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Review Article

Targeting CGRP for the Prevention of Migraine and Cluster Headache: A Narrative Review

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Calcitonin-gene-related peptide (CGRP), a neuropeptide broadly distributed in neuronal and non-neuronal regions throughout the body, plays a fundamental role in migraine and cluster headache (CH) pathophysiology. CGRP functional blockade alleviates neurogenic inflammation and reduces pain pathway sensitization. Two types of CGRP function-blocking modalities, monoclonal antibodies (MAbs), and small molecules (gepants), have been designed to target the CGRP ligands and CGRP receptors. In this narrative review, we summarized the latest clinical trials on gepants and CGRP function-blocking MAbs for migraine and CH prevention. At the time of writing, newer gepants are currently under Federal Drug Administration (FDA) review for migraine management, but there is no study yet on the usage of gepants for CH. Erenumab, fremanezumab, and galcanezumab have been approved by the FDA for migraine prevention while eptinezumab is under FDA review. CGRP MAbs are as effective as and more tolerable than conventional migraine preventives. For CH prevention, galcanezumab has shown some promising findings and was recently approved for use in episodic cluster prevention. CGRP function-blocking therapy not only demonstrates high efficacy and superior safety profile, but also improves headache frequency and quality of life. Convenient monthly dosing for the MAbs can further improve medication adherence, hence better headache control. With CGRP function-blocking therapy showing efficacy even in individuals who failed other preventives, it has become an exciting new therapeutic option in the field of migraine and CH.

Key words: calcitonin gene-related peptide, migraine, cluster headache, gepant, monoclonal antibody

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INTRODUCTION

Migraine and cluster headache (CH), though clinically distinguishable by ICHD-3 criteria,[1] share a common pathophysiology: the trigeminovascular pathway.[2] Trigeminal afferents are pseudo-unipolar neurons with cell bodies forming the trigeminal ganglion (TG) where neurons interact with the surrounding satellite glial cells and other cell types.[3] These afferents (primarily ophthalmic branch) innervate pain-sensitive structures in the head and send sensory signals to trigeminal cervical complex (TCC), which then projects to multiple nuclei (eg, thalamus,

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hypothalamus, brainstem, basal ganglia) involved in processing head pain and associated symptoms. In particular, the trigeminal nerve connects with the parasympathetic system through the superior salivatory nucleus and the sphenopalatine ganglion, which are responsible for autonomic symptoms (eg, conjunctival injection, tearing, and rhinorrhea). In migraine, abnormal activation of the trigeminovascular system causes not only vasodilation and neurogenic inflammation but also peripheral and central pain sensitization that leads to sustained headache.[3] In CH, dysfunctional hypothalamic, trigeminovascular, and parasympathetic communication have been implicated.[4] Better understanding of the trigeminovascular pathway allows for the development of new therapeutic targets specific for migraine and CH.

Great challenges remain in managing migraine and CH, since these are complex neurovascular pain syndromes. Based on the attack frequency or cluster period, migraine and CH can be categorized as episodic or chronic.[2] Many clinically effective preventive medications are used off-label and each demonstrates a unique adverse effect (AE) profile, possibly impacting medication adherence and leading to headache chronification. Historically, preventive medications used in migraine and CH management have been initially designed for other medical conditions (eg, hypertension, epilepsy, depression, etc.) Until May 2018, the Federal Drug Administration (FDA) approved 6 oral preventives for migraine, 1 injectable preventive specifically for chronic migraine (CM), but still none are FDA-approved for CH. Now, a new class of headache therapeutic that targets the calcitonin-gene-related peptide (CGRP) ligand and receptor has emerged. At the time of writing, 3 CGRP function-blocking monoclonal antibodies (MAbs), namely erenumab (Amgen, Thousand Oaks, CA), fremanezumab (TEVA, Petah Tikva, Israel), and galcanezumab (Eli Lilly, Indianopolis, IN), have been approved by the FDA for migraine prevention. Another CGRP MAb, eptinezumab (Alder, Bothell, WA), and 2 CGRP antagonizing small molecules (gepants), ubrogepant (Allergan, Dublin, Ireland), and ramigepant (New Haven, CT), are under FDA review. Galcanezumab recently also received FDA approval for episodic CH prevention. This is the first time a preventive therapeutic has ever been developed specifically for migraine and CH. It is, therefore, of great interest to understand the role of CGRP in migraine/CH pathophysiology and to compare the efficacy of different CGRP antagonizing modalities available to date.

