CGRP Therapeutics For The Treatment Of Migraine – A Narrative Review

Hsiangkuo Yuan [1], Anna Y. Chen [2], Stephen D. Silberstein, [3]*
[1] Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA
[2] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA
[3] Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA

*Corresponding Author: Stephen D. Silberstein, MD, FACP
Address: Jefferson Headache Center, Thomas Jefferson University
900 Walnut Street, Suite 200, Philadelphia, PA 19107
Email: Stephen.silberstein@jefferson.edu

Abstract

Migraine is a highly prevalent, disabling, and costly primary headache disorder whose pathogenesis involves the dysfunctional activation of the trigeminovascular system. Calcitonin gene-related peptide (CGRP) is the most prevalent neuropeptide released by activation of trigeminal afferents and is considered to play a major role in pain sensitization within the trigeminovascular system. Novel therapeutic agents have been developed to prevent and treat migraine by targeting and antagonizing CGRP functions. These agents consist of gepants, which are small molecule CGRP antagonists, and monoclonal antibodies (mAbs) that target either the CGRP ligands or receptors.

There are currently 4 second-generation gepants being studied: ubrogepant, rimegepant, and vazegepant for the treatment of acute migraine attacks, and atogepant for migraine prevention. CGRP mAbs are currently indicated for migraine prevention; the three FDA-approved mAbs for migraine prevention are erenumab, galcanezumab, and fremanezumab. Eptinezumab is currently under FDA review. Gepants and CGRP mAbs are effective and safe in the treatment of migraine. CGRP mAbs even work among those who failed multiple other preventive medications. These medications are emerging as promising treatment options for migraine patients.

Introduction

Migraine is a common primary headache disorder affecting more than a billion people worldwide. It has been ranked as the second-highest cause of years lived with disability by the World Health Organization (WHO).[1] The projected financial burden of migraine in the United States is estimated to be about US $11 billion.[2] Migraine attacks typically last between 4-72 hours. Common migraine characteristics include unilateral location, pulsating quality, aggravation by routine physical activity, and association with nausea, vomiting, and/or photophobia and phonophobia. Migraine can be classified as with aura or without aura. An aura is a complex of fully reversible visual, sensory, or other central nervous system symptoms that usually occur before the onset of headache but may also begin after the headache has started or continue into the headache phase. Visual aura is the most common type and is present in 90% of patients with migraine with aura, but sensory and speech/motor disturbances may also occur. In addition to aura, migraine is often accompanied by a nonpainful prodrome and postdrome. Prodrome (premonitory) symptoms such as fatigue/cognitive change, homeostatic alterations, and sensory sensitivities (e.g., nausea, photophobia, phonophobia) can start hours to days before the headache phase with possible involvement in the hypothalamus, brainstem, and some cortical areas.[3] Postdrome symptoms (neuropsychiatric, sensory, gastrointestinal, general symptoms, etc.) also can last for several hours after the headache resolves.[4] Based on the attack frequency, migraine can be classified as chronic ($\geq$ 15 headache days per month) or episodic (< 15 headache days per month).[5] It is estimated that 2.5% of episodic migraine (EM) patients progress yearly to chronic migraine (CM), which affects roughly 1-3% of population. The risk factors of migraine chronification include acute medication overuse, depression, anxiety, poor sleep, caffeine overuse, stress, obesity, noncephalic pain, head/neck injury, allodynia, and poor self-efficacy.[6] With such a profound socioeconomical impact, there is a strong need to further understand the pathophysiology of migraine and develop new migraine-specific treatments.

Great challenges remain in managing migraine. Many clinically effective migraine medications, FDA-approved or off-label, display unique adverse event (AE) profiles that influence medication compliance. It has been shown that adherence to preventive medication drops significantly after 30 days with only 25% adherence at 6 months,[7] mainly due to drug AEs and poor efficacy. As of May 2018, the FDA has approved six oral preventives for migraine, one injectable preventive specifically for CM, and dihydroergotamine and several triptans for acute treatment. Recently, calcitonin-gene related peptide (CGRP) antagonizing therapy has emerged as an effective preventive medication with minimal AEs. At the time of writing, the FDA has approved 3 CGRP-targeting monoclonal antibodies (mAbs): erenumab (Aimovig; Amgen, Thousand Oaks, CA), fremanezumab (Ajovy; TEVA, Petah Tikva, Israel), and galcanezumab (Emgality; Eli Lilly, Indianopolis, IN). There is also another CGRP-targeting mAb, eptinezumab (Lundbeck, Deerfield, IL), and 3 CGRP antagonizing small molecules (gepants), namely ubrogepant (Allergan, Dublin, Ireland), atogepant (Allergan, Dublin, Ireland), and rimegepant (New Haven, CT) currently under FDA review. In this article, we discuss the role of CGRP in migraine pathophysiology and compare the efficacy of different CGRP antagonizing modalities available to date.

Migraine Pathophysiology

The pathophysiology of migraine involves a dysfunctional activation of the trigeminovascular nociceptive system leading to the sensation of head pain.[8] Trigeminal afferents are pseudo-unipolar neurons whose cell bodies form the trigeminal ganglion (TG) and interact with the surrounding satellite glial cells and other cell types. Together with afferents from the upper cervical cord, they innervate pain-sensitive structures in the head and communicate with the trigeminal cervical complex (TCC), then project to multiple central nuclei (e.g., thalamus, hypothalamus, brainstem, basal ganglia, etc.) that are involved in processing head pain as well as other migraine-associated symptoms. Activation of the trigeminovascular nociceptive system in migraine causes neurogenic inflammation, and also leads to pain sensitization both peripherally and centrally

with subsequent sustained headache.[9] Trigeminal afferent activation releases a variety of neuropeptides, including CGRP, substance P, and others, with CGRP being the most abundant.[10, 11, 12]

Neuropeptides play a major role in pain signaling and modulation.[13] Unlike neurotransmitters which are synthesized at the presynaptic terminals, neuropeptides are synthesized by the rough endoplasmic reticulum, loaded into dense core vesicles (DCVs), transported to the distant varicosities along the axon, and released via exocytosis. Different neuropeptides often colocalize in the same DCV. These peptides are released mostly from nonsynaptic sites and act locally on nerve fibers or cells within a few microns nearby.[14] Since there is no known reuptake system for neuropeptides, they are degraded by mast cell tryptase, neutral endopeptidase and matrix metalloproteinase II.[15] Most neuropeptides act by binding to their corresponding G protein-coupled receptors (GPCRs) that are usually heterogeneously distributed throughout the nervous system. In contrast to neurotransmitters that act on fast ion channels, the neuropeptide receptive nerve fibers or cells typically respond in seconds to minutes thereby modulating the neuronal or glial activities. The exact roles of these neuropeptides, albeit not fully known, are becoming more understood.

