were also able to evaluate for adverse effects (AEs) over longer periods of time. In this narrative review, we provide an overview of the effectiveness and safety of CGRP-targeted therapy for migraine, as reported in real-world studies.

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## Erenumab

Erenumab is a fully human mAb that binds the CGRP receptor. It was approved by the FDA in May of 2018 for migraine prevention.

The efficacy and safety profile of erenumab has been established in several clinical trials. STRIVE and ARISE trials evaluated erenumab in patients with episodic migraine (EM) with no more than 2 previous unsuccessful preventive treatment trials, and each reported a statistically significant reduction in mean monthly migraine days (MMD) compared to placebo (2.9–3.7 versus 1.8) [8, 9]. Other than injection site pain, adverse event (AE) rates were similar to placebo in both studies and included nasopharyngitis (5.3–11%), upper respiratory tract infection (4.7–6.7%), sinusitis (2.1–3.4%), constipation (1.4–3.4%), nausea (1.9–2.5%), and fatigue (1.9–3.5%). Rates of discontinuation due to AEs were low and comparable across groups. These phase 3 trials were followed by studies showing efficacy of erenumab in patients with CM [10] and patients with episodic migraine (EM) who had 2–4 previous unsuccessful preventative trials [11]. When both EM and CM were enrolled in the same study, they showed similar 50% responder rates (32% versus 17% placebo), with constipation reported more frequently in the erenumab group versus placebo (4.6% versus 0.8%) [12]. When erenumab was compared to a more traditional preventative therapy (topiramate) in a double-blind controlled trial, erenumab had a higher 50% responder rate in reduction of MMD (55% versus 31%, $p < 0.001$) and a lower rate of discontinuation due to AEs (11% vs. 39%, $p < 0.001$) [13].

Long-term open-label extensions (OLE) on clinical trials have demonstrated sustained efficacy in EM and CM populations, with 50% responder rates of 45–59% over study periods of 64 weeks to 5 years and no significant new safety concern [14–16]. Most AEs were mild to moderate. In a 5-year OLE, serious events were reported by 49 patients (13%), though there was no clear treatment-related pattern, and the exposure-adjusted AE incidence rates were comparable to the placebo arm of the original double-blind phase of the study [17]. Of note, there was no clinically significant change in blood pressure from baseline.

Being the first CGRP mAb approved for migraine treatment, there are more real-world studies of erenumab compared to other available CGRP mAbs. One retrospective cohort study that combined structured clinical interview and chart review looked at real-world effectiveness and tolerability of 295 patients given a prescription for erenumab, focusing on patient-perceived benefit and AEs. Of the 241 patients who took at least 1 dose, 70% ($n = 169$) had at least 1 AE; most commonly constipation (43%), injection site reaction (24%), fatigue (15%), worsening headache (12%), and dizziness (11%). One serious AE of small bowel obstruction occurred that was felt to be medication related. Overall, 70% patients felt the benefits outweighed the drawbacks. Cost was felt to be prohibitive and prevented initiation or continuation in 17% patients. Overall the effectiveness of erenumab was demonstrated though higher rates of AEs than reported in initial clinical trials were noted [18].

A Dutch study used a rigorous daily electronic diary and clinical visits to look at real-world efficacy and safety of erenumab over 6 months in migraine patients who had at least 4 prior unsuccessful preventative treatment trials and were not taking concurrent preventatives or overusing analgesics. Among the 100 patients included in the study, 36% of patients had ≥ 50% reduction in MMD (50% responders) in 3 out of 6 months. Responder rates were higher in those with EM versus CM. Of those who were 50% responders in the initial 3 months, 72% of those had sustained response in later months. In those who had < 50% reduction in MMD in the first 3 months, 23% went on to become 50% responders in months 4–6. AEs were reported in 93% of patients, including constipation (72%), fatigue (43%), and injection site reaction (27%). For patients who did not respond in the first 3 months, escalating the dose from 70 to 140 mg resulted in additional benefit, with 21% of the 140 mg group (vs. 14% of the 70 mg group) showing response during the last 3 months of treatment. Overall, the study demonstrated sustained effectiveness of erenumab in patients with multiple previous unsuccessful treatment trials, though in some patients, a trial period longer than 3 months was required [19].

An Italian multicenter longitudinal cohort study looking at erenumab in CM and high frequency EM (HFEM) showed the CM group had a higher 50% response rate in MMD or monthly headache days (MHD) than HFEM by week 48 (76% CM versus 56% HFEM). Notably, given an option to increase from 70 to 140 mg, 63% patients chose to escalate the dose. Twenty-one (9%) of the original 242 enrolled patients discontinued the study prematurely, 7 due to lack of efficacy and 6 for adverse events. AEs were reported in 19% and were typically mild, most commonly constipation (10%) and injection site erythema (3%). Three patients (1%) had serious AEs—one of which was considered treatment-related (paralytic ileus requiring hospitalization). Of note, median monthly analgesic intake at baseline was 11 days/month for HFEM and 20 days/month for CM, dropping after the 48-week treatment period to 5 and 6 days, respectively. Overall, the study demonstrated sustained reduction of analgesic use, MMD/MHD, disability, and pain severity for both HFEM and CM, with low discontinuation rate for either AEs or inefficacy [20].