CGRP'S ROLE IN MIGRAINE AND CLUSTER HEADACHE PATHOPHYSIOLOGY

CGRP belongs to the calcitonin family, which consists of structurally related neuropeptides including calcitonin, amylin, adrenomedullin, and adrenomedullin-2.[5] CGRP is broadly distributed in neuronal and non-neuronal regions throughout the body serving sensory, digestive, vascular, vestibular, hemopoietic, immunomodulatory, nociceptive, and tissue healing functions. Unlike neurotransmitters that act locally at synapses and get taken back, neuropeptides released from large dense vesicles act at varicosities along the axon, have no reuptake system (metabolized by proteinase), and can diffuse far via volume transmission. Undegraded intracranial neuropeptides may enter the glymphatic and venous systems, thus are measurable in serum.[6] In the trigeminal system, CGRP is the most abundant neuropeptide. It is found mainly in small-sized capsaicin-sensitive sensory C fibers (less in medium- and large-sized A-/B-fibers) that run along the cerebral/meningeal arteries then spread into tissue. CGRP binds to the canonical CGRP receptor and the amylin 1 (AMY_1) receptor, activating cAMP and subsequent intracellular messengers depending on the cell type. It is one of the most potent cerebral vasodilators. CGRP interacts with its receptors on trigeminal Aδ fibers/neurons, satellite glial cells, endothelial cells, immune cells, and blood vessel smooth muscle cells, inducing vasodilation, neurogenic inflammation and subsequently peripheral/central sensitization, leading to a dysfunctional activation of the trigeminovascular system. To date, the function of CGRP in migraine or CH is becoming understood.

CGRP plays a fundamental role in migraine and CH pathophysiology. Although the reliability of serum CGRP measurement is still a debatable issue, elevated CGRP levels have been frequently reported during spontaneous migraine or CH attacks.[7-9] Treatment

with triptans not only aborts the headache but also ameliorates the risen serum CGRP level.[8,10] CGRP levels are also elevated interictally in CM, whereas onabotulinumtoxinA treatment decreases the interictal CGRP levels.[11] In those who developed a migraine or CH after receiving low-dose sublingual nitroglycerin (NTG), CGRP concentration correlates with the timing of headache and was reversed by triptan administration as well. The mean onset of NTG-provoked migraine-like and cluster-like attacks were several hours and around 40 minutes, respectively.[12,13] While NTG-provoked migraine-like attacks were observed mostly in those with migraine but not healthy controls, NTG-provoked CH-like attacks were observed only in those with CH in the active period but not in remission. Similarly, CGRP infusion triggers delayed migraine-like attacks in roughly 68% migraine subjects but not in healthy controls and individuals with tension-type headaches or familial hemiplegic migraine.[14-17] CGRP infusion also provokes CH-like attacks in active-phase episodic CH and chronic CH but not in remission-phase episodic CH.[18] These observations, where CGRP triggers delayed headache only in those with migraine or active CH, reflect that a possible underlying genetic predisposition and heightened sensitivity of the trigeminal nociceptive network is likely required for CGRP provocability. With CGRP being blood-brain barrier (BBB) impermeable and unable to directly activate or sensitize meningeal nociceptors in rodents, the mechanism of action of CGRP in migraine and CH probably takes place in regions outside the BBB (eg, neural ganglia, dura) and involves nociceptive pathways within brainstem, insula, caudate, thalamus, and cingulate cortex.[19] Keep in mind that the onset of migraine-like and CH-like headaches are hours different so the CGRP provocation mechanism in migraine and CH may differ. Nonetheless, these provocation studies clearly implicate a rational strategy for the use of CGRP functional blockade in alleviating migraine and CH.