CGRP is a 37-amino acid neuropeptide broadly distributed in both neuronal and non-neuronal regions throughout the body. CGRP belongs to the calcitonin family of peptides, which include calcitonin, amylin, adrenomedullin, and adrenomedullin-2.[16] There are two isoforms of CGRP, α-CGRP and β-CGRP, that are encoded by two different genes and differ in three amino acids.[17, 18] CGRP serves many purposes throughout the body, including sensory, digestive, vascular, vestibular, hematopoietic, immunomodulatory, nociceptive, and tissue healing functions.[19] It is the most potent vasodilator currently known, and has been shown to have a potency that is ~10-fold higher than most potent prostaglandins and 10-100 times greater than other vasodilators such as acetylcholine and substance P.[20] In particular, CGRP is the most abundant neuropeptide in the trigeminal system. It is found mainly in small capsaicin-sensitive C fibers that follow the cerebral

and meningeal arteries and innervate pain-sensitive structures; no CGRP is found in the second-order trigeminal neurons. CGRP is not permeable across the blood brain barrier; it acts on nearby receptive cells and can diffuse beyond the release site via volume transmission. Unmetabolized intracranial CGRP may re-enter circulation but exhibits a rather short serum half-life (~7 minutes).[21] Activation of trigeminal nociceptive fibers results in antidromic release of CGRP, which binds to both the canonical CGRP receptor and the amylin 1 (AMY$_1$) receptor on the neurons, nodes of Ranvier, glia, blood vessel smooth muscles, immune cells, and others. The CGRP receptor is a GPCR that requires the heterodimerization of 2 components (calcitonin receptor-like receptor and a single transmembrane-spanning protein called receptor activity-modifying protein 1) that is then coupled to receptor component protein for effective CGRP signaling. Upon activation, the adenylyl cyclase catalyzes the synthesis of cAMP along with other subsequent intracellular messengers generating a variety of functions depending on the cell type.[22, 23]

CGRP's Role In Migraine

CGRP was first demonstrated to play a role in migraine in 1990, when it was revealed that CGRP levels were increased in the jugular venous outflow following triggered migraine attacks.[3] CGRP level increase was later confirmed during spontaneous migraine attacks; treatment with triptans normalized headaches and CGRP levels.[24, 25, 26] Such normalization was also observed in subjects who received topiramate and onabotulinumtoxin A;[27, 28] onabotulinumtoxin A directly inhibits CGRP release from C-fibers,[29] and the 5-HT$_{1B/1D/1F}$ receptors found on CGRP-containing trigeminal neurons that are targeted by triptans also inhibit the release of CGRP.[30, 31] In addition, CGRP infusion triggers delayed migraine-like attacks in roughly 68% of migraine subjects but not in healthy controls or individuals with tension-type headaches or familial hemiplegic migraine.[32, 33, 34, 35] This highly suggests CGRP's pathogenic role in migraine but the exact migraine triggering mechanism remains unknown. In animal models, even at vasodilatory doses, neither intravenous (IV) nor topical dural application of CGRP sensitized meningeal nociceptors.[36] Since the vascular theory of migraine

is no longer favored, it has been theorized that CGRP mediates neurogenic inflammation and modulates nociceptive inputs that contribute to migraine.[37] CGRP and nitric oxide (NO) from activated TG stimulate adjacent satellite glial cells to release IL-1β, IL-6, and other cytokines and increase cyclooxygenase activity and PGE2 production.[38, 39, 40, 41] Since glial inhibition reversed CGRP-induced thermal nociception,[38] neuro-glial crosstalk likely maintains a state of sensitization interaction. These studies suggest that CGRP, rather than eliciting a direct excitation effect, likely promotes and maintains pain sensitization. Also, CGRP serum levels were found to be elevated after NO donor administration to sumatriptan-sensitized rather than non-sensitized rats.[42] These findings may explain why CGRP infusion triggered a delayed headache only in subjects with migraine. The exact CGRP mechanism of action is likely multifactorial within the trigeminovascular nociceptive system but remains to be explored. Nonetheless, disrupting this sensitization process by blocking the CGRP function appears to be clinically relevant in migraine. To date, there are 2 types of CGRP functional blocking agents: small molecule CGRP antagonists known as gepants and CGRP targeting mAbs.

CGRP Antagonists - Gepants

CGRP antagonists are small molecules known as "gepants" that were developed in the 1990s for the treatment of migraine. They bind to CGRP receptors and can reverse CGRP-induced vasodilation as well as neurogenic inflammation that leads to migraine. Olcegepant (Boehringer Ingelheim GmbH, Germany), telcagepant (Merck, Kenilworth, NJ) and MK-3207 (Merck, Kenilworth, NJ) are early gepants whose efficacy were found to be better than placebo and comparable to that of triptans.[43, 44, 45, 46] However, further development of these first-generation gepants was halted by their potential hepatotoxic effects when dosed regularly.[47] Currently, second-generation gepants are being developed with no major hepatotoxicity seen so far. The 4 gepants in this generation are ubrogepant (Allergan, Dublin, Ireland), atogepant (Allergan, Dublin, Ireland), rimegepant (Biohaven, New Haven, CT), and vazegepant (Biohaven, New Haven, CT). Gepants are competitive receptor antagonists. They bind to CGRP receptors, block

cAMP production, and inhibit trigeminovascular nociceptive activation.[48] In animal studies, IV olcegepant pretreatment inhibited capsaicin-induced Fos expression in the spinal trigeminal nucleus but not in the TG.[49] Olcegepant blocks cAMP response element-binding protein (CREB) phosphorylation more potently than cAMP accumulation in TG neurons, especially those with AMY1 receptors.[50] These features may be unique to olcegepant, but TG neurons likely are a target of interest. Satellite glial cells, the predominant cell type in TG, express CGRP receptors and may also be another target. However, TG-derived glia cells have a weaker response to CGRP,[50, 51] and may react differently to CGRP antagonism. The effect of CGRP antagonism on other cell types in TG remains unclear. In a human PET study, a clinically effective dose of telcagepant showed minimal receptor occupancy in the brain, suggestive for a lack of central action.[52] Since earlier gepants with limited BBB permeability still achieved clinical efficacy, a peripheral site of action seems likely.[53] TG seems to be a probable site of action for gepants but the actual target location, cell type, receptor type, and other central mechanism still need to be examined.

There were concerns that blocking CGRP's vasodilatory effects could lead to vasoconstriction. In contrast to triptans that exhibit a risk of coronary vasoconstriction, gepants are a safer alternative. Ubrogepant and atogepant inhibited the vasodilatory responses to CGRP in the middle meningeal artery and coronary artery but exhibited no vasoconstrictive effect, with atogepant being a more potent vasodilatory antagonist than ubrogepant.[54] An ex vivo study on rimegepant also showed no vasoconstriction of human coronary or cerebral arteries.[55] However, although there is no vasoconstrictive effect, the long-term cardiovascular impact from chronic gepant use should still be investigated as long-term CGRP antagonism inhibits CGRP's cardioprotective effect and may worsen cardiac dysfunction in chronic hypertensive mice.[56]

Acute Migraine Treatment

Ubrogepant has been studied for the treatment of acute migraine attacks **(Table 1)**. In a phase IIb

Table 1. Summary of ubrogepant related clinical trials		
Trial name	Dosage	Primary endpoint
NCT01613248[57] Phase 2b, EM, n=527	100, 50, 25, 10, 1mg vs. placebo	2-hr pain freedom (p<0.001 for trend test): 25.5%[a], 21.0%[b], 21.4%[b], 14.8%, 5.6%, vs 8.9%.
NCT02828020[58] Phase 3, EM, n=1327	100, 50mg vs. placebo	2-hr pain freedom gain: OR 2.04 (95%CI 1.41-2.95), p<0.001; OR 1.83 (95%CI 1.25-2.66), p=0.002. 2-hr absence of MBS gain: OR 1.63 (95%CI 1.22-2.17), p=0.002; OR 1.70 (95%CI 1.27-2.28) p=0.002.
NCT02867709[59] Phase 3, EM, n=1465	50, 25mg vs. placebo	2-hr pain freedom gain: 7.5% (95%CI 2.6%-12.5%), p=0.01; 6.4% (95%CI 1.5%-11.5%), p=0.03. 2-hr absence of MBS gain: 11.5% (95%CI 5.4%-17.5%), p=0.01, 6.7% (95%CI 0.6%-12.7%), p=0.07
[a]p<0.01 when compared to placebo, [b]p<0.05 when compared to placebo. EM: episodic migraine. MBS: most bothersome symptom. OR: odds ratio.		