Several other studies have reported real-world patient experience of erenumab in tertiary headache centers who have a high proportion of patients with CM (75–100%),

MO (19–91%), and at least 3 prior preventive medication failures (49–100%), including onabotulinumtoxinA failures [21–27]. These studies demonstrated overall effectiveness of erenumab, with a 50% responder rate of 31–100% with AEs reported in 0–71%. Discontinuation rates due to AEs ranged from 0 to 12% [21, 23–27]. Severe adverse events resulting in discontinuation included constipation, worsening headache, flu-like symptoms, itchiness, mood deterioration, allergic reaction, worsening of migraine, skin rash, and new onset hypertension. One patient reported new-onset hypertension without other identified cause that resolved within 6 weeks of discontinuation [24]. We identified a total of 15 studies reporting real-world patient experience of erenumab that included at least 75 patients and had available data regarding headache characteristics and response to treatments. Patient demographics and key treatment outcomes are summarized in Table 1 (baseline characteristics) and Table 2 (response to treatment) [19–33].

Of note, several studies reported the predictors of erenumab treatment response. In the study by Barbanti et al., predictors for success in those with HFEM included cutaneous allodynia and a lower number of prior unsuccessful treatment trials. In those with CM, positive predictors for treatment response included higher migraine frequency at baseline, lower analgesic use, fewer previous unsuccessful treatment trials, cutaneous allodynia, and positive treatment response to triptans. Responder was defined as having a 50% or greater reduction in MMD or MHD [20]. Another study looked at baseline characteristics and symptoms of psychiatric comorbidities in patients with refractory CM treated with up to 6 monthly doses of erenumab. Responders to erenumab had lower baseline MMD frequency, lower scoring on migraine-related disability assessment (MIDAS), lower MO rates, and lower pain catastrophizing scores compared to non-responders. They did not see a meaningful difference in scoring related to comorbidities of depression, anxiety, or sleep quality when comparing erenumab responders to non-responders. In this study, responder was defined as those who had 30% or greater reduction in MMD [28].

**Table 1** Erenumab: characteristics of study participants at baseline [19–33]

| Study | *n* | Headache type (%) | % Patients with > 3 unsuccessful preventive medications | # past preventive medications (mean) | % with prior trial of Botox | % with MOH |
|---|---|---|---|---|---|---|
| Robblee (2020) | 101 | EM: 5% | | 11.2 | 83% | 19% |
| | | CM: 94% | | | | |
| De Vries Lentsch (2021) | 100 | EM: 54% | 100% | (all ≥ 4) | | 0% |
| | | CM: 46% | | | | |
| Barbanti (2019) | 78 | HFEM: 17% | | 5.13 | | 62% |
| | | CM: 83% | | | | 85% |
| Barbanti (2021) | 242 | HFEM: 25% | 100%[a] | 3.7 | | 30% |
| | | CM: 75% | 100% [a] | 4.9 | | 88% |
| Ornello (2020) | 89 | EM: 6% | 42% | | 49% | 72% |
| | | CM: 94% | | | | |
| Silvestro (2021) | 84 | CM: 100% | 100% | 6.3 | 100% | 64% |
| Lambru (2020) | 162 | CM: 100% | 100% [a] | 8.4 | 91% | 54% |
| Scheffler (2020) | 100 | EM: 26% | 100% | (all ≥ 5) | | |
| | | CM: 74% | | (all ≥ 6) | | 66% |
| Raffaelli (2020) | 139 | CM: 100% | 100% | (all ≥ 5) | 100% | |
| Russo (2020) | 70 | CM: 100% | 100% | 4.7 | 77% | 91% |
| Straube (2021) | 542 | EM: 50%, CM 50% | 100% | 4.6 | 38% | |
| Cheng (2020) | 170 | CM: 100% | 100% [a] | | 95% | 50% |
| Schoenen (2021) | 156 | EM: 51%, CM: 49% | 74% [a] | | 0% | |
| Belvis (2021) | 210 | EM: 10%, CM: 90% | | 7.8 | 95% | 70% |
| Ornello (2021) | 1410 | EM: 26%, CM: 76% | | 5.5 | | 52% |

Table includes real-world studies of erenumab that had $n > 75$ and had available data regarding headache characteristics and response to treatments