CGRP FUNCTION-BLOCKING THERAPY IN MIGRAINE AND CLUSTER HEADACHE

To date, several CGRP function-blocking gepants and MAbs have been investigated for migraine and CH management. Gepants were initially designed for acute migraine treatment. They bind to CGRP receptors (less at AMY_1) and reverse CGRP-induced vasodilation but were not vasoconstrictive on their own, thus can be a favorable alternative when a triptan is contraindicated.[20] Further clinical development was hampered for a while due to hepatotoxicity. Recently, newer gepants were found to have safety and tolerability profiles being comparable to placebo with no significant cardiac or hepatic AEs.[21] MAbs, compared to gepants, have a much higher target specificity and a longer circulating half-life, as well as lower drug-drug interactions and off-target AEs. They are humanized immunoglobulin class G (IgG) with reduced host immunogenicity. The MAb can be tailored to picomolar affinity with basically no off-site targeting (ie, does not bind to other ligands or receptors) nor MAb-drug interaction (ie, does not bind to other drugs). The extended serum half-life, which is primarily facilitated by the neonatal Fc receptor, allows for convenient monthly or quarterly dosing. However, MAbs can only be administered parenterally through a vein or subcutaneous tissue, where the latter also affects MAb's absorption kinetics and bioavailability as well as causing local injection site pain or reaction. Once extravasated from blood vessels, MAbs stay in the tissue acting continuously until being degraded by reticuloendothelial cells locally. Since the MAb is impermeable to the BBB, its action likely occurs outside the BBB, such as in neural ganglia (eg, vagal, trigeminal, sphenopalatine, etc.) In a mechanical cortical spreading depression (CSD) animal model, fremanezumab reduces the sensitivity to dural indentation in the high-threshold (HT) neurons and prevents receptive field expansion.[22] It has been suggested that CGRP MAb possibly blocks mechanical CSD activation via Aδ fibers but not C fibers. The effect of CGRP MAb blockade on other CGRP/AMY_1 receptor-expressing non-neural cells likely also plays a role.

So far, multiple clinical trials have demonstrated the efficacy of CGRP functional blockade in migraine management but only a few in CH management. A recent systematic review (consensus article) by the European headache federation found variable quality of evidence from the available CGRP MAb trials for migraine; most trials are of medium to high quality with a few of low quality.[23] Since not all studies follow

the prophylactic control trial guideline and each trial has different patient baseline characteristics, it is difficult to compare head-to-head their efficacies based on published data.[24] In particular, there is significant variation in the number of active or failed migraine preventives allowed rendering a substantial sampling bias among studies. Nonetheless, we can still observe some trends from these studies. In the following paragraphs, we summarize the latest findings from the gepants and CGRP MAb related clinical trials.

Gepants are Probably Effective in Preventing Migraine but Uncertain in CH.—Atogepant (Allergan, Dublin, Ireland) and rimegepant are the only 2 gepants under investigation for migraine prevention in phase 2b/3 trials. After 12 weeks of daily atogepant use (10 mg QD to 60 mg BID) in subjects with episodic migraine (EM), there were significantly less mean monthly migraine/probable migraine days (3.55-4.23 absolute days and 0.7-1.38 placebo-adjusted days).[25] The results were similar to those reported from EM preventive trials using CGRP MAbs (see below). The most common AEs were nausea, fatigue, nasopharyngitis, constipation, and urinary tract infection. The liver safety profile was similar to placebo. Rimegepant is currently recruiting subjects with migraine frequency of 6-18 days per month (NCT03732638). One key advantage for choosing a gepant is its high safety profile rendering it an effective alternative especially for those who cannot tolerate other available preventive medications. At the moment, there is no study on gepant usage for managing CH.

CGRP MAbs have Similar Efficacies in Preventing Migraine in Episodic Migraine Subjects.—As shown in Table 1 and Figure 1(a,b), these phase 3 trials showed monthly migraine day (MMD) reduction of 1.8-4.7 absolute days and 0.7-1.9 placebo-adjusted days.[26-31] The clinical trial completion rates were high (80-95%). This MMD reduction is in line with those from topiramate, which reported MMD reduction of 2.1-2.2 absolute days and 1.3-1.4 placebo-adjusted days.[32] The days of acute medication use were reduced to 0.5-3 placebo-adjusted days. 10.2-23.7% more subjects in the treatment than placebo groups achieved ≥50% reduction in MMD. The subcutaneous-administered CGRP MAb onset of action was observed within the first week while IV MAb formulation may work even after the first day.[26,33] The clinical therapeutic effect seems to persist over 6 months and even up to a year (open-label extension data) with a MMD change of 4.2-5.3 absolute days.[31,34-36] A portion of the initial poor responders in the double-blind studies of fremanezumab and galcanezumab later became responders in the open-label study.[37,38] In short, CGRP MAbs work in preventing EM, even in some of the initial non-responders.