randomized, double-blind, placebo-controlled trial, 834 patients received either various doses of ubrogepant or placebo to treat one acute migraine attack. After two hours, there was a positive response trend in the proportion of patients achieving pain freedom (p<0.001), with ubrogepant 25mg, 50mg and 100 mg being significantly superior to placebo (21.4% vs. 8.9%, p=0.013; 21.0% vs. 8.9%, p=0.02; 25.5% vs. 8.9%, p=0.003).[57] In addition, there have been two phase 3 trials (ACHIEVE I [NCT02828020] and II [NCT02867709]) that evaluated the efficacy, safety, and tolerability of ubrogepant compared to placebo in a single migraine attack in adults. In the ACHIEVE I trial, both ubrogepant 50mg and 100mg gained significantly more pain freedom at 2 hours (19.2%, 21.2%) than placebo (11.8%) and an increased absence of the most bothersome symptom at 2 hours (38,6%, 37.7%) than placebo (27.8%).[58] In the ACHIEVE II trial, ubrogepant 25mg (20.7% vs. 14.3%, OR 1.56 [95%CI 1.09-2.22], p=0.03) and 50mg (21.8% vs. 14.3%, OR 1.62 [95%CI 1.14-

2.29], p=0.01) both reported significant pain freedom at 2 hours. Therapeutic gains were 6.4% and 7.5% respectively. Absence of the most bothersome symptom and pain relief were also significantly different from placebo.[59] In a *post* hoc analysis, ubrogepant 50mg was also responsive in triptan-ineffective subjects in regards to 2-hour pain freedom (16% vs. 8%, OR 2.16 [95%CI 1.19-3.95]) and absence of MBS (36% vs. 23%, OR 1.76 [95%CI 1.16-2.68]).[60] In another *post hoc* analysis, the onset of pain relief for ubrogepant 50mg was achieved at 1 hour (43% vs. 37%, OR 1.3 [95%CI 1.06-1.59]).[61] In an open-label 52-week extension trial, the therapeutic efficacy was maintained over the 1-year period.[62] In a PK study, co-administration of ubrogepant and sumatriptan resulted in a 24% reduction of ubrogepant C_{max} but the area under curve (AUC) remained unchanged.[63] Co-administration of acetaminophen led to a 40% increase of ubrogepant C_{max} and AUC but there was no change when co-administered with naproxen.[64] These findings showed no clinically significant drug interaction with triptan and naproxen. In a study of high frequency dosing (2 days on and 2 days placebo alternating vs. all placebo), 7/516 subjects were found to have liver function test elevation $\geq$ 3x the upper limit of normal (five placebo, two ubrogepant), with only two cases (one placebo, one ubrogepant) judged possibly related to treatment and one (ubrogepant) probably related. All were transient and resolved with continued dosing. Ubrogepant was well tolerated, and demonstrated a safety profile similar to placebo with the most common AEs being upper respiratory infection, nausea and dizziness but with no clinically relevant signs of hepatotoxicity.[65] Ubrogepant is expected to receive an FDA decision in December this year.

Rimegepant has been studied for acute treatment of migraines **(Table 2)**. In a phase 2 study comparing multiple dosages of rimegepant (BMS-927711 at that time) against placebo and sumatriptan, rimegepant at doses 75 mg, 150mg, 300mg, and 600mg but not 25mg and 10mg were found to have greater pain freedom at 2 hours when compared to placebo. Sumatriptan was more effective than rimegepant but the study was not designed for such comparison.[66] In a multicenter, double-blind, phase 3 trial involving

1186 patients who were randomized to receive either rimegepant or placebo after a single migraine attack, significantly more subjects in the rimegepant group were pain-free 2 hours after treatment compared to placebo (19.6% vs. 12.0%, p<0.001); therapeutic gain was 7.6%. In addition, the percentage of patients free from their most bothersome symptom two hours after treatment was 37.6% in the rimegepant group vs. 25.2% in the placebo group (p<0.001); therapeutic gain was 12.4%.[67] Interestingly, in 2 patients who started erenumab after 2 and 6 months of rimegepant usage, acute rimegepant still treated their breakthrough migraines successfully.[68] The actual utility of gepants on top of CGRP mAbs remains to be examined and could be an open-label placebo effect. Another multicenter, double-blind, randomized phase 3 trial assigned 1466 patients to receive either 75 mg of rimegepant orally disintegrating tablet (ODT) or placebo to treat a single migraine attack of moderate or severe pain intensity. At 2 hours post-dose, rimegepant was superior to placebo in both freedom from pain (21% vs. 11%, therapeutic gain 10.4%, p <0.0001) and freedom from the most bothersome symptom (35% vs. 27%, therapeutic gain 8.3%, p=0.0009). Significant pain relief was also observed at post-dose 1 hour (p<0.05). The most common AEs were nausea and urinary tract infection, and no serious AE was reported.[69] It is worth mentioning that there was a 2-fold increase in AUC and C_{max} in subjects with severe hepatic impairment (Child-Pugh score 10-15) but no difference in subjects with mild to moderate hepatic impairment (Child-Pugh score 5-9) when compared to matched controls;[70] dose adjustment in severe hepatic impaired patients is likely needed. In addition, vazegepant, which is administered intranasally using the Aptar Pharma Unidose System, has just completed its phase 2/3 trial (NCT03872453) but the result has not been published yet.

Overall, these trials demonstrated clinical efficacy of gepants for acute migraine management with 5-10% of therapeutic gain when compared to placebo **(Figure 1)**. Such gain seems slightly lower than those reported from acetaminophen or triptans.[71] Gepants may benefit those with poor response to triptans.[72] With their superior AE profile, gepants are an alternative to triptans. However, the clinically relevant benefit of gepants over triptans is yet to be seen once gepants become available. Whether gepants work acutely for patients with CM or in the presence of CGRP mAbs remains to be studied.

| Table 2. Summary of rimegepant related clinical trials		
Trial name	Dosage	Primary endpoints
NCT01430442[66] Phase 2b, EM, n=799	600, 300, 150, 75, 25, 10mg sumatriptan vs. placebo	2-hr pain freedom: 20.7%[a], 36.1%[a], 28.2%[a], 27.9%[a], 16.4%, 12.7%, 26.0%[a] vs. 7.4%.
NCT03237845[67] Phase 3, EM, n=1186	75mg vs. placebo	2-hr pain freedom gain: 7.6% (95%CI 3.3%-11.9%)[b] 2-hr absence of MBS gain: 12.4% (95%CI 6.9%-17.9%)[b]
NCT03461757[69] Phase 3, EM, n=1351	75mg vs. placebo	2-hr pain freedom gain: 10.4% (95%CI 6.5%-14.2%)[b] 2-hr absence of MBS gain: 8.3% (95%CI 3.4%-13.2%)[b]
[a] p<0.01 when compared to placebo. [b] p<0.001 when compared to placebo		
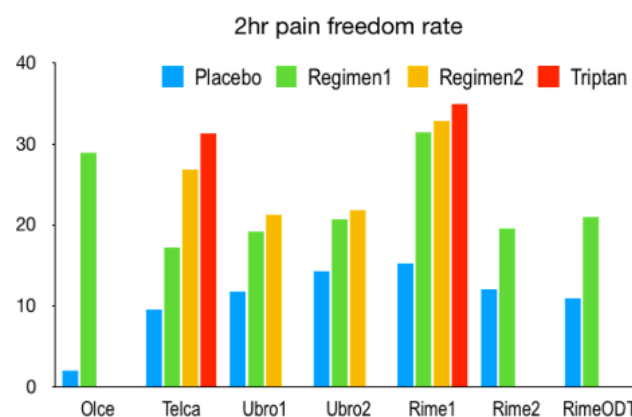
Figure 1. 2hr pain freedom rate based on published gepant related clinical trials.