[a]Refractory to ≥ 3 preventives

**Table 2** Erenumab: response to treatment [19–33]

| Study | Length of study (months) | Mean reduction of MMD | Mean reduction of MHD | 30% responder rate[a] | 50% responder rate[a] | 75% responder rate[a] | 100% responder rate[a] |
|---|---|---|---|---|---|---|---|
| Robblee (2020) | ≤6 | 8.4 | 6.5 | | 55%MMD 35% MHD | 38% | 9% |
| De Vries Lentsch (2021) | 3 | 3.8 | 3.5 | | | | |
| | 6 | 4.8 | 4.7 | 60%[b] | 36%[b] | | |
| Barbanti (2019) | 1 | EM: 3.8 | | | 50% | 25% | 0% |
| | | CM: 12.2 | | | 68% | 41% | 0% |
| | 2 | EM: 7 | | | 100% | 100% | 100% |
| | | CM: 15 | | | 88% | 38% | 0% |
| Barbanti (2021) | 12 | HFEM: 4.3 | | | 56%[c] | 32%[c] | 9%[c] |
| | | | CM: 12.8 | | 76%[c] | 45%[c] | 1%[c] |
| Ornello (2020) | 6 (analyzed monthly) | 15 (median) | | 41–71% | 32–57% (71.9% anytime) | 16–46% | 1–11% |
| Silvestro (2021) | 6 | | | 65% | | | |
| Lambru (2020) | 3 | 6 | 6.3 | 49% | 35% | 13% | 0% |
| | 6 | 7.5 | 6.8 | 60% | 38% | 22% | 0% |
| Scheffler (2020) | 3 | EM: 3.43 | 3.33 | | 58% MMD 46% MHD | | |
| | | CM: 4.72 | 5.47 | | 42% MMD 32% MHD | | |
| Raffaelli (2020) | 3 | | 3.7 | 51% MHD | 31% MHD | | |
| Russo (2020) | 3 | | 9.7 | 70% MHD | 53% MHD | 18% MHD | |
| | 6 | | 12.2 | 80% MHD | 70% MHD | 26% MHD | |
| Straube (2021) | 3 | 6.2 | 7.5 | | | | |
| Cheng (2020) | 3 | 9.7 | 8.4 | | 58.8% | | |
| | 6 | 10.4 | 9.3 | | 46.5% | | |
| Schoenen (2021) | 3 | | EM: 4.2 | 68% MHD | 55% MHD | 16% MHD | 4% MHD |
| | | | CM: 7.8 | 60% MHD | 43% MHD | 17% MHD | 3% MHD |
| Belvis (2021) | 3 | 6.5 | 8.6 | | 37.0% | | |
| Ornello (2021) | 3 | Men: 7.1 | 6.9 | 61% MHD | 47% MHD | 18% MHD | |
| | | Women: 7.7 | 7.9 | 58% MHD | 46% MHD | 19.1% MHD | |

[a]Reported as reduction of MMD unless otherwise noted

[b]Responder if 50% reduction in any 3 of the 6 months

[c]Reduction in MMD **or** MHD

## Galcanezumab

Galcanezumab is a humanized mAb that targets the CGRP ligand to prevent the binding of CGRP to its receptor. It was approved by the FDA in September 2018 for preventative treatment of migraine in adults and in June 2019 for episodic cluster headache in adults [34].

The efficacy and safety of galcanezumab have been established in several pivotal studies. The EVOLVE-1 and EVOLVE-2 trials demonstrated efficacy of galcanezumab for preventative treatment in patients with EM [35, 36]. Both were 6-month, multicenter, double-blind, placebo-controlled trials that randomized patients to receive monthly galcanezumab (120 mg or 240 mg monthly) or placebo. Both trials demonstrated a statistically significant reduction of mean MMD in subjects receiving galcanezumab, with a reduction of 4.7 days (120 mg) and 4.6 days (240 mg) in EVOLVE-1; 4.3 days (120 mg) and 4.2 days (240 mg) in EVOLVE-2; compared to those receiving placebo (2.8 days in EVOLVE-1; 2.3 days in EVOLVE-2); $p < 0.001$ for all. REGAIN, a multicenter phase 3 randomized clinical trial with a 9-month open-label extension, demonstrated the efficacy of galcanezumab (120 mg monthly with a 240 mg loading dose or 240 mg monthly) for prevention of CM, with a statistically significant reduction in mean MMD in subjects receiving galcanezumab (4.8 days (120 mg) and 4.6 days (240 mg)) compared to those receiving placebo (2.7 days)); $p < 0.001$ for both [37]. REGAIN participants receiving 240 mg monthly



galcanezumab had a higher rate of injection site reactions, including injection site erythema (5%), pruritis (2%), and sinusitis (3%) compared to placebo. The CONQUER study, another multicenter randomized placebo-controlled trial, demonstrated efficacy in subjects with treatment-resistant migraine (EM or CM) [38].

