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OTHER PAIN (A KAYE AND N VADIVELU, SECTION EDITORS)

CGRP Antagonists for the Treatment of Chronic Migraines: a Comprehensive Review

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Abstract

Purpose of Review The purpose of the following review is to summarize the most recent understanding of migraine pathophysiology, as well as of basic and clinical science pharmacologic literature regarding the development of calcitonin gene receptor peptide (CGRP) antagonists as a novel therapeutic modality for the treatment of migraine headaches. A review is provided of erenumab, the first of its class FDA approved CGRP antagonist.

Recent Findings Despite its high prevalence, the occurrence and treatment of migraine headaches is poorly understood. Erenumab and CGRP antagonists as a whole significantly reduce the average number of migraine days experienced in migraine sufferers.

Summary CGRP antagonists appear to significantly improve treatment outcomes in patients who suffer from episodic and chronic migraines. Erenumab is the first CGRP antagonist to be FDA approved for public use; however, further development of biologics in this class is underway.

Keywords Chronic migraines · Episodic migraines · Calcitonin gene receptor peptide (CGRP) antagonist · Erenumab

Introduction

Migraine disorder is the most common form of chronic headache and is characterized by episodic, incapacitating headaches [1]. According to the International Headache Society, diagnostic criteria for migraine headache include duration of 4 to 72 h with at least two of the following characteristics: unilateral pain, pulsating quality, moderate pain, and pain aggravated by movement with at least one of associated nausea with or without vomiting, photophobia, and phonophobia [2]. The four phases of migraine include premonitory, aura, headache, and postdrome. The prodromal phase may occur up to 48 h prior to headache onset and may include yawning, mood changes, food cravings, neck stiffness, or constipation [3]. Migraines may occur with or without an aura, which manifest as sensory or motor disturbances [4]. The postdrome period may persist for up to 24 h and consists of lethargy, difficulty concentrating, stiffness, and pain aggravated by movement in the distribution of the original headache [5].

Current understanding suggests that the pathophysiology of a migraine is triggered by cortical spreading depression. It has been suggested that this phenomenon is responsible for the visual aura, activation of matrix metalloproteinases causing increased blood-brain barrier permeability, and activation of trigeminal nerve afferents [6, 7]. These neurons act to supply sensory innervation to large vessels within the cerebrovascular system and meninges. The development of migraine headache is thought to occur as a result of cascading events; pannexin-1 megachannels open, which activate caspase-1 and

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lead to release of pro-inflammatory agents subsequently causing astrocytic activation of nuclear factor kappa-B and ultimately transduction of the inflammatory response down sensory trigeminal nerves that innerviate pial vasculature [8].

Migraines have been found to impact approximately 12% of the US general population, more commonly affecting women, 18.2%, compared to 6.5% in men [9]. Peak occurrence is in the 30- to 39-year-old age group, in which, 24% of women are affected and 7% of men are affected [10]. The lifetime prevalence of migraine for women is 43% and 18% for men [11]. There is some evidence for familial association with migraine incidence; however, this phenomenon is not yet completely understood [3]. Accepted migraine triggers include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, and wine [12]. Other suggested triggers include sleep disturbances, aspartame, smoke, heat, exercise, and sexual activity [13].

Traditional prophylactic treatment of migraines includes tricyclic antidepressants such as amitriptyline, beta blockers, calcium channel blockers, or anticonvulsants such as topiramate [14]. These medications all produce approximately 50% frequency reduction but require dosages with considerable frequency of intolerable side effects [15]. Acute migraine treatment includes NSAIDs and acetaminophen for mild symptoms, while triptans, antiemetics, and ergots are reserved for severe cases [16].

CGRP and Receptor

Calcitonin gene receptor peptide (GCRP) is a 37-amino acid neuropeptide containing both a N-terminal disulfide bond and an amidated C-terminus. Both moieties are necessary for receptor-substrate interaction [4]. CGRP's larger family of peptides includes alpha and beta forms of CGRP, amylin, adrenomedullin 1 and 2, and calcitonin, across which there is a conserved alpha-helical structure between amino acids 8 and 18 [17]. Some experts advocate for the inclusion of procalcitonin in this family as it has partial agonist activity at the CGRP receptor [18]. The alpha form of CGRP predominates in the trigeminal ganglia [19].