Migraine Prevention

Atogepant is an oral CGRP receptor antagonist in development for the prevention of migraine. It has a higher potency and longer half-life compared to ubrogepant. In a phase 2b/3 clinical trial, 795 patients with EM were randomized to placebo or various doses of atogepant and treated for 12 weeks under double-blind conditions for migraine prevention. All active treatment groups showed a statistically significant reduction from baseline in mean monthly migraine/probably migraine days (-0.7 to -1.39 days) across the 12-week treatment period. The most common AEs were nausea, fatigue, constipation, nasopharyngitis, and urinary tract infection. Liver safety profile (LFT >3x ULN) was similar to placebo (0.6-2.2% vs. 1.7%).[73] In a *post hoc* analysis, therapeutic gain was 12-22% for ≥50% responders rate (significant for 30mg QD, 30mg BID, 60mg BID).[74]

Rimegepant has also been studied for long-term use. In an interim analysis, 2867 subjects with 2-14 monthly migraine attacks were assigned to use rimegepant as needed (up to 1x/day) for up to 52 weeks with a subgroup getting scheduled every other day (QOD) dosing supplemented by as needed dosing for 12 weeks. Rimegepant was well tolerated with major treatment-associated AEs (≥3%) being upper respiratory tract infection (8.5%), nasopharyngitis (6.4%), sinusitis (4.8%), urinary tract infection (3.8%), and influenzas (3.0%). 2.7% discontinued due to AEs. In 244 subjects who received the QOD regimen, 48.4% had a ≥50% reduction in mean monthly migraine days (MMDs).[75]

Overall, gepants are a new orally available migraine preventive with minimal AEs. They can be an attractive alternative for patients who cannot tolerate conventional migraine preventives or who cannot receive CGRP mAbs. The therapeutic gain (-0.7 to -1.39 days) seems less than that from CGRP mAbs but the clinical dosage has not been optimized. It remains to be studied against other oral preventives or CGRP mAbs regarding clinical efficacy. Whether frequent use of gepants leads to medication overuse headache should be examined as well. At the time of writing, both rimegepant (NCT03732638) and atogepant (NCT02848326) are currently under investigation for migraine prevention.

CGRP-Targeting Monoclonal Antibodies

Monoclonal antibodies (mAbs) that target either the CGRP ligand or the CGRP receptor have been developed. **Table 3** lists three CGRP-targeting mAbs that are FDA approved for the prevention of migraine (either chronic or episodic, with or without aura): erenumab, fremanezumab, and galcanezumab, along with eptinezumab, which is currently undergoing FDA review. All are humanized mAbs targeting the CGRP ligand except for erenumab, which is a fully human mAb targeting the CGRP receptor. They are indicated only for preventive use due to their slow absorption profile. Eptinezumab is the only one with IV formulation, and has a potential for acute treatment but has yet to be confirmed.

Table 3. CGRP targeting monoclonal antibodies							
Name	Sponsor	IgG	Route	$T_{1/2}$	T_{max}	Dose	Frequency
Erenumab	Amgen	IgG$_2$	SC	28D	6D	70mg 140mg	QM QM
Fremanezumab	Teva	IgG$_2$	SC	32D	5D	225mg, 675mg	QM, QLT
Galcanezumab	Eli Lilly	IgG$_4$	SC	27D	5D	120mg[a]	QM
Eptinezumab	Lundbeck	IgG$_1$	IV	26D	1-3h	100mg 300mg	QLT QLT
[a] Start with 240mg loading IV: intravenous. SC: subcutaneous. QLT: quarterly. QM: monthly.							

General Behavior Of Therapeutic Antibodies

An antibody is an immunoglobulin (Ig) produced by B cells. There are 5 subtypes, namely α (IgA), δ (IgD), ε (IgE), γ (IgG), and μ (IgM), with different structural properties. IgD and IgM act as antigen receptors on B cell membranes. IgG is a monomer, IgA is a dimer, and IgM is a pentamer. Among them, IgG constitutes 70% of all immunoglobulins in the body and is the most commonly used therapeutic antibody. It is made up of 2 light chains and 2 heavy chains joined by a disulfide bridge with a mass of 150 kDa (~7-10 nm). It is structurally divided into 3 parts (2 Fab and 1 Fc regions). The Fab parts contain complementarity-determining regions (CDRs) allowing for specific antigen binding that determines its major pharmacological function, and the Fc part plays a major role in activating effector cells and recycling antibodies from degradation. When the antibodies exhibit monovalent affinity, they are called mAbs. Using an immortalized hybridoma, a fusion of antibody-producing B cells and immortalized myeloma cells, Milstein and Köhler pioneered the production of mAbs in 1975 and later won the Nobel prize in physiology in 1984. However, the earlier therapeutic mAbs produced from murine antibodies unfortunately triggered a strong immune reaction in humans. Chimerization and humanization were developed to lower the foreign content thereby reducing the immunogenicity. Traditionally, chimeric antibodies (-ximab) are defined by having <85% human sequence on V gene, while humanized antibodies (-zumab) have ≥85% derived from human DNA with only the CDR of the variable domains being foreign (e.g., non-human or synthetic). To further reduce the immunogenicity, fully human antibodies (-umab) were developed using technologies such as phage display and transgenic mice. However, many other antibody engineering techniques are employed as well, rendering the definition of "human" ambiguous. Thus, the WHO and American Medical Association proposed in 2017 a new naming system based not on the species but on the target, such as -ne- for neural or -ta- for tumor.[76] Without the species information, the protein properties and immunogenic risks should therefore be documented separately.

The mechanism of action of therapeutic mAbs depends on what and where they bind, i.e., the pharmacodynamics (PD) and pharmacokinetics (PK). Since mAbs are structurally different from small molecules, their physical properties (e.g., size, charge, glycosylation pattern, target/off-target affinity) and chemical properties (e.g., degradation, metabolites, clearance) are strikingly distinct from small molecules. Similar to small molecules that bind to receptors or ion channels creating an agonistic or antagonistic effect, mAbs bind to ligands or receptors blocking their targets from action. Conversely, on immune cells, mAb binding enhances effector functions such as antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity. To date, most mAbs are created with high target specificity in the picomolar range and basically no off-target affinity. The distribution of mAbs thus play a major role in the mechanism of action. Keep in mind there is a significant variation in PK between individuals even with the same mAbs. Here, we discuss some basic PK behavior of mAbs.[77]

Absorption
The route of administration determines the mechanism of absorption. Since protein gets degraded in the gastrointestinal tract, mAbs are typically administered IV or subcutaneously (SC). Only newborns can absorb antibody through GI absorption. Compared to IV injection, SC injection is more convenient but may be more painful and have lower bioavailability. The large size, positive surface charge, local proteolysis, and immunophagocytosis hinder the convection of mAbs to traverse SC tissue before entering the lymphatic system and circulation. Typically, it takes 3-7 days postdosing after SC injection to reach maximal serum concentration with 50-90% bioavailability.

Distribution
Once in the circulation, unlike small molecule that diffuse through blood vessel and tissue, mAbs extravasate and convect through vessel and tissue. Extravasation depends on the hydrostatic/oncotic pressure and the size of the paracellular pores in the vascular epithelium. This is a rather passive convective process, but sometimes receptor-

mediated transcytosis may play a role. In a tight endothelium, the mAb tissue:blood ratio is usually low. In contrast, mAb leaks out in areas with fenestrated capillaries or sinusoid. This explains why mAbs are distributed mostly in organs such as the thyroid (67.5%), skin (15.7%), and liver (12.1%) but much less in the brain (0.35%).[78] Once in the tissue, mAbs convect through the extracellular matrix (comprising of a negatively-charged scaffold that hinders the transport of positively charged mAbs) until they bind to the target, get metabolized, or recirculate back to the lymphatic system. In other words, mAbs that are retained in the tissue either bind to the targets or wait for the targets to appear before being eliminated; non-bound or non-trapped IgGs then convect back to the surrounding leaky veins or lymphatic ducts before entering the circulation. In the central nervous system, the dura mater, pituitary, circumventricular organs, and ganglia are much leakier than the blood-brain barrier or brain-CSF barrier (arachnoid mater). This explains why there is minimal accumulation of mAbs in the brain parenchyma or CSF. In contrast, sensory ganglia (TG, cervical, vagus, sphenopalatine, etc.) are highly permeable but interganglionic differences exist among them.[79] Since all these ganglia play certain roles in the headache pathogenesis, they are hence presumably the action sites for CGRP mAbs used for headache. Keep in mind that even though the IgG accumulation in dura (11%) and TG (5.2%) are much higher than that in cortex (0.23%), hypothalamus (0.34%), or CSF (0.12%),[80] IgG is not completely devoid in the parenchyma. Whether that small amount of IgG creates a centrally acting mechanism remains to be determined. Nonetheless, it is reasonable to believe that mAbs' mechanism of action depends heavily on their distribution.