Real-world effectiveness of galcanezumab was recently demonstrated in the GARLIT study, a multicenter prospective observational cohort study [39]. In this study, 163 patients with HFEM or CM were treated with galcanezumab (240 mg loading dose followed by 120 mg monthly) for 6 months [39]. Patients were 18 years of age or older, had no history of involvement in CGRP mAb trials, and met American Headache Society [40] and European Headache Federation [41] guideline recommendations for use of galcanezumab. Patients with HFEM and CM had a median of 4 and 5 previous unsuccessful preventive treatment trials, respectively. MO was reported in 20.6% of patients with HFEM and 85.3% of patients with CM. At the end of the 6th month of galcanezumab use, patients with HFEM had 8 fewer MMD, and patients with CM had 13 fewer monthly moderate-or-greater headache days. A 50% or greater response rate was noted in 76.5% of the HFEM group and 63.5% of the CM group. Ten (6.1%) patients discontinued galcanezumab use early, due to inefficacy. There was a significant decrease in the days with acute headache medication use and both headache impact test (HIT-6) and MIDAS scores. At 6 months, 77.2% patients with CM converted to EM, and 82% patients with MO at baseline no longer had MO (Table 3). AEs were noted in up to 10% of patients, the most common being injection site reactions and constipation (each in > 2% of participants). No serious AEs occurred, and no participants discontinued due to AEs. Of note, the authors reported that lower BMI ($p = 0.0180$) and fewer prior unsuccessful treatments ($p = 0.013$) were associated with having ≥ 50% reduction in MHD in patients with CM (Table 4) [39].

Kwon et al. evaluated the real-world efficacy of galcanezumab in 54 patients with migraine (78% CM, 22% EM) in a prospective study [42]. A majority (83%) of participants had at least 3 prior unsuccessful preventive treatment trials, and 26% had MO. Response was assessed after 3 monthly doses of galcanezumab. Reductions were noted in mean MHD (−7.4 days ± 8.61, $p < 0.001$), moderate to severe headache days (−5.0 days ± 11.18, $p = 0.003$), days with acute headache medication use (−4.0 days ± 9.40, $p = 0.005$), as well as in HIT-6 and MIDAS scores. The 50% responder rate in patients who had previously failed ≤ 3, 4, and 5 classes of preventative medications were 76.9%, 56.3%, and 44.0%, respectively. The authors concluded that the effectiveness of galcanezumab was comparable to, or better than, results from major clinical trials.

## Fremanezumab

Fremanezumab, a fully humanized monoclonal antibody targeting the CGRP ligand, was FDA-approved in September 2018 for prevention of migraine in adults.

Randomized clinical trials have established the efficacy of fremanezumab for prevention of both EM [43] and CM [44]. In a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel group trial, patients with EM who had prior unsuccessful treatment response to no more than one other class of migraine preventative were randomized to receive monthly (125 mg) or quarterly (675 mg) dosing of fremanezumab [43]. Over a 3-month trial period, the groups receiving fremanezumab had a significant reduction in MMD compared to those receiving placebo (−3.9 to 4 days vs. −2.6 days; $p < 0.001$). The HALO-CM trial, a randomized controlled phase 3 study, demonstrated efficacy of fremanezumab for prevention of CM [44]. In this study, patients with CM receiving monthly (125 mg) or quarterly (675 mg) doses had a significant reduction ($p < 0.001$) of mean MHDs (−4.6 days in fremanezumab monthly and −4.3 days in fremanezumab quarterly) compared to placebo (−2.5 days) over a 3-month trial period [44]. Compared to those receiving placebo, a significantly higher ($p < 0.001$) percentage of patients receiving fremanezumab had a 50% or greater reduction in average MHD (41% in the fremanezumab-monthly group, 38% in the fremanezumab-quarterly group, and 18% in the placebo group). Injection site reactions were noted in 47% of both groups receiving fremanezumab, compared with 40% of patients receiving placebo ($p = 0.08$ for fremanezumab-quarterly vs. placebo; $p = 0.03$ for fremanezumab-monthly vs. placebo). In the FOCUS trial, fremanezumab was effective and well-tolerated as preventative therapy in patients with EM (39%) and CM (61%) who had prior unsuccessful preventive treatment trials from 2 to 4 drug classes in the last 10 years [45]. In its OLE, efficacy and tolerability were sustained

**Table 3** Galcanezumab: characteristics of study participants at baseline [39, 42]

| Study | *n* | Headache type (%) | # past preventive medications | % with prior trial of Botox | % with MO |
|---|---|---|---|---|---|
| Vernieri | 163 | HFEM: 20%<br>CM: 80% | 4 (median)<br>5 (median) | 45.4% | 71.8% |
| Kwon | 54 | EM: 22%<br>CM: 78% | 4 (mean) | 59.2% | 26% |

**Table 4** Galcanezumab: response to treatment [39, 42]

| Study | Length of study (months) | Mean reduction of MMD | Mean reduction of MHD | 30% responder rate | 50% responder rate | 75% responder rate | 100% responder rate |
|---|---|---|---|---|---|---|---|
| Vernieri | 6 | HFEM: 8 | | | 76.5% | 32.4% | 11.8% |
| | | | CM: 13 | | 63.5% | 37.8% | 7.1% |
| Kwon | 3 | | 7.4 (overall) | EM: 66.7% | 58.3% | 41% | 25% |
| | | | 5.0 (mod/sev) | CM: 61.9% | 54.8% | 33.3% | 11.9% |

at 6 months [46]. Another multicenter, double-blind, randomized, parallel group study assessed the long-term efficacy and safety of fremanezumab in adults with EM and CM and noted reductions in MMD, MHD, and headache-related disability over 52 weeks. Fremanezumab was well-tolerated during the study period [47].

