Neuropsychiatric Disease and Treatment

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REVIEW

# Review of Tolerability of Fremanezumab for Episodic and Chronic Migraine

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**Abstract:** Calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) were the first class of medication specifically developed for the prevention of migraine. Fremanezumab is one of four CGRP mAbs currently available and is approved by the US Food and Drug Administration (FDA) for the preventative treatment of episodic and chronic migraines. This narrative review summarizes the history of fremanezumab development, the trials that led to its approval, and the later studies published evaluating its tolerability and efficacy. Evidence of fremanezumab for clinically significant efficacy and tolerability in patients with chronic migraine is especially important when considering the high level of disability, lower quality of life scores, and higher levels of health-care utilization associated with this condition. Multiple clinical trials demonstrated superiority of fremanezumab over placebo in terms of efficacy while demonstrating good tolerability. Treatment-related adverse reactions did not differ significantly compared to placebo and dropout rates were minimal. The most commonly observed treatment-related adverse reaction was mild-to-moderate injection site reaction, described as erythema, pain, induration, or swelling at the injection site.

**Keywords:** calcitonin gene related peptide, CGRP, monoclonal antibodies, mAbs, chronic migraine

## Introduction

Migraine is a common disease affecting 36 million people in the United States.[1] Due to loss of productivity as well as health-care costs, it is the second highest cause of years lived with disability.[2] Despite migraine severity ranging considerably on an individual basis, 87% of patients with migraine feel that their headaches negatively affect their lives.[3] An estimated 11–15% of the US adult population meet criteria for migraine, approximately 18% of adult females and 6% of males.[4] Migraines are not only more common in women than in men but tend to be more severe as women report higher intensity pain, more frequent associated symptoms, and higher rates of headache-related disability.[5]

### Migraine Classification

The International Headache Society has published the International Classification of Headache Disorders, version 3 (ICHD-3), which describes the diagnostic criteria of migraine (Table 1).[6] Migraine is a recurrent headache lasting 4–72 h per episode and has at least two of the following four characteristics: unilateral location of pain, pulsating quality, moderate-to-severe intensity, aggravated by routine physical activity. It must also be associated with nausea and/or photophobia and phonophobia.

Migraine can be further characterized and divided into episodic migraine or chronic migraine based on frequency. Chronic migraine pertains to patients who have experienced at least 15 days of headache per month for the prior three-month period. Of the 15 days with headache, at least 8 days must meet the criteria for migraine (Table 1). It is estimated that approximately 8% of migraine patients suffer from chronic migraine.[8] Several risk factors have been identified for the "progression" of migraine from episodic to chronic, such as headache day frequency, depression, and acute medication use.[9] It is estimated that 2.5% to 3% of people with EM transition to CM every year.[5]

Received: 10 December 2022
Accepted: 10 February 2023
Published: 20 February 2023

**Table 1** Original Table Adapted from the IHS Classification International Classification of Headache Disorders (ICHD) Diagnostic Criteria for Migraine Without Aura and Diagnostic Criteria for Chronic Migraine

| |
|---|
| ICHD-3 Migraine Without Aura |
| A. At least five attacks fulfilling criteria B-D |
| B. Headache attacks lasting 4–72 hours |
| C. Headache has at least two of the following four characteristics:<br>• Unilateral<br>• Pulsating<br>• Moderate or severe pain<br>• Aggravation by or causing avoidance of routine physical activity |
| D. During headache at least one of the following:<br>• Nausea and/or vomiting<br>• Photophobia and phonophobia |
| E. Not better accounted for by another diagnosis |
| ICHD-3 Chronic Migraine |
| A. Headache (migraine or tension-type) at least 15 days per month for at least 3 months<br>• At least 8 of the 15 headaches per month meet criteria for migraine with or without aura |

**Notes**: Adapted from IHS Classification ICHD-3. Available from: https://ichd-3.org/1-migraine/1-2-migraine-with-aura/1-2-2-migraine-with-brainstem-aura/.[7]

## Migraine and Quality of Life

The disease typically begins in adolescence and carries significant functional impairment, impaired quality of life (QOL), and comorbid medical and psychiatric conditions, with the most common associated conditions being insomnia, depression, and anxiety.[10,11] The associated functional impairment affects occupational, academic, social, leisure, and family aspects of life. Patients with migraine experience loss of productivity equivalent to approximately 4 days per year.[12]

The degree of disability tends to be higher in chronic migraine compared to episodic migraine.[13] Chronic migraine patients have increased headache-related disability, lower socioeconomic status, lower QOL, increased rate of comorbid medical and psychiatric disease, higher levels of health-care utilization, and higher treatment costs than patients with episodic migraine.