Elimination

IgG elimination usually takes place inside cells. It cannot be filtered by the kidneys nor metabolized by the liver. Rather, IgG gets taken up into cells by either receptor-mediated endocytosis (minor) or nonspecific pinocytosis (major). Receptor-mediated endocytosis takes place at the target cells' surface (target-mediated drug disposition) or the immune cells' surface that expresses Fc-gamma-receptors (FcγR). An example of this is the internalization of the antibody-receptor complex through membrane trafficking. These processes, however, play a minor role in IgG elimination. In contrast, pinocytosis is a nonspecific fluid-phase endocytosis utilized by endothelial cells throughout the body. It was estimated that skin, muscle, liver, and gut account for approximately 33, 24, 16, and 12% of IgG elimination;[81] therefore, body surface area or body weight is often a common factor to determine mAb dosing. Since pinocytosis takes all the surrounding proteins, it requires a protective mechanism to salvage IgGs. This salvage pathway is mediated by neonatal Fc receptor (FcRn), which is also called the Brambell receptor. In neonates, FcRn mediates IgG transport from the mother via placental and intestine. FcRn is highly expressed in skin, muscle, liver, and spleen where vascular endothelia and reticuloendothelial cells are the major sites of IgG homeostasis.[82] FcRn is also expressed in the brain microvascular endothelium and choroid plexus epithelium, facilitating the transport of IgG from the brain back to vessels.[83] The mechanism of such a salvage pathway relies heavily on the IgG-FcRn affinity difference upon pH change. In the acidified endosome (i.e., low pH), FcRn binds to IgG. During exocytosis, IgG-FcRn returns to the cell surface and then releases the IgG at physiological pH. This recycling process is faster than IgG production and accounts for the relatively long half-life of the IgG, particularly IgG_1, IgG_2, and IgG_4.[84] Without FcRn, IgG catabolism is 10-fold faster.[85] Higher IgG concentrations can also saturate the FcRn recycling pathway thereby increasing the IgG clearance rate. This explains why higher dosing with longer intervals may perform worse than lower dosing with shorter intervals. Besides intracellular degradation, immunogenicity to mAbs generates anti-drug antibodies (ADA), even if the mAb is completely analogous to human IgG. ADA is usually a polyclonal response that can be either neutralizing or non-neutralizing. Neutralizing ADAs eliminate the specific binding to the target; non-neutralizing ADAs may form ADA-mAb immune complexes that can increase clearance via the reticuloendothelial system.

With more understanding of the typical behavior of IgG, we can now discuss the mechanism of action of CGRP mAbs. Unfortunately, there are not many studies addressing this fundamental issue. CGRP

mAbs likely act in a similar way to gepants by blocking CGRP's function but exhibit certain unique features. While galcanezumab and erenumab bind to their targets reversibly, fremanezumab and eptinezumab engage the CGRP ligand irreversibily.[86, 87] Additionally, in a cortical spreading depression rodent model, CGRP mAb was shown to selectively inhibit the responsiveness of Aδ-fibers but not C-fibers of afferent meningeal nociceptors.[88] CGRP mAb did not prevent CSD-induced arterial dilatation and plasma protein extravasation but prevented CGRP-induced arterial dilatation; thus, the CSD model likely differs from the CGRP infusion model.[89] CGRP mAbs (either ligand or receptor) are believed to elicit no effect in the absence of CGRP. Rather, they interrupt CGRP-induced cAMP accumulation and, at a 10-fold higher dosage, receptor internalization.[90] CGRP mAbs prevented the development of basal hyperalgesia and cutaneous mechanical hypersensitivity,[91] and also inhibited bright light stress- and NO donor-induced cutaneous allodynia in animals previously primed with sumatriptan or morphine.[92] These mAbs have been shown to inhibit neurogenic vasodilatation mediated by CGRP without affecting heart rate or arterial blood pressure in rats.[93]

Acute Migraine Treatment

Due to their slow absorption kinetic, there is no acute treatment trial involving the SC-injected CGRP function-blocking mAbs. In contrast, eptinezumab, which is administered IV with onset of action possibly within a few hours,[91] is currently under investigation for subjects experiencing acute migraine attack (NCT04152083).

Migraine Prevention

Erenumab is a fully human mAb that targets the CGRP receptor. Erenumab was not associated with vasoactive properties per se but specifically inhibits CGRP-induced relaxation.[94] It has been studied in the prevention of both CM and EM **(Table 4)**. For CM, one phase 2, randomized, double-blind, multicenter study enrolled 667 patients with CM and randomly assigned them to either placebo, erenumab 70 mg, or erenumab 140 mg given every 4 weeks for 12 weeks. At the end of the study period, both erenumab 70 mg and 140 mg

reduced MMDs compared to placebo (both doses -6.6 days vs. placebo -4.2 days, p<0.0001). The safety profile was similar to placebo, with the most frequent AEs being injection-site pain, upper respiratory tract infection, and nausea. [95] There are also several studies investigating erenumab's efficacy in preventing EM. In one multicenter, randomized, double-blind phase 2 trial, 483 patients with EM were randomized to SC injections of placebo, erenumab 7 mg, erenumab 21 mg, or erenumab 70 mg in monthly doses for a total of 12 weeks. There was a significant mean change in MMDs at week 12 with erenumab 70 mg compared to placebo (-3.4 days vs -2.3 days, p=0.021). However, there was no significant difference between the 7 mg and 21 mg with placebo [96]. In addition, a phase 3, randomized, double-blind study known as the ARISE trial was conducted in which 577 patients with EM were randomized to monthly SC injection of placebo or erenumab 70 mg for 12 weeks. At the end of the study period, those receiving erenumab experienced a mean -2.9 days change from baseline in MMDs compared

Table 4. Summary of erenumab related clinical trials		
Trial name	**Dosage**	**Primary endpoint**
NCT02066415[95] Phase 2, CM, n=667	140, 70mg vs. placebo	MMD reduction: both -2.5 (95%CI -3.5 to -1.4), p<0.0001
NCT01952574[96] Phase 2, EM, n=483	70, 21, 7mg vs. placebo	MMD reduction: -1.1 (95%CI -2.1 to -0.2), p=0.021; -0.1 (95%CI -1.1 to 0.9), p=0.83; 0.1 (95%CI -0.8 to 1.1), p=0.82
NCT02483585[97] Phase 3, EM, n=577	70mg vs. placebo	MMD reduction: -1.0 (95%CI -1.6 to -0.5), p<0.001.
NCT02456740[98] Phase 3, EM, n=955	140, 70mg vs. placebo	MMD reduction (by 6 months): -1.9 (95%CI -2.3 to -1.4), p<0.001; -1.4 (95%CI -1.9 to -0.9), p<0.001.
NCT03096834[99] Phase 3b, EM*, n=246	140mg vs. placebo	≥50% responder rate: 30% vs. 14%, OR 2.7 (95%CI 1.4-5.2), p=0.002.
All studies were evaluated over 12-week unless otherwise specified. EM: episodic migraine. CM: chronic migraine. MMD: mean monthly migraine day. OR: odds ratio. * failed 2-4 migraine preventives.		