CGRP MAbs have Similar Efficacies in Preventing Migraine in Chronic Migraine Subjects.—As shown in Table 2 and Figure 1(c,d), these studies exhibit similar outcomes with MMD reduction of 4.6-8.2 absolute days and 1.7-2.8 placebo-adjusted days.[39-42] This MMD reduction is in line with those from onabotulinumtoxinA PREEMPT studies,[43,44] which reported MMD change of 7.6-8.7 absolute days and 1.5-2.4 placebo-adjusted days. These MAb trials showed a ≥50% responder rate of 27-61% (placebo-adjusted response 12-23%). *Post hoc* subgroups analyses revealed that CM subjects with medication overuse (MO) still responded to erenumab (MMD change of 6.6 days in 140 and 70 mg groups, and 3.5 days in placebo group over 12 weeks) and fremanezumab (55% of 675 mg quarterly-, 61% of 225 mg monthly-, 46% placebo-treated subjects reported no MO during the 12 weeks).[45,46] In contrast to onabotulinumtoxinA in PREEMPT studies, acute medication use was reduced 3.5-4.2 days (placebo 1.6-1.9 days) after 12 weeks and 5.2-6.7 days during the open-label extension period.[45,47-51] It is possible that CGRP MAbs alleviate medication overuse headache (MOH). CM subjects receiving eptinezumab, an intravenous formulation, showed a treatment response on day 1 post-infusion; the reduction of migraine was 50.3% (100 mg), 51.6% (300 mg), and 27.1% (placebo).[52] In the fremanezumab study, an early therapeutic effect was seen at the end of the first week.[53] An intravenous formulation has a quicker onset than that of a subcutaneous formulation. In addition, at the end of 12-weeks, 32-35% (placebo 23%) of fremanezumab-treated subjects and 52-56% (placebo 38%) of erenumab-treated subjects were converted from chronic to episodic migraine.[54,55] Erenumab-treated subjects demonstrated a MMD reduction of 10.5 days (140 mg) and 8.5 days (70 mg)

Table 1.—CGRP MAbs Phase 3 Trials for EM Prophylaxis

Name	Key Inclusion Exclusion Criteria	Dosing	Mean MMD Change (days)	≥50% MMD Change Rate (%)	Adverse Effects
Eptinezumab[26]	Ages 18-75, ≥4 MD/month, <15 HD/month, onset	300 mg/Q	−4.3	56.3	Nasopharyngitis, URI,
PROMISE-1	<50 y/o. Exclude Botox use in 4 months	100 mg/Q	−3.9	49.8	nausea, dizziness, UTI,
NCT02559895		30 mg/Q	−4.0†	50.2	arthralgia
		Placebo	−3.2	37.4	
Erenumab[27]	Ages 18-65, 4-14 MD/month, <15 HD/month,	140 mg/M (N = 318)	−3.7	50.0	Nasopharyngitis, URI,
STRIVE‡	onset <50 y/o. Exclude Botox in 4 months,	70 mg/M (N = 312)	−3.2	43.3	injection site pain,
NCT02456740	failed >2 preventive categories, allows 1 stable preventive	Placebo (N = 316)	−1.8	26.6	arthralgia, fatigue, nausea, constipation, UTI
Erenumab[28]	Ages 18-65, 4-14 MD/month, <15 HD/month,	70 mg/M (N = 286)	−2.9	39.7	Nasopharyngitis, URI,
ARISE	onset <50 y/o. Exclude Botox in 4 months,	Placebo (N = 291)	−1.8	29.5	injection site pain,
NCT02483585	failed >2 preventive categories, allows 1 stable preventive				influenza, fatigue, nausea, constipation
Erenumab[57]	Ages 18-65, 4-14 MD/month major comorbidity,	140 mg/M (N = 121)	−1.8	30.3	Nasopharyngitis, injection
LIBERTY	onset <50 y/o, failed 2-4 preventives. Exclude	Placebo (N = 125)	−0.2	13.7	site pain, back pain,
NCT03096834	chronic pain, major comorbidities				dizziness, fatigue
Fremanezumab[29]	Ages 18-70, ≥4MD/month, 6-14 HD/month,	675 mg/Q (N = 291)	−3.4	44.4	Injection site reaction,
HALO	onset <50 y/o. Exclude Botox use in 4 months.	225 mg/M (N = 290)	−3.7	47.7	nausea, sinusitis,
NCT02629861	Exclude failure of ≥2 classes of preventives, ≥4 days opioid or barbiturates, Botox in 4 months	Placebo (N = 294)	−2.2	27.9	dizziness, URI
Galcanezumab[30]	Ages 18-65, 4-14 migraine or probable migraine	240 mg/M (N = 208)	−4.6	60.9	Injection site pain, naso-
EVOLVE-1‡	days/month, onset <50 y/o. Exclude fail-	120 mg/M (N = 210)	−4.7	62.3	pharyngitis, URI
NCT02614183	ure ≥3 preventive classes, ≥2 days opioid or barbiturate	Placebo (N = 425)	−2.8	38.6	
Galcanezumab[31]	Ages 18-65, 4-14 migraine or probable migraine	240 mg/M (N = 223)	−4.2	56.5	Injection site pain,
EVOLVE-2‡	days/month, onset <50 y/o. Exclude fail-	120 mg/M (N = 231)	−4.3	59.3	nasopharyngitis, URI
NCT02614196	ure ≥3 preventive classes, ≥2 days opioid or barbiturate	Placebo (N = 461)	−2.3	36	