# Migraine Pathophysiology

The science and understanding behind the pathophysiology of migraine is changing and rapidly advancing. There exist several risk factors for the development of migraine, including genetics, hormones, and a person's environment.[14,15] Family history is considered to be a predisposing factor for the development of migraine, though outside of some of the hemiplegic migraine syndromes, most migraine patients with a positive family history are unlikely to develop migraine based on the involvement of a single gene.[15] Other data has shown a relative deficiency of serotonin levels in migraine patients, which may increase the propensity to develop the disease.[16,17] This has been supported by various neuroimaging studies.[18,19] Finally, an individual's environment is an influential factor in developing the disease, especially socio-economic status.[20] Evidence has demonstrated that migraine prevalence increases as household income decreases.[21] This has been explained by the "social causation" hypothesis.[22]

Various anatomical locations within the central nervous system are involved in the physiology of migraine, including the brainstem, hypothalamus, thalamus, and cortex. Migraine development may also be related to abnormal alterations of sensory processing, connectivity, or excitability. Activation and sensitization of the trigeminovascular system is of particular importance in the physiology of migraine. Conversely, a purely vascular origin of migraine headache has

been debated over the years as several experiments have demonstrated conflicting data regarding whether sufficient or significant vasodilation occurs with spontaneous or evoked migraine episodes.[23,24] Despite the lack of consistent evidence, many studies demonstrate data supporting the theory that vasodilation is involved in the underlying physiology of migraine.[25–27]

## Phases of Migraine Attacks

Migraine attacks can be divided into four phases based on the occurrence of symptoms surrounding the headache itself, namely the premonitory, aura, headache, and postdrome phases. These phases can all differ in length and severity and may overlap with one another.[14] The premonitory phase can be accompanied by mood changes, irritability, and light sensitivity; these symptoms seem to be correlated with changes in the hypothalamus, occipital cortex, and brainstem.[28] The hypothalamus, in particular, appears to have a major role in the premonitory phase symptoms of change of mood, energy, and appetite. Imaging studies demonstrating increased blood flow to this region before and after a migraine attack support this hypothesis.[29] Electrophysiological studies have also shown activation and involvement of thalamic and thalamo-cortical circuits that play a key role in the sensory processing within a migraine attack.[30]

Approximately 30% of patients with migraine experience a migraine aura. This is defined as a focal neurological disturbance (eg visual, sensory, or motor) that typically precedes migraine pain, though the aura may occur concurrently with other aspects of a migraine attack.[31,32] The most common type of aura is visual.[27] Cortical spreading depression is thought to be the mechanism by which a migraine aura develops and progresses during a migraine.[33] This was first postulated in 1940s and has remained the theory behind migraine aura. It is characterized by spreading "waves" of excitation followed by inhibition of neural and glial activity across the cortex. Although we are currently lacking definitive evidence of its causative relationship to migraine aura, the circumstantial evidence is supportive.

The headache phase of migraine appears to have strong involvement with the trigeminovascular system, including the meningeal vasculature and sensory innervations from the trigeminal ganglia.[34] Pain sensory inputs from the trigeminal nerve as well as nerves from C1, C2, and C3 converge at the trigeminal nucleus caudalis in the medulla and cervical spinal cord.[35] Afferent signals subsequently travel to regions such as the periaqueductal gray, the dorsolateral pons, the rostral ventromedial medulla, the thalamus, and the parietal cortex.[9] Several pharmacological targets have been identified and investigated for the treatment of migraine, including serotonin, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide, and prostaglandins.[15] CGRP is of particular interest considering the approval of several migraine-specific treatment options for the prevention and, more recently, acute treatment of migraine.