The CGRP receptor is a G protein coupled receptor with three components: calcitonin-like receptor, receptor activity-modifying protein 1, and receptor component protein [20]. Calcitonin-like receptor is a seven-transmembrane receptor. Receptor activity-modifying protein 1 is required for both the trafficking of calcitonin-like receptor to the plasma membrane and the coupling of calcitonin-like receptor with CGRP. Receptor component protein is involved in receptor and G protein association [21].

The binding of CGRP to its receptor requires both the association of CGRP's C-terminal residues to a structure comprised of the N-terminus of calcitonin-like receptor and receptor activity-modifying protein 1 and subsequent binding of CGRP's N-terminus residues to the juxtamembrane domain of calcitonin-like receptor [22]. CGRP has also been shown to associate with amylin receptor 1, which consists of the calcitonin receptor protein associated with receptor activity-modifying protein 1 [23]. The cascade following receptor-substrate binding is classically initiated when the G protein associated with the complex activates adenylate cyclase leading to a cAMP-dependent signaling pathway. The result is gene expression alterations affecting plasma membrane receptor and ion channel activity [24]. Both the CGRP receptor and amylin receptor 1 are expressed within the trigeminal ganglia [25].

The trigeminal system is critical to controlling cranial vasculature tone and in transmitting cranial sensory information [23]. The components of the trigeminovascular system include the trigeminal nerve, cranial vasculature, and the spinal trigeminal ganglion. It is well documented that neurons of the trigeminal system express CGRP, and more recent histological studies have shown expression of both the components of CGRP receptor and amylin receptor 1 in intracranial vascular tissues [26]. The action of CGRP in cranial vasculature leads to vasodilation of cranial arterioles but not venous sinuses. This allows CGRP to act in the maintenance of cerebrovascular resting tone [23]. Physiologically, it is proposed that CGRP induces vasodilation in response to cerebrovascular vasoconstriction [27]. CGRP's potential role in migraine was first suspected when it was shown that during migraine, levels of CGRP are increased in cranial, but not peripheral, circulation [28]. This suspicion was elevated following studies demonstrating that CGRP levels in cranial circulation can be elevated by trigeminal stimulation and decreased using traditional migraine treatments [29]. Additionally, it has been demonstrated that injection of CGRP can induce symptoms of migraine [30].

CGRP is implicated in causing migraine via cerebral vessel vasodilation, neurogenic inflammation, and nervous system sensitization. The vasodilatory effects of CGRP are mediated through the aforementioned adenylate cyclase pathway in contrast to a nitric oxide- or endothelium-driven pathway. Neurogenic inflammation in migraine is driven by vasodilation, plasma extravasation, and inflammatory agent release [4]. CGRP is indirectly involved in plasma extravasation. The process of plasma extravasation is stimulated by neurokinin A and substance P which are both co-released with CGRP and have their release activated by CGRP [21]. The role of CGRP in the release of inflammatory agents is dependent on interaction with receptors on mast and glial cells [31]. CGRP acts as a neuromodulator to produce central nervous sensitization. This occurs via enhancement of presynaptic release of CGRP and glutamate as well as by an increase of postsynaptic neuron excitability via cAMP cascade-dependent receptor phosphorylation. The result is enhanced

central perception of painful stimuli [32]. CGRP causes peripheral nervous sensitization via increase of $P2X_3$ and brain-derived neurotrophic factor gene expression. Both genes produce factors that enhance the activity of nociceptive sensory transmission in trigeminal afferent nerves, leading to increased pain sensation [33, 34].