A recent retrospective, observational cohort study demonstrated the effectiveness of fremanezumab for migraine prevention in a real-world population [48]. In this study, data of 172 patients receiving fremanezumab were extracted from the Midwest component of EMRClaims + and manual chart review. Patients were ≥ 18 years old and not on other CGRP-targeted therapies. One hundred sixty-eight patients (98%) received fremanezumab monthly, and 3 patients (2%) received fremanezumab quarterly. Data were collected from before and ≥ 1 month after initiation of fremanezumab. Fifty-four patients were eligible for analysis of headache frequency, demonstrating a mean MHD reduction of 14 days ($p < 0.0001$). Migraine pain intensity data were available for 74 patients and demonstrated an 18% reduction ($p = 0.014$) in mean visual analog scale (VAS) pain score (from $5.47 \pm 3.19$ prior to fremanezumab to $4.51 \pm 3.34$ ≥ 1 month after initiation of fremanezumab). Of 129 patients with data of patient-reported improvement, 108 (83.7%) reported improvement, and 21 (16.3%) reported no improvement ≥ 1 month after initiation of fremanezumab. Significant reductions were seen in mean monthly ER visits (from $0.72 \pm 1.26$ prior to fremanezumab to $0.54 \pm 0.89$ ≥ 1 month after initiation of fremanezumab; $p = 0.003$) and in mean monthly outpatient visits (from $1.04 \pm 1.19$ prior to fremanezumab to $0.81 \pm 0.87$ ≥ 1 month after initiation of fremanezumab; $p < 0.001$), but the change in associated costs was not significant. The authors concluded that fremanezumab significantly reduced headache frequency, migraine pain intensity, and healthcare resource utilization in patients with migraine in a real-world setting.

## Eptinezumab

Eptinezumab, a humanized mAb targeting the CGRP ligand, was approved in February 2020 for migraine prevention in adults.

The efficacy and safety of eptinezumab were demonstrated in adults with EM and CM in the PROMISE-1 and PROMISE-2 studies, respectively [49, 50]. Both were multicenter phase 3 double-blind, placebo-controlled, randomized controlled trials. In the PROMISE-1 study, eligible adults with EM were randomized to receive eptinezumab 30 mg, 100 mg, 300 mg, or placebo every 12 weeks for up to 1 year. Compared with placebo, significant reductions in MMD were noted in groups receiving eptinezumab 100 mg (−3.9 days) and 300 mg (−4.3 days). In the PROMISE-2 trial, significant reductions in MMD were noted in eligible adults with CM receiving eptinezumab 100 mg (−7.7 days) and 300 mg (−8.2 days) compared to those receiving placebo (−5.6 days, $p < 0.0001$). Nasopharyngitis was seen in 9.4% of patients receiving eptinezumab 300 mg versus 6% in placebo and was the only adverse effect reported in more than 2% of the eptinezumab group with an incidence of at least 2% over placebo.

The PREVAIL trial was an open-label study that evaluated eptinezumab 300 mg every 12 weeks for up to 8 administrations [51]. Patient-reported improvements were sustained throughout the trial. A total of 8 patients (6.3%), among the 128 patients analyzed, discontinued eptinezumab for AEs, including 3 patients who had a hypersensitivity reaction to infusion. The most frequent treatment-emergent AEs included nasopharyngitis (14%), upper respiratory tract infection (8%), sinusitis (8%), influenza (6%), bronchitis (6%), and migraine (6%). To date, there have not been real-world studies specifically reported on eptinezumab.

## Real-World Evidence for the Use of CGRP Monoclonal Antibodies and OnabotulinumtoxinA

When used for CM, onabotulinumtoxinA is injected into head and neck muscles that contain trigeminal and cervical sensory neurons and inhibits the exocytosis of pro-inflammatory and excitatory neuropeptides including CGRP and glutamate and others and ultimately reduces pain transmission and prevents central sensitization [52]. While onabotulinumtoxinA is thought to primarily prevent activation of C-fibers, CGRP-targeted therapies prevent activation of A-delta fibers, raising