Finally, the postdrome period often follows the resolution of a migraine headache. Common symptoms include fatigue, brain fog, weakness, euphoria, depression, residual head pain, and nausea.[36] Functional imaging studies indicate that physiological changes that were present during the earlier phases of migraine may persist following the resolution of headache.[37] Activation of various locations including the dorsolateral pons, midbrain, and hypothalamus have all been demonstrated in migraine patients following the resolution of a migraine headache.[29,38,39]

## Calcitonin Gene-Related Peptide (CGRP)

CGRP is a neuropeptide involved in regulating the cardiovascular system, mediating neurogenic inflammation, and modulating nociceptive input.[40,41] CGRP is a 37 amino acid neuropeptide, present in both alpha and beta forms.[42,43] The alpha form of CGRP is distributed in both the central and peripheral nervous systems. Conversely, the beta subtype is found in enteric nerves and the pituitary gland. The neuropeptide CGRP likely has several physiological roles including the mediation of migraine and pain, and contributing to vasodilation, particularly following a period of vasoconstriction.[44]

As the alpha CGRP is localized in the central and peripheral nervous system, it is considered a more relevant subtype in regard to migraine. It is also predominantly expressed in the trigeminal ganglia and is known to be a mediator in arterial dilatation.[45,46] The peripheral nervous system CGRP receptors may prove to be significant in the treatment of migraine considering how CGRP monoclonal antibodies (mAbs) are not thought to be able to cross the blood–brain barrier due to their relatively large size.[47]

CGRP is released during acute migraine attacks with activation of dural C fiber nociceptors.[48] This leads to sensitizing the nociceptors and activating adjacent A? pain fibers. Experimental models also demonstrated its release with trigeminal ganglion stimulation.[49] Along with the release of CGRP in the setting of pain, CGRP levels have been demonstrated to be elevated during a migraine attack in external jugular vein blood. This has not been consistently reproducible.[50] While not completely reproducible, patients with chronic migraine have elevated CGRP between migraine attacks relative to patients with episodic migraine and individuals without migraine.[51,52] A decrease in CGRP levels has been observed after migraine episodes in patients who are treated with a triptan medication.[51,53,54] Further evidence of the role of CGRP in migraine physiology has been demonstrated in experimental studies involving the induction of a migraine episode by iatrogenically infusing CGRP.[55]

## CGRP Monoclonal Antibodies

Given its widespread effects, CGRP gained traction as a therapeutic target for migraine in the late 1990s.[40] A Phase II proof-of-concept trial established the clinical validity of CGRP as a therapeutic target in the treatment of acute migraine attacks in 2004.[56] As a result, several different CGRP receptor antagonists were studied. While the first trials evaluating small-molecule CGRP receptor antagonists demonstrated symptomatic improvement in migraine, some patients developed elevated liver transaminases suggestive of liver toxicity.[40,57] This unfortunate side effect led to the development of the use of CGRP Monoclonal Antibodies (mAbs) as biological drugs directed against the CGRP ligand or its receptor.

CGRP mAbs are relatively large molecules, approximately 150 kilodaltons in size.[47] This makes them unlikely to cross the blood–brain barrier in significant quantities, reducing the risk of central nervous system side effects. As with most mAbs, they carry a high target specificity for their receptor. The half-life of CGRP mAbs (3–6 weeks) is significantly longer than that of the CGRP small-molecule antagonists. Their long half-life makes them ideal for a monthly, or even quarterly, dosing schedule.

Several studies demonstrated favorable tolerability and safety amongst CGRP mAbs.[58,59] Of the currently available mAbs, the most common side effect observed in the trials of fremanezumab, erenumab, and galcanezumab was injection site irritation. Erenumab, the only one of the current four CGRP mAb directed against the CGRP receptor, also carries a risk of constipation and a warning of hypertension.[60]

### Fremanezumab: Development

Fremanezumab (TEV 48125) is a humanized IgG2a monoclonal antibody that binds to the CGRP ligand.[61] Initial in vitro evaluation found that fremanezumab produced an effective and selective blockade of the vasomotor responses to CGRP.[62] Pharmacokinetic evaluation showed plasma concentrations were reached within 5 to 7 days of subcutaneous administration, while the half-life ranged from 31 days to 38 days depending on the dosage given.[63] A Phase 1 study by Bigal et al administered single doses to 94 subjects with the most common treatment-related adverse event being injection-site reactions, which was similar between placebo and fremanezumab dosages.[64]