to -1.8 days in placebo (p<0.001). Participants in the erenumab group also had an increased number of people who experienced a ≥50% reduction in MMDs (40% vs. 30% placebo, p=0.010) and a greater reduction in monthly acute migraine-specific medication use (-1.2 days vs. -0.6 days placebo, p=0.002) [97]. Another phase 3, randomized, double-blind study known as the STRIVE trial enrolled 955 patients with EM who were randomized to receive monthly SC injection of placebo or erenumab 70 mg or 140 mg for 24 weeks. There was a significant reduction in MMDs in both the 70 mg and 140 mg erenumab groups compared to placebo (-3.2 and -3.7 respectively vs. -1.8 placebo, p<0.0001 for both). In addition, a ≥50% reduction in MMDs was achieved by 43% and 50% of the erenumab 70 mg and 140 mg groups compared to 27% in the placebo group (p<0.0001 for both) [98]. For subjects who failed 2-4 preventive medications, at week 12, 36 (30%) patients in the erenumab had a 50% or greater reduction from baseline in the mean number of MMDs, compared with 17 (14%) in the placebo group. MMDs were reduced 1.6 days (95%CI -2.7 to -0.5; p=0.004). The tolerability and safety profiles of erenumab and placebo were similar. The most frequent treatment-emergent AE was injection site pain, which occurred in seven (6%) participants in both groups.[99] At week 64 (52 weeks of open-label), 85% completed the week 52 visit. Overall, 47.1% achieved ≥50% reduction in MMD and a MMD reduction of -3.7±4.1 days.[100] In an interim analysis from an open-label study lasting 4+ years, MMDs were reduced by 5.8±3.8 days and acute medication days were reduced 4.6±3.3 days. The most common AEs were nasopharyngitis (10.9%), upper respiratory tract infection (6.8%), and influenza (4.7%) but there was no worsening of constipation.[101, 102] However, serious constipation requiring hospitalizations was reported in post-marketing analysis.; "constipation with serious complications" was then added to the Aimovig FDA label.

Fremanezumab, a humanized mAb that targets both the α- and β-CGRP ligands, has been studied for the prevention of both CM and EM **(Table 5)**. It has been shown to block CGRP-induced dilatation in human cerebral, middle meningeal, and abdominal arteries.[103] In one multicenter, randomized, double-blind phase 2b study investigating fremanezumab for preventive treatment of CM, 264 patients were randomly assigned to receive either placebo or 2 different treatment regimens of fremanezumab SC for 3 28-day treatment cycles (either 675 mg in the first treatment cycle and 225 mg in the second and third cycles or 900 mg in all three cycles). Primary endpoints were change from baseline in number of headache-hours during the third treatment cycle (weeks 9-12) and safety and tolerability. Both treatment groups showed significant reduction in headache-hours compared to placebo, with a least square mean difference of -22.74 hours between the placebo and 675/225 mg group (p=0.0386) and -30.41 hours between the placebo and 900 mg group (p=0.0057). The most common AEs were mild injection-site pain and pruritis.[104] A similar multicenter, randomized, double-blind phase 2b study also investigated the use of fremanezumab in preventing EM. 297 patients with high-frequency EM were enrolled and randomized to either placebo or 2 different doses of fremanezumab SC for 3 28-day treatment cycles (225 mg or 675 mg). Primary endpoints were change from baseline in migraine days during the third treatment cycle (weeks 9-12) and safety and tolerability. Results showed significant reductions in migraine-days from baseline between both treatment groups compared to placebo, with a least square mean change of -2.81 days between the 225 mg dose group and placebo (p<0.0001) and -2.64 days between the 675 mg dose and placebo (p<0.0001). AE incidence was similar between placebo and treatment groups.[105]

In addition, fremanezumab has been studied in two 16-week, multicenter, randomized, double-blind phase 3 trials, known as the HALO studies, for the prevention of both CM and EM. In the CM study, 1130 patients were randomized to receive SC injections of either fremanezumab 675 mg at initiation followed by monthly 225 mg for 2 months (monthly dose regimen), fremanezumab 675 mg at initiation followed by placebo for two months (quarterly dose regimen), or three monthly doses of matching placebo. At the end of the study period, patients treated with fremanezumab experienced statistically significant reduction in mean monthly headache days (MHDs) of at least moderate

Table 5. Summary of fremanezumab related clinical trials

Trial name	Dosage	Primary endpoint
NCT02021773[104] Phase 2b, CM, n=264	900, 675/225mg vs. placebo	Headache hours: -30.41 (95%CI -51.88 to -8.95), P=0.0057; -22.74 (95%CI -44.28 to -1.21), p=0.0386
NCT02025556[105] Phase 2b, EM, n=297	675, 225mg, vs. placebo	MMD reduction: -2.64 (95%CI -3.9 to -1.38), p<0.0001; -2.81 (95%CI -4.07 to -1.55), p<0.001
NCT02621931[106] Phase 3, CM, n=376	675 once, 675/225mg, vs. placebo	MHD reduction: -1.8 (95%CI -2.4 to -1.2), p<0.001; -2.1 (95%CI -2.7 to -1.5), p<0.001
NCT02629861[107] Phase 3, EM, n=875	675 once, 675/225mg vs. placebo	MMD reduction: -1.3 (95%CI -1.79 to -0.72), p<0.001; -1.5 (95%CI -2.01 to -0.93), p<0.001
NCT03308968[109] Phase 3b, EM/CM*, n=838	675 once, 675/225mg vs. placebo	MMD reduction: -3.1 (95%CI -3.8 to -2.4), p<0.0001; -3.5 (95%CI -4.2 to -2.8), p<0.0001

All studies were evaluated over 12 weeks. EM: episodic migraine. CM: chronic migraine. MMD: mean monthly migraine day. MHD: mean monthly headache day. * Failed 2-4 classes of migraine preventives

severity compared to placebo (-2.5 days) during the 12-week period after the first dose for both monthly (-4.6 days, p<0,0001) and quarterly (-4.3 days, p<0.0001) dosing regimens. The most common AE was injection site pain, with similar rates in the placebo and active groups.[106] In the EM study, 875 patients were randomized to receive SC injections of fremanezumab 225 mg as a monthly dose for 3 months, 675 mg at initiation followed by placebo for 2 months, or 3 monthly doses of matching placebo. At the end of the study period, fremanezumab given monthly resulted in a 41.6% reduction in migraines relative to baseline (-3.7 days vs. -2.2 days for placebo, p<0.0001) and the quarterly dose of fremanezumab also showed significant improvement in migraine days (-3.4 days or 37.0%, p<0.0001).[107] In a *post hoc* analysis of both HALO studies, it was shown that the effect was observed at week 1 (-0.5 days [95%CI -0.7 to -0.3],

p<0.0001).[108] In a recent study involving 838 subjects (EM 39%, CM 61%) who failed 2-4 classes of migraine preventives with similar treatment assignment as the HALO study, reductions from baseline in monthly average migraine days over 12 weeks were greater versus placebo (least-squares mean [LSM] change −0.6 [SE 0.3]) with quarterly fremanezumab (LSM change −3.7 [0.3]; LSM difference vs placebo −3.1 [95% CI −3.8 to −2.4]; p<0.0001) and with monthly fremanezumab (LSM change −4.1 [0.34]; LSM difference vs placebo −3.5 [−4.2 to −2.8]; p<0.0001). AEs were similar for placebo and fremanezumab. Serious AEs were reported in four (1%) of 277 participants with placebo, two (<1%) of 276 with quarterly fremanezumab, and four (1%) of 285 with monthly fremanezumab.[109] Interestingly, the therapeutic gains were much higher than that from the HALO studies, most likely due to low placebo response.