the possibility of synergistic effects when combining these treatments [53]. To address the efficacy of dual therapy in a real-world setting, a retrospective review was conducted of 257 CM patients who received 2 or more consecutive cycles of onabotulinumtoxinA and at least 1 month of combination therapy with a CGRP mAb added to the onabotulinumtoxinA. In this study, 78%, 16%, and 6% patients received erenumab, galcanezumab, and fremanezumab, respectively (Table 5) [54]. Compared with baseline (onabotulinumtoxinA only), patients on combination therapy had a significant decrease in MHD, 3.8 days at 6 months and 4 days at 12 months in patients in the primary analysis cohort. At 6 months, 36.7% of patients in the primary analysis cohort had ≥ 50% reduction in MHD compared with baseline, and 45.1% of patients in the primary analysis cohort had a 5 or greater point reduction in MIDAS score. AEs were noted in 28% of patients, of which the most common were constipation, nausea, musculoskeletal pain, and neck pain. Another retrospective chart review study evaluating the safety and efficacy in adult patients treated with onabotulinumtoxinA plus CGRP mAb therapy had similar observations [55]. This study included 148 patients ≥ 18 years old with a physician diagnosis of CM at a single institution who received at least 2 consecutive cycles of onabotulinumtoxinA prior to administration of a CGRP mAb (56.7% erenumab, 42.6% fremanezumab, 0.7% galcanezumab) and underwent at least 1 month of combination therapy. After addition of CGRP mAb, patients were followed for up to 4 post-index visits at approximately 3-month intervals. Compared with baseline (onabotulinumtoxinA alone), mean MHDs were reduced by 2.56, 3.78, 3.70, and 4.60 days at the 1st ($n = 113$), 2nd ($n = 90$), 3rd ($n = 69$), and 4th ($n = 43$) post-index visits, respectively. With respect to baseline (onabotulinumtoxinA alone), a ≥ 50% reduction in MHD was noted in 34.9% (95% CI 21.0–50.9) of patients at the 4th post-index visit. AEs were noted in 12.2% of patients, the most common of which was constipation (5.4%) followed by injection site reaction (3.4%). The above studies demonstrated that the addition of a CGRP mAb to onabotulinumtoxinA for chronic migraine was associated with clinically meaningful improvement and was largely well-tolerated.

## Side Effects of CGRP Monoclonal Antibodies

Since erenumab was FDA approved in May 2018, several cases of serious constipation have been reported, including cases requiring hospitalization and surgery, prompting the addition of a post-marketing warning to the product insert [56]. Cases of constipation often, but not always, occurred after the first administration of erenumab. The risk may be higher when used concurrently with other medications that may affect GI motility. Patients on erenumab should be monitored for constipation and managed individually [56].

The erenumab product insert was additionally revised to include a warning regarding a risk of hypertension. A post-market report from the FAERS database (May 2018 to April 2020) identified 61 cases of erenumab-related elevated blood pressure, including aggravation of pre-existing hypertension (31%) and development of hypertension de novo (69%) in patients on erenumab. Seven patients required hospitalization [57]. Hypertension most often occurred within the week following first administration; however, it has been observed to occur at any time during erenumab use. The observation raises the question whether all CGRP-targeted therapy carry a similar risk. The FOCUS and HALO studies along with their long-term follow-up data assessed for hypertension in patients receiving 6–12 months of fremanezumab [58]. Both studies had two blood pressure-related AEs, with one increase and one decrease in blood pressure parameters in each study. In FOCUS and its OLE, mean blood pressure values were unchanged or slightly decreased. In HALO long-term study (LTS), it was noted that in subjects on anti-hypertensive medications for hypertension, mean blood pressures were unchanged or lower at the end of treatment compared with baseline [58]. More studies are needed to assess how CGRP-targeted therapies affect blood pressure and its cardiovascular/cerebrovascular safety. Until then,

**Table 5** Studies looking at CGRP mAb (erenumab, fremanezumab, or galcanezumab) with concurrent onabotulinumtoxinA [54, 55, 84]

| Study | *n* | Headache type | Length of study (months) | Mean reduction of MHD (after addition of CGRP to onabotulinumtoxinA therapy) | 50% responder rate |
|---|---|---|---|---|---|
| Mechtler | 148 ($n = 43$ at 12 months) | CM | 6 | 3.8 | 28.9% (10.0% with 75% response) |
| | | | 12 | 4.6 | 34.9% (11.6% with 75% response) |
| Blumenfeld | 257 (primary analysis cohort) | CM | 6 | 3.8 | 36.7% |
| | | | 12 | 4.0 | 31.5% |
| Cohen | 66 | CM | 2.81 (mean, range of 2–4 months) | 5.7 | |

patients on CGRP-targeted therapy should be monitored for elevated blood pressure, and if no alternative etiology is found for de novo or worsening hypertension, consider discontinuation.

Raynaud's phenomenon has also been identified as a potential complication of CGRP-targeted therapy. A retrospective cohort study assessed 169 patients with Raynaud's who received a CGRP mAb [59]. Nine patients (5%) had microvascular complications after receiving galcanezumab ($n = 3$), fremanezumab ($n = 1$), or erenumab ($n = 5$). Of these 9 patients, 5 carried a known history of primary or secondary Raynaud's phenomena prior to CGRP mAb use. Four received a new diagnosis of Raynaud's phenomena after starting a CGRP mAb, one of whom had gangrene and autonecrosis of two digits. Four patients had worsening of pre-existing Raynaud's. One patient with a history of scleroderma and dermatomyositis had worsening facial telangiectasias and acro-osteolysis of both thumbs with subcutaneous calcinosis. Of note, macrovascular complications occurred at a mean of 163 days after the beginning of a CGRP mAb [59]. A possible explanation of this observation is that blocking CGRP could potentially affect vasodilation and autoregulation at a microvascular level. More studies are needed to investigate the association of CGRP-targeting therapy and microvascular complications and the safety of using such therapy in patients with known Raynaud's phenomenon and associated connective tissue disease.