A multicenter, randomized, double-blind, placebo controlled phase II study for high-frequency episodic migraine prevention evaluated the safety and tolerability of subcutaneously administered fremanezumab (two dosing regimens of monthly and quarterly) versus placebo.[65] Once again, the most common treatment-related adverse event was injection site pain or erythema and was found to occur at a similar rate among treatment and placebo groups.[65] Patients reported a reduction of −3.46, −6.27, and −6.09 migraine days in the placebo, monthly and quarterly groups, respectively – consistent with a significant reduction ($P < 0.0001$) in the number of migraine days for fremanezumab versus placebo.[65]

A multicenter, randomized, double-blind, double dummy, placebo-controlled, phase IIb trial for the preventive treatment of chronic migraine was also performed by Bigal et al.[66] At baseline, subjects had a mean of 162 headache hours, 16.8 migraine days, and 21.1 headache days of any duration per month. In addition to placebo dosing, two doses of fremanezumab (675/225 and 900 mg) were used. In weeks 9–12, patients reported a reduction of −37.10, −59.84, and −67.51 headache hours in the placebo, 675/225-mg, and 900-mg groups, respectively, and decreases in the number of moderate or severe headache days of −4.20, −6.04, and −6.16 for each of the three groups, respectively.[66]

A Phase III randomized clinical trial on fremanezumab efficacy for prevention of episodic migraine and chronic migraine was then completed. For prevention of episodic migraine, subjects were assigned to receive fremanezumab

225 mg (monthly regimen), 675 mg (quarterly regimen), or placebo. The primary endpoint of reduction in mean number of migraine days per month from baseline was achieved with reduction of the three respective groups being −3.7, −3.4, and −2.2 (P = 0.001).[67] In the phase III randomized clinical trial for the prevention of chronic migraine, two different dose regimens of fremanezumab or matching placebo were administered to patients (675 mg quarterly or 225 mg monthly).[68] The primary endpoint of the study was a reduction in the mean number of headache days per month. A reduction of at least 50% of headache days per month was seen in 38%, 41%, and 18% of patients treated quarterly, monthly, and placebo, respectively.

The Food and Drug Administration approved fremanezumab in the United States on September 1, 2018, for the treatment of episodic and chronic migraine in adults. It was later approved by the European Union on March 28, 2019, for the prophylaxis of migraine in adults experiencing at least four migraine days per month.[34] It is delivered via a self-administered subcutaneous injection on a monthly or quarterly basis. The monthly dosing is 225 mg, whereas the quarterly dosing is 675 mg. An auto injector pen is available, but patients have access to a prefilled syringe, as well. Quarterly and monthly dosing regimens were evaluated for the treatment of chronic migraine (HALO CM), episodic migraine (HALO EM), and patients with difficult-to-treat chronic or episodic migraine (FOCUS).[67–69] Finally, a 12-month trial was performed to evaluate the long-term effects of the therapy (HALO LTS).[59] All studies demonstrated statistically significant efficacy in reduction of monthly migraine days compared to placebo. Improvements were also observed in headache-related disability scores.

## Fremanezumab: Safety and Tolerability

In addition to significant efficacy in migraine reduction, tolerability of fremanezumab is favorable. Four major trials assessed the tolerability of fremanezumab (HALO EM, HALO CM, FOCUS, and HALO LTS).[59,67–69] The most common adverse effects seen with administration of fremanezumab are presented, as it was described in the original manuscripts in Tables 2, 3, and 4.

**Table 2** Summary of Significant Study Endpoints and Rate of Most Common Adverse Reaction in Pivotal Trials and Studies on fremanezumab[59,67–69]

| | n | Dosing | Monthly Migraine Days | 50% Responder Rate | Injection Site Reaction Rate* |
|---|---|---|---|---|---|
| HALO-EM | 875 | Monthly | −4.2 | 47.7% | 43% |
| | | Quarterly | −4.0 | 44.4% | 45% |
| | | Placebo | −2.7 | 27.9% | 38% |
| HALO-CM | 1130 | Monthly | −4.6 | 40.8% | 43% |
| | | Quarterly | −4.3 | 37.6% | 45% |
| | | Placebo | −2.5 | 18.1% | 38% |
| FOCUS | 838 | Monthly | −4.1 | 34% | 14% |
| | | Quarterly | −3.7 | 34% | 15% |
| | | Placebo | −0.6 | 9% | 12% |
| HALO-LTS | 1890 | Monthly | EM: −5.1 | EM: 68% | 23% |
| | | | CM: −8.0 | CM: 57% | 32% |
| | | Quarterly | EM: −5.2 | EM: 66% | 18% |
| | | | CM: −7.2 | CM: 53% | 19% |