Galcanezumab is another humanized mAb antagonist that targets the α- and β-CGRP ligands **(Table 6)**. In a randomized, multicenter, double-blind, phase 2 proof-of-concept study, 218 patients with migraine were randomly assigned to a SC injection of either galcanezumab 150 mg or placebo every two weeks for twelve weeks. At the end of twelve weeks, there was a significant reduction from baseline in the number of migraine headache days in the galcanezumab group compared to placebo (-4.2 days vs. -3.0 days, least-squared mean difference -1.2, p=0.0030). AEs that occurred more frequently with galcanezumab included injection site pain, erythema, upper respiratory infections, and abdominal pain. No serious AEs were found that were related to the study drug. [110] Two phase 3, randomized, double-blind, controlled clinical trials titled EVOLVE-1 and EVOLVE-2 were also conducted to investigate the efficacy and safety of galcanezumab for the prevention of EM. In EVOLVE-1, 858 patients with EM were randomized (2:1:1) to monthly SC injection of placebo, galcanezumab 120 mg, or galcanezumab 240 mg for 6 months. Treatment with galcanezumab significantly reduced MMDs in both the galcanezumab 120 mg and 240 mg groups compared to placebo (-4.7 days and -4.6 days respectively vs. -2.8 days placebo, p<0.001 for both). The incidence of discontinuation due to Aes

Table 6. Summary of galcanezumab related clinical trials

Trial name	Dosage	Primary endpoint
NCT01625988[110] Phase 2, EM, n=218	150mg vs. placebo	MMD reduction: -1.2 (90%CI -1.9 to -0.6), p=0.003
NCT02614183[111] Phase 3, EM, n=858	240, 120mg vs. placebo	MMD reduction (at 6 month): -1.8 (95%CI -2.5 to -1.4), p<0.001; -1.9 (95%CI -2.5 to -1.4), p<0.001
NCT02614196[112] Phase 3, EM, n=915	240, 120mg vs. placebo	MMD reduction (at 6 month): -1.9 (95%CI -2.4 to -1.4), p<0.001; -2.0 (95%CI -2.6 to -1.5), p<0.001
NCT02614261[114] Phase 3, CM, n=1113	240, 120mg vs. placebo	MMD reduction: -1.9 (95%CI -2.7 to -1.1), p<0.001; -2.1 (95%CI -2.9 to -1.3), p<0.001
All studies were evaluated over 12-week unless otherwise specified. EM: episodic migraine. CM: chronic migraine. MMD: mean monthly migraine day.		

was less than 5% across all treatment groups.[111] In EVOLVE-2, 915 patients with EM were enrolled with the same treatment regimen as the EVOLVE-1 trial. After 6 months, MMDs were reduced by 4.3 and 4.2 days by galcanezumab 120 mg and 240 mg respectively compared to 2.3 days by placebo (p<0.001 for both). In addition, significantly greater mean proportions of patients in the galcanezumab 120 mg and 240 mg groups experienced ≥50% reduction in migraine headache days compared to placebo (59% and 57% vs. 36%, p<0.001). Injection site pain was the most common AE and was reported at similar rates in all treatment groups, but both galcanezumab doses had significantly more injection site reactions and pruritis compared to placebo.[112] In a *post hoc* study pooling EVOLVE 1 and 2 studies for those who failed ≥2 prior preventives, overall in 6 months there were reductions of -2.60 days (95%CI-3.95 to -1.25) and -3.37 days (95%CI -4.78 to -1.96) for the 120mg and 240mg doses, respectively.[113] Another phase 3 trial known as the REGAIN study evaluated the safety and efficacy of galcanezumab in the prevention of CM. In this study, 1113 patients with CM were randomized (2:1:1) to monthly SC injections of

placebo, galcanezumab 120 mg (with a 240 mg loading dose), or galcanezumab 240 mg for a total of 3 months. After 3 months, both the galcanezumab 120 mg and 240 mg groups demonstrated greater overall mean reduction in the number of MMDs compared to placebo (-4.8 days and -4.6 days respectively vs. -2.7 days placebo, p<0.001 for both). There were no significant differences between the groups on any safety or tolerability outcomes other than a higher incidence of injection-site reaction, erythema, and pruritis as well as sinusitis in the galcanezumab 240 mg group relative to placebo [114]. In a long-term open-label study (n=270), 77.8% completed the open-label phase, and 4.8% discontinued due to AEs. Overall the migraine days were reduced (-5.6 for 120mg, -.6.5 for 240mg). Treatment emergent AEs with a frequency ≥ 10% of patients in either dose group were injection site pain, nasopharyngitis, upper respiratory tract infection, injection site reaction, back pain, and sinusitis.[115]

Eptinezumab is a humanized mAb targeting both the α- and β-CGRP ligands and is produced by yeast as opposed to mammalian cells like the other mAbs. It has been studied for prevention of both CM and EM **(Table 7)**. In a randomized, double-blind, placebo-controlled, exploratory, proof-of-concept phase 2 trial, 174 patients with EM were randomly assigned to receive either in intravenous dose of 1000 mg of eptinezumab or placebo and assessed for safety 12 weeks after infusion and change in baseline to weeks 5-8 in the frequency of migraine days. The mean change in migraine days between baseline and weeks 5-8 was statistically significant, with -5.6 days in the treatment group compared to -4.6 days in the placebo group (p=0.0306). The most common AEs included upper respiratory tract infection (URI; 9 vs. 7%), urinary tract infection (UTI; 1 vs. 5%), fatigue (4% both groups), back pain (4 vs. 5%), nausea and vomiting (4 vs. 2%), and arthralgia (1 vs. 5%) in the eptinezumab versus placebo groups, respectively.[116] Another phase 2b, parallel-group, double-blind, randomized clinical trial investigated the safety, tolerability, and effectiveness of eptinezumab for the prevention of CM. 616 patients with CM were enrolled and randomized (1:1:1:1:1) to eptinezumab 10 mg, 30 mg, 100 mg, or 300 mg or placebo, administered as a single IV infusion with

Table 7. Summary of eptinezumab related clinical trials

	Dosage	Primary endpoint
NCT01772524[116] Phase 2, EM, n=163	1000mg vs. placebo	MMD reduction: -1.0 (95%CI -2.0 to 0.1)
NCT02275117[117] Phase 2b, CM, n=616	300, 100, 30, 10mg vs. placebo	≥75% responder rates: 33.3%, 31.4%, 28.2%, 26.8%, vs. 20.7% (p=0.033, 0.072, 0.201, 0.294).
NCT02559895[118] Phase 3, EM, n=888	300, 100, 30mg vs. placebo	MMD change[a]: -4.3, -3.9, vs. -3.2 (p=0.0001, 0.0179)
NCT02974153[119] Phase 3, CM, n=1072	300, 100mg vs. placebo	MMD change: -8.2, -7.7, vs. -5.6 (p<0.0001, <0.0001)

All studies were evaluated over 12-week unless otherwise specified. EM: episodic migraine. CM: chronic migraine. MMD: mean monthly migraine days. [a] Data from 30mg was not reported.

the primary endpoint being the percentage of patients with a ≥75% decrease in MMDs over weeks 1-12. Patients in the eptinezumab 300 mg group had significant ≥75% migraine responder rates compared to placebo (33.3% vs. 20.7%, p=0.033). However, patients in the eptinezumab 10 mg, 30 mg, and 100 mg did not achieve statistically significant results compared to placebo. AE rates were similar to placebo [117]. Two randomized, double-blinded phase 3 trials also investigated the safety and efficacy of eptinezumab for the treatment of EM (PROMISE-I) and CM (PROMISE II). In PROMISE-I, 888 patients were randomized to eptinezumab 30 mg, 100 mg, 300 mg, or placebo by IV infusion once with the primary end point being the mean change from baseline in MMDs over the 12-week treatment period. Patients in the eptinezumab 100 mg, and 300 mg groups all had significant reductions in MMDs compared to placebo (-3.9 [p=0.0179], and -4.3 [p=0.0001] vs. -3.2, respectively). AEs for eptinezumab were similar to placebo [118]. In PROMISE-II, 1072 patients with CM were randomized to eptinezumab 100 mg, 300 mg, or placebo administered intravenously every 12 weeks for 2 infusions with the primary endpoint being the change from baseline in MMDs over weeks 1-12. Patients in both eptinezumab 100 mg and 300 mg treatment groups showed significant reduction from baseline in MMDs compared to placebo over months 1-3 (-7.7 days and -8.2 days

respectively vs. -5.6 days, p<0.0001 for both) and months 4-6 (-8.1 days and -8.8 days respectively vs. -6.1 days, p<0.0001 for both). Rates of AEs were again similar between groups.[119] In the PREVAIL study, which is an open-label 1-year safety study, treatment emergent AEs were reported for 64.8% of patients, with the most common (≥5%) being nasopharyngitis (13.3%), upper respiratory tract infection (7.0%), sinusitis (6.3%), and influenza (5.5%).[120]