There have been case reports of other vascular complications that could potentially be related to CGRP mAb treatment. One is a 55-year-old man with CM in the setting of MO with triptans, hypertension (controlled) and hyperlipidemia (on treatment), and history of myocardial infarction 7 years prior; during his fifth monthly treatment with 70 mg erenumab, he had myocardial infarction with complete thrombotic occlusion of the right coronary artery with symptom onset minutes after using subcutaneous sumatriptan [60]. In this case, the triptan overuse in the setting of a history of myocardial infarction and other vascular risk factors for atherosclerosis were more likely to be associated with the acute myocardial infarction, though blocking CGRP and compensatory vasodilation in the setting of acute coronary syndrome could potentially be detrimental. Note that coronary artery disease is listed as a contraindication in the package insert of most triptans. Another 41-year-old woman with HFEM and no identified vascular risk factors other than oral contraceptive use had acute ischemic thalamic stroke 4 h after taking rizatriptan and 34 days after initiation of erenumab 70 mg [61]. A case of reversible vasoconstriction syndrome (RCVS) was diagnosed in a 43-year-old woman with HFEM after sudden onset of acute moderate headache immediately after orgasm 2 and 4 days after second monthly dose of erenumab 70 mg and then had thunderclap headache onset during exercise after 6 days. During the course of her symptoms, she took a total of 5 doses of eletriptan, which she typically used for her migraine, without improvement or worsening of her symptoms. CT angiogram showed multiple areas of narrowing involving the left middle cerebral artery and anterior cerebral artery suggestive of RCVS [62]. In the above reports, there could be other contributing factors to the vascular or ischemic complications, such as the use of triptans in the RCVS case and the thalamic stroke case. Although CGRP-targeting therapy does not directly cause vasoconstriction, its presence could potentially affect cerebral autoregulation in the setting of acute ischemic infarct. A study in mice demonstrated that pretreatment with olcegepant and rimegepant increased the risk of infarction and was associated with increased infarct volumes, worsened neurologic deficits/mortality, decreased collateral flow, and reduced success of reperfusion after middle cerebral artery occlusion when compared to pretreatment with vehicle [63].

Despite the concerns, a few case reports of patients with genetic small vessel diseases have demonstrated patients who responded well to erenumab without significant ischemic complications. A 58-year-old man with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and long-standing CM with aura had significant improvement of migraine intensity, frequency, duration, and accompanying symptoms after 6 months of 70 mg monthly erenumab [64]. Another case report demonstrated that a young woman with mitochondrial encephalopathy, lactate acidosis, and stroke-like episodes syndrome (MELAS) who had multiple prior unsuccessful treatments had significant improvement of migraine from erenumab, with no complications clinically or radiographically in follow-up [65]. However, a young man with cerebral proliferative angiopathy and CM developed status epilepticus with diffusion restriction on MRI and multiorgan dysfunction 2 days after initiation of erenumab 70 mg, thought to be related to compromised blood brain barrier [66]. Some cautioned that blockade of CGRP could potentially worsen ischemic events for patients with small vessel diseases given that CGRP may act as a vasodilatory safeguard during cerebral or cardiac ischemia [67]. More studies are needed to evaluate the vascular safety with CGRP-targeting therapies.

The CGRP molecule has been identified as an important modulator of the immune system in the setting of systemic inflammation or injury [68]. A case series ($n = 8$) reported patients with new onset or significantly worsened inflammatory conditions correlating with initiation of CGRP mAb therapy (ranging from 14 days to 16 months of treatment); conditions involved various organ systems and included autoimmune hepatitis, ocular Susac's syndrome, granulomatosis with polyangiitis, and psoriasis [69].

## Gepants

Gepants are small molecule CGRP receptor antagonists. First generation gepants, including olcegepant, telcagepant, MK3207, and BI44370, were discontinued in phase II or III studies due to accessibility (olcegepant only available in intravenous form) or side effects including hepatotoxicity and paresthesias. Second-generation agents were shown to have better accessibility (oral medications) and safety, with currently three gepants—ubrogepant, rimegepant, and atogepant—now approved for migraine therapy, and have become a unique class of medication with indications for both the acute and preventive treatment of migraine.