A Brief History of CGRP Receptor Antagonists for the Treatment of Migraines

The first hypothesis regarding the participation of CGRP in the pathophysiology of migraines was established in 1985 [35]. In years since, serotonin receptor antagonizing triptans have been used to treat migraines due to their ability to decrease the release of CGRP. A definitive link was subsequently observed as increasing levels of CGRP in saliva were shown to be elevated during the course of an acute migraine [36]. Moreover, CGRP levels have been found to increase in jugular venous blood during migraine attacks and remain elevated throughout refractory periods in the peripheral blood of patients who suffer from episodic and chronic migraine. The role of CGRP in the pathogenesis of this primary headache disorder has been upheld by phase 2 and 3 trials of both small molecule CGRP receptor antagonists and those of monoclonal antibodies specifically targeting the CGRP pathway [37••]. As a class, triptans provide symptom relief in about 60% of cases. However, in addition to their inconsistent efficacy, a major contraindication of this class of drugs is cardiovascular disease, justifying the need for further research [38].

Gepants were created as a class of direct CGRP receptor antagonists that were directed primarily at the trigeminal system. Despite a relatively small molecular size, penetration of the blood-brain barrier is minimal, with an observed CSF/plasma ratio of approximately 1.5% and as such minimal activity within the CNS. This was demonstrated via findings of a study that implemented PET scan to evaluate CGRP activity. Despite administration of supraclinical doses of telcagepant, no additional efficacy was observed, suggesting a mechanism of action that does not depend on BBB penetration [39]. The utility of gepants is most likely in the trigeminal ganglion given a preponderance of CGRP within smooth muscle and satellite glial and moreover an absence within the dura mater and middle meningeal artery [38]. Unfortunately, gepants as a class were discontinued from further development before ever achieving approval for clinical use due to hepatotoxicity with prolonged exposure [38, 40].

The latest development in antimigraine therapy has come in the form of CGRP and CGRP receptor biologics. This class of drug is too large to diffuse through the BBB and thus function within peripheral tissue. The mechanism of action of these humanized monoclonal antibodies relies on the prevention of trigeminal nociceptive signaling via direct antagonism of CGRP receptor binding sites. Due to a low membrane permeability and poor bioavailability, these compounds must be administered parenterally [40]. Although there is variation among experimental drugs, the half-lives of CGRP and CGRP receptor biologic in general are significantly longer than those of gepants, weeks to months compared to hours, respectively [4]. As a result, extended half-lives tend to improve patient compliance and better protect against the development of migraines. While individual drugs in development of the CGRP antagonist class vary slightly, their shared mechanism of action functions via selective inactivation of the α- and β-CGRP receptors to provide relief in acute migraine settings as well as offer prophylactic protection [40].

Erenumab (AMG 334): the First of Its Class

Erenumab (AMG 334) is a fully human monoclonal antibody (mAb) that selectively binds to the canonical CGRP receptor and functions as a competitive, reversible inhibitor [37••, 41, 42]. The drug is the first human mAb to target the CGRP receptor rather than the CGRP ligand itself [43]. Binding of the drug to its receptor has been characterized as high affinity, with a dissociation equilibrium constant (K_D) of 20 pM, 20-fold greater than Merck's CGRP receptor antagonist, telcagepant. Its potency is comparable to telcagepant and indicative of complete inhibition of the production of cAMP that is stimulated by CGRP binding to its receptor [42, 44]. Further, the drug shows species, human and cynomologus monkey, specificity [44]. In humans, the selectivity of erenumab to the CGRP receptor is 5000-fold greater than to any other human calcitonin family receptor including calcitonin, adrenomedullin, and amylin [37••, 44]. Notably, like all other mAbs and unlike small molecules, the drug is not eliminated via hepatic, biliary, or renal routes and thus raises few hepatotoxicity and drug interaction concerns [44].

Pharmacokinetics and Pharmacodynamics

The capsaicin-induced dermal blood flow model (CIDBF) is a validated, non-invasive method used to assess target engagement of CGRP-blocking therapeutics during early clinical development. As previously discussed, CGRP is a neuropeptide that serves as a mediator of migraine onset and progression, via vasodilation. Studies have shown that neutralizing endogenous CGRP or blocking its receptor may provide therapeutic benefit to patients who suffer from migraines. The CIDBF model relies on the ability of capsaicin, when applied topically to human forearm skin, to activate the transient receptor potential vanilloid type I (TRPV1) receptor on nociceptive nerve endings and to induce local release of CGRP. In the model, the increases in dermal blood flow (DBF) that are associated with

the release of CGRP are measured in order to evaluate the efficacy of CGRP-blocking compounds [42].