†Not statistically significant.
‡6 months double-blind phase.
HD = headache days; MD = migraine days; MMD = monthly migraine days; URI = upper respiratory tract infection; UTI = urinary tract infection.

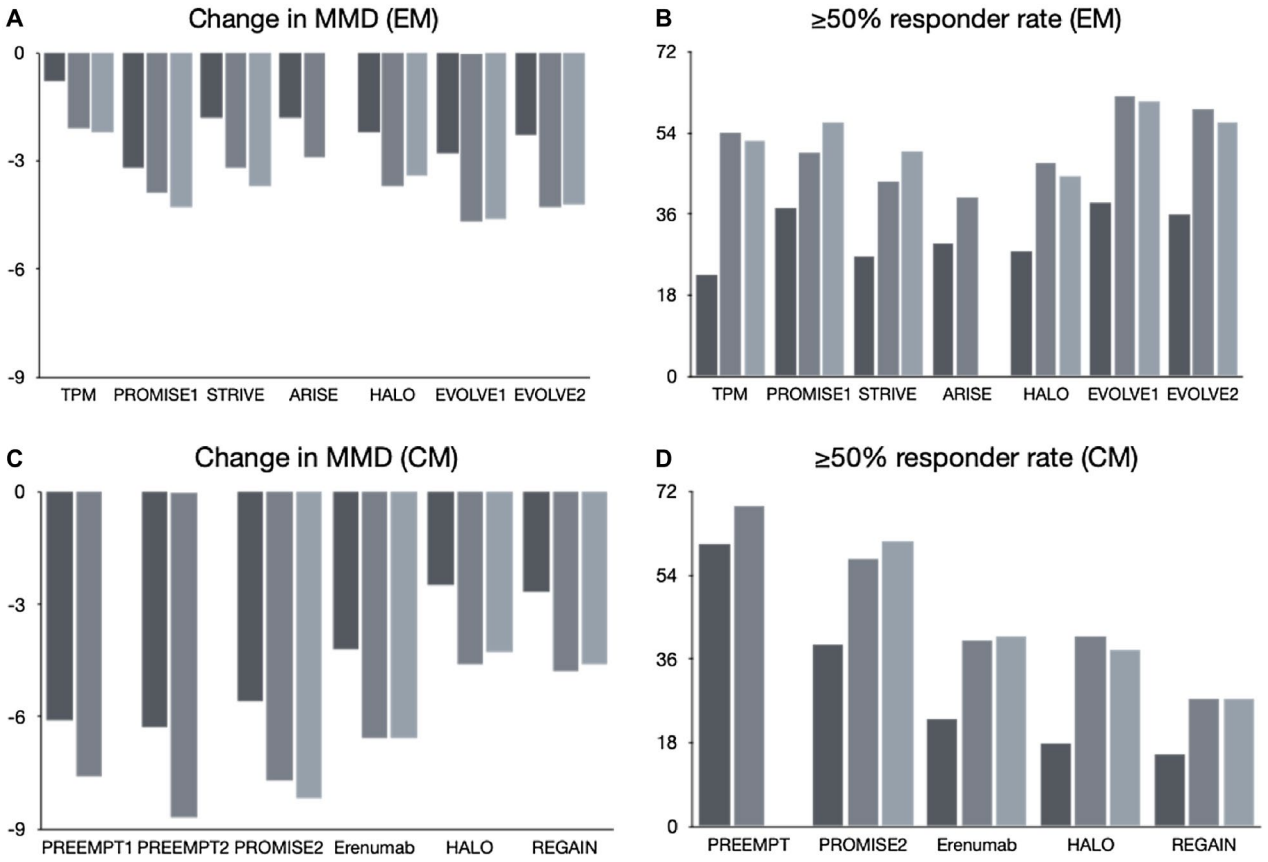

Fig. 1.—Comparison of CGRP MAbs trials for migraine prevention. The change in monthly migraine days (MMD) and ≥50% responder rate (%) on EM and CM subjects after 3 months of treatment (6 months for PREEMPT1/2, TPM, STRIVE, EVOLVE1/2). All presented trials are phase 3 study except Erenumab CM study being a phase 2 studies. Black bar: placebo, dark grey bar: regimen 1, light grey bar: regimen 2. [Color figure can be viewed at wileyonlinelibrary.com]

that continued after the open-label extension of 52 weeks without tachyphylaxis.[51] A similar response was also observed in fremanezumab-treated subjects after 6 months with MMD change of 6.5 days (675 mg quarterly) and 7.6 days (225 mg monthly).[56] CGRP MAbs likely work for both CM and MOH. It also reduces acute medication use days; which was not significant in PREEMPT trials. Overall, the effect seems comparable to onabotulinumtoxinA and can continue for months.

CGRP MAbs are Effective in Migraine Subjects who Failed Preventives.—In EM subjects who failed 2-4 preventives, erenumab decreased MMD by 1.6 days (placebo adjusted), acute medication use by 1.8 days (placebo adjusted), and had a low placebo response rate (0.2 days).[57] Significantly more erenumab, than placebo-treated subjects, achieved ≥50% reduction in MMD (30% vs 14%). In CM subjects who failed 0 vs >1 preventive (n = 214 vs 327) erenumab achieved a change in MMD of 6.1 vs 7.0 (140 mg), 7.9 vs 5.4 (70 mg) and 5.7 vs 2.7 (placebo) days.[58] A higher erenumab dosage seemed to work better in CM subjects who have failed previous preventives. In EM subjects who failed ≥1 preventive, fremanezumab significantly reduced MMD in those taking 225 mg monthly (−2.3 placebo-adjusted days) and 675 mg quarterly (−2.0 placebo-adjusted days) dosage groups.