**Table 3** Most Common Side Effects to Fremanezumab Seen During Development

| | HALO-E Monthly Dose (n=290) | HALO-E Higher Dose (n=291) | HALO-C Monthly Dose (n=379) | HALO-C Quarterly Dose (n=379) | FOCUS Monthly Dose (n=285) | FOCUS Quarterly Dose (n=285) |
|---|---|---|---|---|---|---|
| General Adverse Event | | | | | | |
| • At least 1 adverse event | 192 | 193 | 270 | 265 | 129 | 151 |
| • At least 1 severe event | 3 | 3 | 5 | 3 | 4 | 2 |
| • Study discontinuation | 5 | 5 | 7 | 5 | 4 | 1 |
| • Death | 0 | 1 | 0 | 0 | NA | NA |
| Dermatologic | | | | | | |
| • Injection site pain | 87 | 86 | 99 | 114 | 9 | 11 |
| • Injection site induration | 71 | 57 | 90 | 75 | 13 | 12 |
| • Injection site erythema | 52 | 55 | 75 | 80 | 16 | 19 |
| • Injection site hemorrhage | 3 | 9 | 8 | 7 | NA | NA |
| • Injection site pruritus | NA | NA | NA | NA | 2 | 5 |
| Endocrine and metabolic | | | | | | |
| • Hepatic enzyme increase | 2 | 2 | 5 | 5 | NA | NA |
| Gastrointestinal | | | | | | |
| • Nausea | 2 | 7 | 6 | 4 | 2 | 4 |
| • Diarrhea | NA | NA | NA | NA | 2 | 7 |
| • Constipation | NA | NA | NA | NA | 1 | 7 |
| General | | | | | | |
| • Fatigue | 2 | 6 | NA | NA | NA | NA |
| • Weight Gait | NA | NA | NA | NA | 3 | 4 |
| Immunogenicity | | | | | | |
| • Fremanezumab antibody response | 4 | NA | NA | NA | NA | NA |
| Infectious | | | | | | |
| • Upper respiratory tract infection | 16 | 11 | 16 | 18 | NA | NA |
| • Nasopharyngitis | 11 | 11 | 15 | 19 | 7 | 13 |
| • Urinary tract infection | 7 | 10 | NA | NA | 3 | 3 |
| • Bronchitis | 6 | 4 | NA | NA | NA | NA |
| • Sinusitis | 4 | 2 | 4 | 10 | NA | NA |
| • Influenza | NA | NA | NA | NA | 6 | 2 |
| Neuropsychiatric | | | | | | |
| • Dizziness | NA | NA | 11 | 9 | 4 | 5 |
| • Anxiety | NA | NA | NA | NA | 2 | 3 |

**Notes**: Numbers listed represent the number of patients (n) who reported these symptoms. Data are presented as they were initially described in the reported literature. "NA" is used when no data is available. Less commonly seen adverse events (1% or less) may not have been included in this table and a complete list of all adverse effects reported can be found in the original manuscripts.[67–69]

The most common drug-related adverse reaction noted in these trials was injection site reaction (Table 2).[59,67–69] Patients described injection site reactions as the development of pain, induration, erythema, and/or hemorrhage at the injection site. In the HALO LTS trial, injection site reaction was observed with 23% of chronic migraine patients receiving the monthly injection and 19% of chronic migraine patients receiving the quarterly injections.[59] Very similar rates of injection site reaction were observed in the episodic migraine population. The FOCUS phase 3B clinical trial demonstrated a 14% injection site reaction rate in the monthly injection scheduling arm and a 15% injection site reaction rate in the quarterly injection scheduling arm.[69] The placebo group experienced injection site reactions at a rate of 12%.