The CIDBF model in combination with a population pharmacokinetic-pharmacodynamics (PK-PD) analysis was used to characterize the relationship between erenumab serum concentration and CIDBF inhibition [42]. Prior studies demonstrated that erenumab inhibits CIDBF in both healthy and migraine subjects, supporting the characterization of the drug as a CGRP receptor antagonist [43]. More recently, erenumab was evaluated through repeated capsaicin challenges and DBF measurements conducted in both single-ascending dose (SAD) and multiple-ascending dose (MAD) studies. Of the total 108 subjects from whom data were pooled, 80 (74%) were healthy and 28 (26%) were migraine patients. It is notable that despite the total subject pool being 78% male, all migraine patients were female, so assessment of the sex covariate was equivalent to that of the population. Serum erenumab concentrations were used for population PK analysis while DBF measurements were used for PK-PD analysis [42].

A two-compartment target-mediated drug disposition (TMDD) model assuming binding of erenumab in the central compartment was shown to best characterize the nonlinear PK of the drug, successfully explaining the dose-concentration-dependent elimination of erenumab. Subcutaneous absorption half-life was 1.6 days, bioavailability was 74% (95% CI 66–85%), and maximum inhibition reached 89% (95% CI 87–91%). As expected, the model showed that erenumab serum concentration time courses were similar between healthy subjects and migraine patients. In the PD analysis, an inhibitory E_{max} model was used to characterize the effect of erenumab on the DBF time course. The PD model verified the assumption that DBF before capsaicin challenge does not change relative to the increase of erenumab concentration, indicating that the drug attenuates the action of CGRP in the periphery. Increased body weight was associated with increased clearance but did not affect the inhibitory capacity of erenumab on CIDBF. The PK-DBF relationship was used to determine that 21 mg subcutaneously (SQ), every 4 weeks (q4w), placed more than 50% of subjects at serum concentrations above IC_{99} after the second dose, suggesting this to be the minimum migraine efficacious dose. An administered dose of 70 mg SQ q4w placed subjects above the mean IC_{99} within the first dose with 100% maximum DBF inhibition, thus suggesting improved protection against migraine. Compared to other mAbs that target the CGRP ligand, erenumab requires a lower concentration to achieve and to maintain maximum CIDBF inhibition. Furthermore, the magnitude of maximum inhibition exceeds that of other compounds [42].

These results suggest that erenumab is similar to other mAb therapeutics with nonlinear PK in exhibiting TMDD that can be described by two parallel antibody elimination pathways. One of these pathways is a slow, non-specific elimination through the hepatic reticuloendothelial system, denoted linear clearance. Linear clearance is independent of drug concentration and is similar to the clearance of endogenous IgG [42]. Specifically, at doses of 70 mg and above, erenumab behaves as a typical human IgG2 mAb, characterized by linear PK and a long elimination half-life [43]. The second pathway is a rapid, saturable elimination pathway with nonlinear clearance, mediated by degradation or internalization of erenumab-receptor complex. Nonlinear clearance is dependent not only on erenumab concentration but also on target receptor density; however, neither the density nor the quantity of CGRP receptors in humans is known, so the PK parameters related to target-mediated elimination are data driven. From the data, it is expected that dose regimens equal to or greater than 70 mg SQ q4w would produce erenumab concentrations that saturate the nonlinear elimination pathway at steady state. When these dosing regimens were put into practice in a dose-ranging study for patients diagnosed with episodic migraines, the 70-mg SQ q4w dose was the minimum dose to demonstrate a separation from placebo, suggesting that larger doses than those that produce maximal peripheral CGRP receptor inhibition are necessary for clinical treatment of migraine [42].