[59] Fremanezumab demonstrated efficacy in CM patients who previously used onabotulinumtoxinA (MMD change of 4.0 for quarterly, 4.5 for monthly, 2.3 for placebo).[60] In CM subjects who failed ≤1 vs >1 preventive, galcanezumab showed a change in MMD of 8.1 vs 2.8 (240 mg), 5.2 vs 5.4 (120 mg), and

Table 2.—CGRP MAbs Phase 3 Trials for CM Prophylaxis

Name	Key Inclusion Exclusion Criteria	Dosing	Mean MMD Change	≥50% MMD Change Rate (%)	Adverse Effects
Eptinezumab[39] PROMISE 2 NCT02974153	CM by ICHD3β, 18-65 y/o. Exclude >26 headache days, Botox within 4 months, barbiturate or opioid >4 days/month, device use	100 mg/Q (N = 356) 300 mg/Q (N = 350) Placebo (N = 366)	−7.7 −8.2 −5.6	57.6 61.4 39.3	URI, sinusitis, nasopharyngitis, UTI, fatigue, back pain, arthralgia, nausea, dizziness, anxiety
Erenumab[40] NCT02066415†	CM by ICHD3β, 18-65 y/o. Exclude continuous headache, Botox within 4 months, on preventive, failed >3 preventive categories, opioid >12 days/3month, barbiturate >6 days/3months, device use	70 mg/M (N = 191) 140 mg/M (N = 190) Placebo (N = 286)	−6.6 −6.6 −4.2	40 41 23	Injection site pain, URI, nausea, nasopharyngitis, constipation, muscle spasms
Fremanezumab[41] HALO NCT02621931	CM by ICHD3β, 18-70 y/o. Exclude any preventive use (70%), >1 preventive use (30%). failed >1 preventive category, Botox within 4 months, <4 headache free days, opioid or barbiturate >4 days/month, device use	675,225 × 2 mg/M (N = 379) 675 mg/Q (N = 376) Placebo (N = 375)	−4.6 −4.3 −2.5	41 38 18	Injection site reaction, nasopharyngitis, nausea, sinusitis, dizziness, URI
Galcanezumab[42] REGAIN NCT02614261	CM by ICHD3β, 18-65 y/o. Exclude <1 headache free day, Botox <4 months, on >1 preventive other than topiramate or propranolol	120 mg/M (N = 278) 240 mg/M (N = 277) Placebo (N = 558)	−4.8 −4.6 −2.7	27.6 27.5 15.4	Injection site reactions, URI, nasopharyngitis