**Table 4** Most Common Side Effects to Fremanezumab Seen During the Long-Term Safety, Tolerability, and Efficacy Study (HALO LTS)

| | HALO-LTS CM Monthly (n=559) | HALO-LTS CM Quarterly (n=551) | HALO-LTS EM Monthly (n=386) | HALO-LTS EM Quarterly (n=394) |
|---|---|---|---|---|
| General Adverse Event | | | | |
| • At least 1 adverse event | 498 | 461 | 323 | 330 |
| • At least 1 severe event | 35 | 38 | 21 | 21 |
| • Study discontinuation | 18 | 20 | 18 | 20 |
| • Death | 0 | 0 | 0 | 0 |
| Dermatologic | | | | |
| • Injection site pain | 182 | 157 | 123 | 118 |
| • Injection site induration | 196 | 165 | 145 | 113 |
| • Injection site erythema | 171 | 138 | 103 | 85 |
| • Injection site hemorrhage | 44 | 42 | 28 | 17 |
| • Injection site pruritus | 39 | 26 | 35 | 15 |
| Infectious | | | | |
| • Upper respiratory tract infection | 72 | 77 | 45 | 59 |
| • Nasopharyngitis | 61 | 64 | 51 | 41 |
| • Urinary tract infection | 28 | 39 | 24 | 22 |
| • Bronchitis | 25 | 23 | 14 | 21 |
| • Sinusitis | 39 | 40 | 18 | 19 |
| • Influenza | 30 | 22 | 11 | 11 |

**Notes**: Patients broken into four categories: chronic migraine (CM) with monthly and quarterly dosing and episodic migraine (EM) with monthly and quarterly dosing. Numbers listed represent the number of patients (n) who reported these symptoms. Data are presented as they were initially described in the reported literature.[59]

Most injection site reactions were rated as mild to moderate. The discontinuation rate during the FOCUS phase 3B trial was less than 1% due to adverse events. No severe hypersensitivity events occurred during HALO LTS.[59]

CGRP is involved in several different physiologic functions outside of migraine, including vasodilation, nervous system maturation or repair, utero-placental function and vascular adaptations, and neuro-immune access regulation. For this reason, several areas of potential or theoretical concern exist with the use of CGRP monoclonal antibodies for clinical use. CGRP is a potent vasodilator, but there has been no evidence demonstrating clinically significant vasoconstriction after the administration of CGRP monoclonal antibodies.[70,71] Other areas of potential concern include patients with compromised blood–brain barrier, cardiovascular disease, cerebrovascular disease, bone disease, and immunodeficiency. Use of CGRP monoclonal antibodies should be used with caution in these populations.

Little data exist pertaining to the safety of CGRP antagonism during pregnancy. Experimental rat models demonstrated a dose-dependent relationship between CGRP administration and the outcomes of systolic blood pressure, fetal growth retardation, and fetal mortality.[72] Several safety reports of human patients exposed to CGRP monoclonal antibodies, including, fremanezumab, have been collected with no significantly increased reporting for maternal toxicity, spontaneous, abortion, or major birth defects.[73] Still, the use of CGRP monoclonal antibodies in the setting of pregnancy and breastfeeding is recommended against at this time until more data is gathered and published. Current recommendations exist for the cessation of CGRP monoclonal antibodies at least 6 months prior to conception, considering their long half-lives.

At the time of this writing, clinical trials for the use of CGRP monoclonal antibodies in pediatric and adolescent populations have not been published. A retrospective multi-center study did find similar efficacy and side effects of CGRP monoclonal antibodies in adolescence when compared to adults.[74] The Pediatric and Adolescent Headache Special Interest Group of the American Headache Society published a manuscript for guidelines for the use of CGRP

mAbs in pediatric and adolescent populations.[75] It is recommended to consider the use of CGRP mAbs for younger populations who either experience frequent migraine episodes or experience significant disability related to migraine with cautious monitoring. The use of these medications should be considered only after prior pharmacologic and nonpharmacologic treatments have been attempted.

Interactions with concomitant medications are thought to be unlikely, as the metabolism of fremanezumab is not performed by cytochrome P450 enzymes. This is in contrast to the CGRP small-molecule antagonists, which should either be avoided or their dosing altered if used in patients who are taking cytochrome P450 enzyme inhibitors.