ARISE Trial

The ARISE trial was a randomized, double-blind, placebo-controlled 12-week phase 3 trial that included 577 adults, which was conducted as an efficacy and safety analysis of 70 mg erenumab versus placebo. A dose of 70 mg was chosen based on the results of a phase 2 dose-ranging study that established this to be the minimally effective dose of erenumab. The study took place at 69 sites in eight countries across North America and Europe and included diverse population of adult subjects aged 18 to 64 years old who suffered from episodic migrations. Episodic migraines were defined as occurring at least 4 and fewer than 15 times per month and moreover fewer than 15 headache days per month with or without aura for at least 12 months prior to the start of the trial [45••].

The study determined that erenumab treatment resulted in reduced migraine frequency (quantified as MMD), reduced use of acute migraine abortive medications such as serotonin $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptor agonists (quantified as migraine-specific medication treatment days, MSMD), and decreased disability and headache impact [37••, 45••]. After 3 months of being treated with 70 mg erenumab monthly, patients treated with erenumab had significantly greater odds of achieving at least a 50% reduction in MMD compared to those treated with placebo. Further, reductions in MMD and MSMD became apparent after just 1 month of treatment and were maintained throughout the 12-week trial. The decrease in MSMD was 0.6 days at month 3 for all patients in the study and 0.92 days

for patients who had used acute migraine-specific mediations at baseline [45••].

The ARISE trial also aimed to consider the patient perceptive of treatment with erenumab by measuring patient-reported assessments of migraine impact. Patient-reported outcomes were evaluating using the following standard PRO instruments: Headache Impact Test (HIT-6), modified monthly Migraine Disability Assessment Test (MIDAS), and Migraine-Specific Quality-of-Life Questionnaire (MSQ). These tools indicated that the documented reductions in MMD were accompanied by reductions in patient-reported outcomes, with differences in MSQ-RFR and HIT-6 total score exceeding the group-level minimally important difference (MID). These results suggest that the benefit of erenumab compared to placebo was perceived by patients and made a positive effect on headache impact. The study also implemented the Migraine Physical Function Impact Diary (MPFID), a novel migraine-specific instrument used to evaluate the effects of migraine on physical function in daily life. The MPFID functions as an electronic diary of patient-reported outcomes and determines an average score for each patient each month. Although further work is necessary to determine a MID for change in MPFID domain scores, the ARISE trial assessed continuous scores and found that mean between-group changes in MPFID scores were statistically significant [45••].

An evaluation of adverse effects noted that the double-blind treatment phase completion rate of 95% was considerably greater than that observed for other preventative migraine treatments. Upon further analysis, it was seen that erenumab treatment did not have an apparent effect on liver enzymes, which was in line with the non-hepatic metabolism of mAbs though contrasted the hepatotoxicity observed with other small molecule CGRP receptor antagonists. This result suggests that the hepatoxicity associated with CGRP receptor agonists is due to off-target effects rather than as a result of CGRP receptor inhibition. Only 4.3% of subjects exposed to erenumab were found to have innate binding antibodies, and only one subject (0.4%) was transiently positive for neutralizing antibodies ultimately testing negative at the end of the 12-week trial. Similar to what was previously observed, the ARISE trial demonstrated no associated cardiovascular adverse effects with erenumab use [45••].

Efficacy and Safety

One of the theoretical concerns related to erenumab is cardiovascular risk associated with inhibition of the CGRP pathway [43]. CGRP is one of many vasodilatory and cytoprotective mediators released by cardiac sensory nerves during ischemia [43, 46]. It has been shown that exogenously administered CGRP can exhibit protective vasodilatory effects by increasing total exercise time (TET) during an exercise treadmill test (ETT). It is important to note, however, that the concentrations of exogenous CGRP necessary to increase TET are far greater than those that are released endogenously during response to ischemia [46]. Regardless, due to the potential vasodilatory function of CGRP, it is plausible that blockade of the CGRP receptor may exacerbate ischemic events.