†NCT02066415 is a phase 2 trial.
HD = headache days; MD = migraine days; MMD = monthly migraine days; URI = upper respiratory tract infection; UTI = urinary tract infection.

4.1 vs 1.0 (placebo) days.[50] In a subgroup analysis from EVOLVE-1, EVOLVE-2, and REGAIN studies on subjects who failed onabotulinumtoxinA, galcanezumab showed a change in MMD change of 5.3 (240 mg), 3.9 (120 mg), and 0.9 (placebo) days.[50] It is worth mentioning that migraine subjects who have failed preventives have a much lower placebo response than those who have not.[38,50,57] Based on the complimentary mechanism of action, it is certainly hopeful that CGRP functional blockade can elicit an additive and perhaps even a synergistic effect with current migraine preventives. Further study is required to investigate any therapeutic synergy. Practically, CGRP MAbs can still be introduced to patients who are already on multiple preventives, failed or not, with an additive effect.

CGRP MAbs are Effective for Preventing Episodic Cluster Headache.—The FDA recently approved galcanezumab for use in episodic CH prevention. In a phase 3 study on episodic CH (NCT02397473), galcanezumab (300 mg/month × 2 months) significantly reduced weekly CH attack frequency (the primary end point) of 8.7 vs 5.2 in placebo (P = .036; n = 106). At week 3, 76% galcanezumab-treated subjects vs 57% placebo-treated subjects (P = .04) achieved ≥50% reduction in weekly CH attack frequency. About 8% galcanezumab-treated subjects vs 21% placebo subjects discontinued treatment; 8 subjects in the placebo group and 1 subject in the treatment group discontinued due to lack of efficacy. Safety profiles were similar between galcanezumab-treated vs placebo groups except for slightly more injection site pain and nasopharyngitis reports in the MAb group.[61] Meanwhile, the episodic CH prevention study for fremanezumab (NCT02945046) was terminated early after a prespecified futility analysis during the 4-week treatment period. Fremanezumab was also found to be ineffective for reducing chronic CH frequency after 12 weeks; the trial (NCT02964338) was thus discontinued. No CH study was available for either erenumab or eptinezumab at the time of writing. It would be important to study whether CGRP MAbs can also reduce overall attack intensity.

CGRP Functional Blockade Demonstrates Good Safety Profiles in Clinical Trials but With Some Caveats.—A major consideration based on current data for using gepants and CGRP MAbs is their high safety profile. Particularly for CGRP MAbs, their high target specificity, low drug-MAb interaction, and monthly dosing schedule are the striking benefits when compared to current oral migraine preventives. The most common AEs reported in CGRP clinical trials were nasopharyngitis/URI (both MAbs and gepants) and injection site reaction (MAbs only). High safety profile and convenient dosing potentially improve drug adherence, hence better headache control. Previously there were concerns regarding prolonged CGRP blockade causing cardiovascular AEs. An ex vivo study of an isolated internal mammillary artery (excised from patients undergoing coronary artery bypass surgery) showed no interaction between erenumab and other vasodilatory molecules (eg, PACAP, acetylcholine, nitroprusside, nicardipine).[62] Erenumab displayed no hemodynamic effect during an exercise stress test in patients with coronary artery disease and stable angina.[63] No major cardiovascular AEs were observed in all trial populations and even in patients with stable angina (studied in erenumab).[63] In an open-label extension monitored over 3 years of erenumab use, there was no increase in cardiovascular events.[64] However, constipation was noted in the erenumab and atogepant trials. Since CGRP is associated with gastroprotection and gastric motility, prolonged CGRP receptor blockade may cause constipation by direct inhibition or down-regulation of CGRP receptors on gut smooth muscle. For CGRP receptor MAbs, in addition to blocking the CGRP receptor, free CGRP ligand may still act on AMY_1 receptor causing anorexia and satiety that may further worsen constipation. It is very likely prolonged CGRP receptor and ligand blockades exhibit different AE profiles. In addition, with CGRP being the key neuropeptide in tissue healing, hematopoiesis, and the neuro-immune axis, it is reasonable to speculate that prolonged CGRP blockade can impact certain restorative functions, unmask underlying autoimmunity, or perhaps even worsen active infection. Whether this explains the increased frequency of nasopharyngitis is unknown. Moreover, since 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 realistic AE profiles in susceptible populations remain to be answered by long-term open-label studies or post-marketing analyses.