## Future Directions

Limited evidence exists at this time comparing fremanezumab directly to other migraine treatment options, but the studies that have been performed appear promising. Yang et al performed a meta-analysis comparing the efficacy of the four different CGRP mAbs to topiramate and onabotulinumtoxin A and found fremanezumab had the best overall response rate compared to the other treatments, though the dosing schedule used was not FDA approved (675mg in the first month, 225mg in the second and third months).[76] Another meta-analysis compared the efficacy of topiramate, onabotulinumtoxinA, and CGRP mAbs against placebo and found all three categories to be significantly effective.[77] The CGRP mAbs were more likely to lead to a 50% reduction in monthly migraine days when compared to onabotulinumtoxinA and had a lower dropout rate than topiramate. More comparative evidence regarding efficacy and safety is needed to better understand where fremanezumab stands in the current landscape of preventive migraine treatment.

Another area for future research needed is the effect of fremanezumab when used in combination with onabotulinumtoxin A in patients with chronic migraine. Onabotulinumtoxin A is an FDA-approved treatment for chronic migraine that has been available for this population since 2010.[78] OnabotulinumtoxinA's mechanism of action in the treatment of migraine is thought to be by way of cleaving SNAP-25, which prevents the release of CGRP and other neuropeptides from the C-fiber nerve terminal.[79] Thus, a synergistic effect is suspected to exist when a CGRP mAb is used concomitantly with onabotulinumtoxinA. A retrospective chart review consisting of 257 patients demonstrated a significant reduction in monthly headache days when treated with a CGRP mAb in combination with onabotulinumtoxin A compared to patients treated with onabotulinumtoxin A monotherapy.[80] The majority of patients using a CGRP mAb in this patient population were prescribed erenumab, with only 6% of patients prescribed fremanezumab. Further evidence demonstrating efficacy of CGRP mAbs used concomitantly with onabotulinumtoxinA will undoubtedly act as support in obtaining insurance authorization for both treatments simultaneously in the future.

Pediatric episodic and chronic migraine is an area that is currently lacking evidence in regard to the use of CGRP mAbs. Several areas of potential concern exist in this growing and developing population due to the presence of CGRP and its receptors localized throughout multiple organ systems. Safety and tolerability outcomes will be of paramount importance when these studies are created. An investigation is currently recruiting pediatric patients with episodic and chronic migraine to evaluate the efficacy of erenumab in this population.

## Conclusion

FDA approval of CGRP monoclonal antibodies, including fremanezumab, has led to a substantial addition to preventive treatment options for patients with episodic and chronic migraine. Both the efficacy and tolerability of CGRP monoclonal antibodies appear to be favorable. Prior to the FDA approval of fremanezumab and the other CGRP monoclonal antibodies, the "mainstay" of migraine prevention relied on antidepressants, antihypertensives, and antiepileptic medications, which can frequently cause systemic side effects. The dosing schedule of the CGRP mAbs is favorable, as well, with monthly dosing options and fremanezumab's quarterly 675mg dosing schedule.

Fremanezumab has demonstrated efficacy in patient populations that are often challenging to manage, specifically, chronic migraine patients with several prior medication trial failures in its HALO CM trial and FOCUS trial, respectively. When compared to episodic migraine, chronic migraine is associated with a higher degree of disability, lower quality of life, higher levels of health-care utilization, and overall higher cost. The FOCUS trial, specifically, demonstrated significant reductions in

monthly migraine days compared to placebo in patients who had previously failed two to four classes of migraine preventives. The majority of the patient population in the FOCUS trial (61%) carried a diagnosis of chronic migraine. This further supports fremanezumab's efficacy in the prevention of migraine in chronic migraine patients.

Beyond efficacy, tolerability remains a significant consideration for both prescribers and for patients when choosing a preventive treatment for migraine. As previously mentioned, prior to the approval of CGRP mAbs, patients had to rely on daily, oral medications that were developed for medical conditions other than migraine, such as hypertension, epilepsy, and depression. These medications, although often effective for many migraine patients, carry the potential for a variety of systemic side effects. The side effect profile of fremanezumab appears to be very favorable at this time, with injection site reaction being the most consistent and frequently occurring adverse reaction. Typically, if experienced, the injection site reaction is mild to moderate and resolves over a period of a few days. It is important to note that fremanezumab was FDA approved in 2018, so long-term side effects may not yet be completely realized. In addition, CGRP has actions on several different physiologic functions and in multiple organ systems, so there may be more to learn about its long-term effects in the future. As of now, fremanezumab appears to be an effective and a tolerable treatment option in both episodic, but perhaps, more importantly, chronic migraine.

## Disclosure

The authors report no conflicts of interest in this work.

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