In an in vitro study of the effects of erenumab on isolated human coronary artery, the drug failed to induce vasoconstriction, even at its highest administered dose of 1 μM [46]. Similar results have been observed in phase 2 studies showing no increased incidence of cardiovascular events in individuals treated with erenumab compared to placebo [43]. A study specifically designed to assess potential adverse anti-vasodilatory effects of erenumab on high-risk patients with diagnosed cardiovascular disease found that a 140-mg IV dose of the drug did not have deleterious effects on ETT performance, a surrogate marker of tolerance to myocardial ischemia. Additionally, there was no significant difference in adverse effects observed in the treatment group through the 12-week safety follow-up compared to the placebo group [46]. When the potential role of CGRP as a vasodilator was investigated further, it was shown that concentrations of erenumab that effectively inhibit the capsaicin response are not associated with significant changes in blood pressure or other vital signs in both healthy subjects and patients with migraines. The same results were seen in measurements of blood pressure of healthy volunteers treated with both erenumab and sumatriptan [43, 47].

It has been shown that while erenumab inhibits capsaicin-induced increases in DBF, it does not affect basal DBF. This observation suggests that although CGRP is an endogenous vasodilator, it does not appear to be involved in the maintenance of basal peripheral vascular tone. In combination, these results suggest that CGRP receptor antagonists like erenumab may be free of cardiovascular side effects under resting conditions [42]. In addition to supporting the safety of erenumab in patients with cardiovascular abnormalities, these data point to the existence of a redundant vasodilatory mechanisms since erenumab blocks only the canonical CGRP receptor without acting on other receptors, including the amylin 1 receptor that is bound by the endogenous CGRP ligand [46].

Given that the estimated prevalence of migraine is 14.7% and the more than one billion people who suffer from the neurological disorder, it reasonable to infer that costs associated with the condition are high. Moreover, since approximately 70% of the total costs of migraine are linked to presenteeism, absenteeism, and disability and are therefore indirect, it is necessary to consider drugs that may be used to treat the condition from a societal perspective. A Markov health state transition model was used to estimate the incremental costs, quality-adjusted life-years (QALYs), and value-based price (VBP) range for erenumab. This evaluation compared erenumab to no preventative treatment in patients with

episodic and chronic migraines who had attempted and failed at least one preventative therapy. The model analyzed erenumab clinical trials and migraine studies in order to quantify therapeutic benefit of the drug based on estimated changes in monthly migraine days (MMD). It was determined that erenumab use resulted in incremental QALYs of 0.185 compared to supportive care and reduced costs due to decreased MMD of $8482 over 10 years. After 4–6 months of treatment, the mean number of MMD decreased significantly: starting from an average of 8.3 MMD at baseline, the erenumab group experienced reductions of 3.7 days while the placebo group saw reductions of only 1.8 days. A VBP approach was utilized instead of cost-effectiveness modeling because at the time of the study, erenumab was not approved for use and pricing was unknown, making direct cost analysis impossible. When VBP ranges were estimated for erenumab 140 mg were $14,238–$23,998 compared to supportive care with VBP of placebo estimated to be lower, at $7445–$13,809. Overall, these data were indicative of the ability of erenumab to reduce both direct and indirect cost related to migraine and to increase quality of life [41].

Amgen: Aimovig™

Aimovig (erenumab-aooe), developed by Amgen and Novartis, received its first global approval on May 17, 2018 in the USA for the preventative treatment of migraine in adults. The drug received a positive opinion on May 31, 2018 in the EU for the prophylaxis of migraines in adults who experience at least 4 MMD [48]. Erenumab represents the first recently developed drug specifically for migraine prevention since anticonvulsants, beta blockers, and calcium channel blockers have traditionally been the drugs of choice used for the prevention of migraine [37••, 49]. Many of these commonly used migraine-preventive therapies may not be entirely effective and/or have unacceptable side effects, often leading to poor patient adherence [37••]. Erenumab and other CGRP antagonists that are in queue for Food and Drug Administration (FDA) approval may help move migraine medication away from targeting vasodilation, which has repeatedly been shown not to be a significant factor in migraine pathology [49]. The Amgen patent for erenumab is valid until 2031 in the USA and until 2029 in the EU [48].

The recommended dose of erenumab is 70 mg injected subcutaneously once per month into the upper arm, abdomen, or thigh, with some patients qualifying for a 140-mg monthly dose. The drug is supplied in prefilled autoinjectors or syringes that are sold 1–2 per package, with each containing a single 70-mg dose. If a 140-mg dose is prescribed, patients must inject the contents of two autoinjectors or syringes one after the other [50]. It is notable that the needle shield within the cap of the prefilled autoinjector and the needle cap of the prefilled syringe contain dry natural rubber, which is derived from latex and may cause allergic reactions in sensitive individuals [51].