Certain Additional Aspects Remain to be Determined

1. The role of anti-drug antibody (ADA) is still unknown. ADA is expected to form in some patients with chronic exposure to foreign biologics. In an erenumab study, there were 14 incidences of binding antibodies in the erenumab-treated groups (11 [6%] in the 70 mg group and 3 [2%] in the 140 mg group), and no neutralizing antibodies at any time.[40] In galcanezumab studies, ADA was detected but so far has no effect on galcanezumab's pharmacokinetics, efficacy, or safety.[62] However, these studies were relatively short in duration. ADA after years of MAb exposure may cause some neutralizing effect but this is yet to be determined.[65] It is still uncertain if CGRP MAbs sustain their efficacy after many more years.
2. It remains to be seen whether CGRP MAbs can work for individuals with daily headache, refractory CM who failed >4 preventives, or other headache disorders such as new daily persistent headache, hemicrania continua, post-traumatic headache, or other trigeminal autonomic cephalalgias.
3. It would be interesting to see if precision medicine by pharmacogenetic analysis can tailor the biologic therapeutic to an individual with migraine or CH. A biomarker that predicts the CGRP MAb responsiveness can be appealing.
4. CGRP plays a role in placental vascular adaptation and decidualization.[66] CGRP level is usually elevated during pregnancy. In animal studies, a CGRP antagonist increases fetal mortality in a dose-dependent fashion.[67] Since IgG can be actively transported through placenta and breast alveoli, it is plausible that CGRP MAbs may inadvertently harm the fetus and perhaps the infant. Since potential risk of fetal or infant exposure to CGRP is unknown, it is not recommended for women who are pregnant or breastfeeding. An extended washout time prior to conception and after breastfeeding may be recommended. Future establishment of a CGRP antagonist registry may help answer this question.
5. Insurance coverage and affordability remain an important issue for prescribing CGRP MAbs, even though they display greater safety profiles than many oral preventives as well as cost much less than many other biological therapeutics. The National Institute for Health and Care Excellence (England, UK) has not recommended erenumab even for refractory migraine (those who have failed 3 preventive treatments) due to high cost-effectiveness estimates.[68] We believe this is highly stigmatized thus would argue that the impact of headache and its associated disability is of no less importance than the impact of any other disorder. Since CGRP MAbs work even in those who failed multiple preventives, including onabotulinumtoxinA, there is no reason to withhold such medication when clinically indicated. However, insurance coverage and patient access to expensive medication is a complex issue, which is beyond the scope of this paper. Practically, a specialty pharmacy can be employed to reduce the financial and logistical burden to patients.

CONCLUSION

CGRP function-blocking therapy is a new class of medication for the first time ever developed specifically for the clinical indication of migraine and CH prevention. It exhibits a distinct mechanism from previous preventives, thus can also be used to augment the therapeutic effect when used in conjunction with other preventive medications. The key advantage is that it works not only for EM, CM, and episodic CH subjects but also for migraine subjects who previously failed multiple preventives or overused acute rescue medications. CGRP function-blocking therapy is highly tolerated and thus will likely improve drug compliance and headache control. However, keep in mind that it does not work for everyone as CGRP is not the only player in the pain pathways. Although MAbs long tissue-dwelling time allows for convenient monthly or quarterly dosing, this can be a safety concern in the event of a serious adverse reaction without a known antidote. A wonderful safety profile during the

clinical trial period does not guarantee a worry-free future. The long-term effects from prolonged blockade of CGRP's protective mechanisms in susceptible populations remain to be examined. These emerging CGRP function-blocking therapies overall are positively transforming the headache medicine field.

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