Clinical Perspective

These clinical trials have demonstrated the clinical efficacy of CGRP mAbs. Keep in mind that these trials were conducted under different study populations and calculated differently for their primary endpoints; this inconsistency renders their comparison based on published trials impractical. **Figure 2** illustrates the MMD changes reported in each study. Overall, CGRP mAbs reduced MMDs in subjects with EM (therapeutic gain 0.7-1.9 days) and CM (therapeutic gain 1.5-2.4 days). Acute medication use was also reduced in subjects with EM (therapeutic gain 0.5-3 days) and CM (therapeutic gain 1.9-2.5 days). In addition, less patients reported medication overuse (therapeutic gain 9-15%) after 12 weeks.[121] Interestingly, subjects who previously failed preventive therapy exhibited lower placebo response and a higher therapeutic gain of 1.6-3.5 days.[99, 109,113] The time to onset of action for IV- and SC-administered CGRP mAb are likely within 1 day and 1 week, respectively.[118, 119,122, 123, 124] Early non-responders may still respond by later months.[123] With a complementary mechanism and minimal drug interactions, CGRP mAbs likely will gain additional clinical benefit when used in combination with current preventive medications.[125] The low number needed to treat (NTT) and high number needed to harm (NNH) of CGRP mAbs demonstrates a favorable benefit-risk profile against other migraine preventive therapies[126].

A — Change in MMD (CM)

B — Change in MMD (EM)

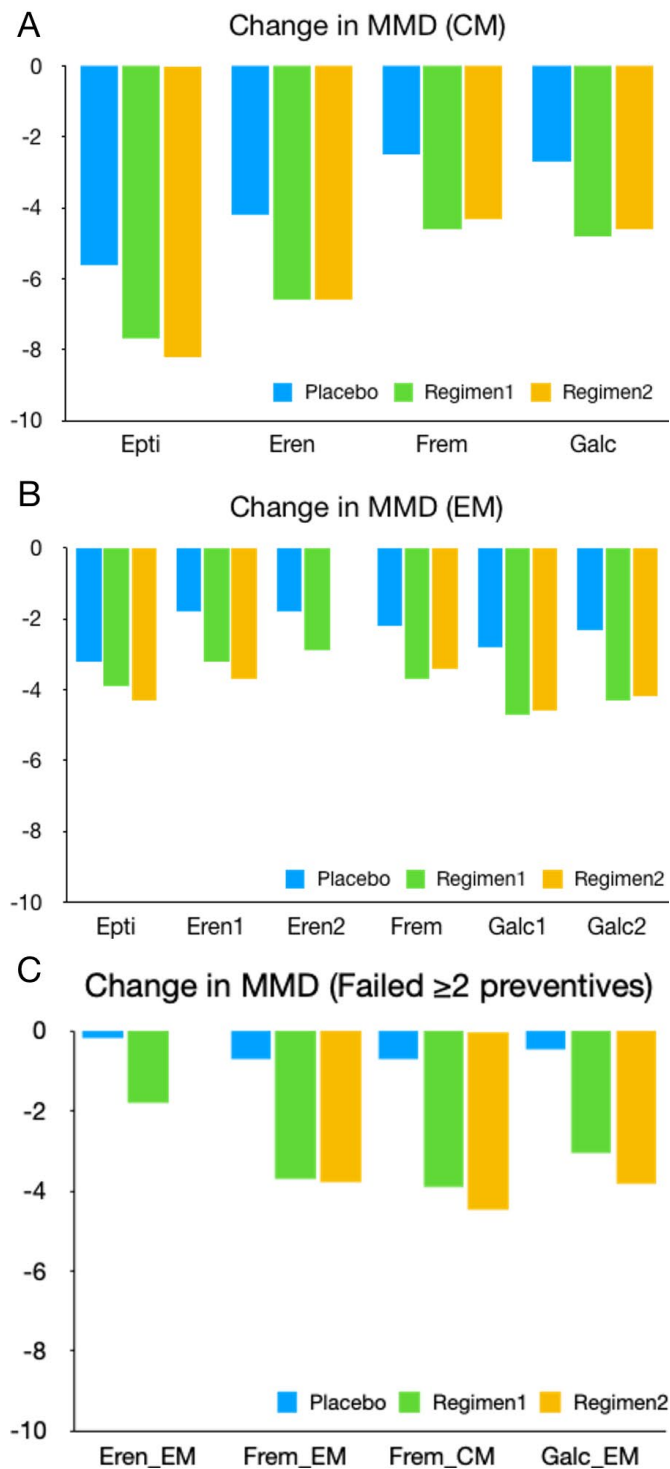## C — Change in MMD (Failed ≥2 preventives)

Figure 2. Change in mean monthly migraine days (MMD) in subjects with (A) chronic migraine (CM), (B) episodic migraine (EM), (C) failure of 2 preventive medications based on published clinical trials.

However, some practical issues remain.

(1) CGRP is a key neuropeptide in tissue healing, hematopoiesis, and the neuro-immune axis. Prolonged CGRP blockade may impact certain restorative functions, unmask underlying autoimmunity, or perhaps even worsen active infection or cardiac dysfunction.

(2) All trials included only patients in a relatively healthy state (BMI<40, age <70 years, no active major cardiovascular or other major health issues, not pregnant or breastfeeding). The clinical response in these unstudied yet vulnerable populations remain to be seen.

(3) IgG, particularly IgG_1 and IgG_4, is readily transported via FcRn across placenta and breast alveoli. CGRP mAb is probably unsafe for fetuses as CGRP plays a role in placental vascular adaptation and decidualization.[127] Per FDA label, no AEs on offspring were observed when pregnant monkeys were administered erenumab throughout gestation. At this moment we do not have sufficient clinical data to justify its safety for use in women who are pregnant or breastfeeding.

(4) It has been our personal experience that a second mAb agent may be successful if the first one fails or has significant AEs.

(5) Insurance coverage and drug affordability remain important issues. Insurers typically require a failure of 2 classes of preventive medications or onabotulinum toxin (Botox) in order to approve coverage. Practically, a specialty pharmacy can be employed to reduce the financial and logistical burden to patients. However, combination therapy of CGRP mAbs with Botox or gepants is still not covered at this moment but hopefully will be in the future.

Conclusion

CGRP plays a fundamental role in migraine pathogenesis. CGRP antagonism, via either gepants or mAbs, has demonstrated clinical efficacy in both acute and preventive treatment of migraine. This is a new class of medication that for the first time ever was developed to be specifically tailored to the underlying pathophysiology of migraine. Gepants likely exhibit slightly less efficacy than triptans but have much less vasoconstrictive

risk; long-term safety on their frequent use remains to be examined. CGRP and CGRP receptor mAbs significantly reduce MMDs, decrease acute medication use, and improve patient's quality of life. They are effective even in those who failed multiple preventive medications. Their convenient monthly dosing and minimal AE profile not only improve medication compliance but may also reduce migraine chronification. However, keep in mind that they do not work for everyone as CGRP is not the only player in the pain pathways of migraine and its functional blockade may cause harm in certain vulnerable populations. More well-designed clinical trials are still needed.

Acknowledgement

Disclosures

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