Ubrogepant was the first oral gepant approved in December 2019 for the acute treatment of migraine. The ACHIEVE I and II trials ($n = 1672$ and 1686) demonstrated 2-h pain freedom rates of 19% (50 mg), 21% (100 mg) versus 12% for placebo ($p = 0.002$, $p < 0.001$; ACHIEVE-1) and 21% (25 mg), 22% (50 mg) versus 14% placebo ($p = 0.01$, $p = 0.03$; ACHIEVE-2) [70, 71]. An open-label trial was completed assessing pharmacokinetics, safety, and tolerability of ubrogepant for acute treatment with coadministered CGRP mAb (erenumab or galcanezumab); pharmacokinetics was unchanged with no safety or tolerability issues identified [72]. Despite the efficacy and safety demonstrated in studies, clinical trials of ubrogepant and rimegepant for the acute treatment of migraine were conducted in patients with episodic migraine with a single-attack study design. Real-world studies are needed to assess the efficacy and tolerability in patients with CM with multiple medical comorbidities and multiple unsuccessful prior acute treatment trials.

A real-world study reported real-world patient experience of ubrogepant in a tertiary headache center [73]. Among the 106 patients included, 87% had CM, and 77.5% patients had tried at least 2 different triptans. At 2 h after taking ubrogepant, 19% patients reported complete headache freedom, and 47.6% patients experienced headache relief for $\geq 75\%$ of the treated attacks. Thirty-one percent of patients were "very satisfied" with ubrogepant, while 31% of patients were not at all satisfied. Most common AEs were fatigue (27.4%), dry mouth (7.5%), nausea/vomiting (6.6%), constipation (4.7%), and dizziness (2.8%); no participants reported serious/severe AEs. Positive predictors of being a good responder (headache relief for $\geq 75\%$ of the treated attacks 2 h after medication intake) included migraine with aura and prior successful treatment response from a CGRP mAb ($> 50\%$ decrease in headache frequency). Negative predictors included CM, $\geq 5$ prior unsuccessful preventive and acute treatment trials, and $< 30\%$ decrease in headache frequency with prior CGRP mAb or onabotulinumtoxinA therapy. The UNIVERSE study is an ongoing real-world study evaluating the effectiveness of ubrogepant for acute treatment of migraine utilizing a smart phone headache diary application. Interim analysis suggests high satisfaction with pain relief and reduction in opioid and barbiturate usage [74].

Rimegepant was approved in February 2020 as an acute migraine treatment. Single-dose treatment demonstrated 2-h pain freedom in 20–21% (11–12% placebo) [75, 76]. Long-term OLE data identified no severe AEs felt to be treatment-related when used up to once daily for up to 52 weeks [77]. Additionally, studies have also investigated the safety of concurrent gepant use, for the acute treatment of migraine, and CGRP mAb for migraine prevention and reported no significant safety concern [78]. Of note, a clinical trial evaluated the efficacy of rimegepant for migraine prevention when given 75 mg every other day. Among the 1375 patients analyzed, 23% patients had CM. Fifty percent or greater reduction of MMD was reported in 49% patients (vs. 41% in placebo, $p = 0.044$) [79]. Rimegepant has since received FDA approval for migraine prevention in patients with EM.

Atogepant was approved in September 2021 as preventive treatment for EM after demonstration of efficacy and safety in the ADVANCE trial [80–82]. Clinical trials demonstrated 50% or greater reduction in MMD in 56–61% versus 29% placebo, with a similar AE rate to that of placebo [82]. Additionally, atogepant was found to have no clinically meaningful pharmacokinetic effects on combination hormonal oral contraceptive pills [83]. Currently, there has not been any real-world study specifically of rimegepant and atogepant. More studies are needed to assess the long-term efficacy and safety of gepants in the general population.

## Conclusion

CGRP-targeting therapies have brought about a new era for migraine treatment. There are four CGRP mAbs and three small molecule CGRP receptor antagonists currently approved for clinical use. While clinical trials have shown efficacy and safety, participants in some studies were selected patients with EM, without MO or complex comorbidities. Emerging real-world studies demonstrated the effectiveness and safety of CGRP-targeted therapy in patients with CM, MO, and multiple prior unsuccessful treatment trials. Studies have also identified predictors of response to these CGRP mAb treatments including concurrent cutaneous allodynia, lower BMI, and a lower number of prior treatment failures. Additionally, real-world studies also showed that the combination of CGRP mAbs and onabotulinumtoxinA may provide meaningful clinical improvement.

Higher rates of AEs have been reported in real-world studies than in clinical trials. While these AEs have predominantly been mild or moderate, there has been concern for


limited cases of severe AEs, including constipation and de novo or worsening hypertension with erenumab. Available real-world studies of gepants (ubrogepant thus far) also demonstrated comparable effectiveness and higher rates of AEs when compared to the phase III clinical trial results. Overall, long-term real-world data is needed to assess the sustained effectiveness and safety of CGRP-targeted therapies. Furthermore, studies investigating predictors of treatment response to CGRP-targeted therapy could also facilitate individualized treatment plans for patients with migraine.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors report no other conflicts of interest in this work.

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