The FDA cited the results of three placebo-controlled clinical trials (one phase 2, two phase 3; Table 1) with a combined total of nearly 2200 participants [37••, 45••, 50, 52••]. Across these clinical trials, erenumab was associated with an average of 1–2 fewer MMD in patients with EM and an average of 2.5 fewer MMD in patients with CM [53]. Erenumab is expected to be particularly appealing to the 20% of migraine patients who do not respond to any existing medications [49].

The most common adverse effects associated with erenumab in clinical trial were injection-site reactions, constipation, and cramps/muscle spasms [48, 51]. Few (1.3%) patients treated with the drug in two phase 3 trials and one phase 2 trial chose to discontinue double-blind treatment citing adverse effects. At present, there is a US phase 1 study being conducted to assess the pharmacokinetics and safety of erenumab in the pediatric population [48]. Additionally, three other companies have CGRP products in phase 3 trials: Eli Lilly (galcanezumab), Teva (fremanezumab), and Alder (eptinezumab) [49] (Table 2).

The main foreseen shortcoming of erenumab is linked to cost. Amgen's list price for the drug is $6900 a year, or $575 a month for both the 70-mg and 140-mg dose, whereas drugs that have been traditionally used like beta blockers are available as inexpensive generics. It is expected that erenumab will be subject to prior authorization and step therapy. Since the current requirement for certain migraine prevention treatments (e.g., Botox) is that patients must fail at least one or two other medications, a similar policy is likely to be adopted for erenumab. Unfortunately, clinicians attest to the fact that it takes time to determine whether or not a patient is responding to a particular medication and side effects often deter patients from attempting multiple regimens. Additionally, QALY benchmarks calculated by the Institute for Clinical and Economic Review showed that while the upper bound of the benchmark for erenumab sits near $150,000 for patients with EM or CM and no other treatment options, the benchmark is staggeringly lower ($5000) for patients who may have other therapies available. For these reasons, it is expected that at least initially, erenumab will fill the role of a third-line therapy for patients with EM or CM [49].

Looking Forward: Drugs in Development

Eptinezumab (ALD403) is a synthetic, humanized α- and β-selective anti-CGRP IgG1 antibody that is used for patients who suffer from chronic migraines, or migraines at a frequency of more than 15 per month. Eptinezumab is unique because it is produced using yeast. The drug is currently in phase 3 trials, with phase 1 and phase 2 trials having been completed in the early 2010s and presented in 2015 showing a half-life of

Table 1 A summary of clinical trials accessing the safety and efficacy of erenumab for the treatment of episodic and chronic migraines

Trial	Indication	Dose	Primary endpoint	Secondary endpoint	Secondary endpoint	Frequent adverse effects	Antibodies
ARISE (NCT02483585) Phase 3 [45••]	Prevention of EM	70 mg SC Q4W ($n = 282$) Placebo ($n = 288$)	MMD 70 mg—2.9 days, placebo—1.8 $P < 0.001$	MSMD 70 mg—1.2 days, placebo—0.6 days $P = 0.002$	MPFID ≥ 5-point reduction rate Physical impairment score 70 mg: 33% Placebo: 27.1% (OR: 1.33, $P = 0.13$) Everyday activities score 70 mg: 40.4% Placebo: 35.8% (OR: 1.22, $P = 0.26$)	Upper respiratory tract infections, injection-site pain, influenza, fatigue, nausea, migraine, sinusitis, nasopharyngitis, constipation	Anti-erenumab binding: 12 Anti-erenumab neutralizing: 1[a]
STRIVE (NCT02456740) Phase 3 [37••]	Prevention of EM	70 mg SC Q4W ($n = 312$) 140 mg SC Q4W ($n = 318$), placebo ($n = 316$)	MMD 70 mg—3.2 days, 140 mg—3.7 days, placebo—1.8 $P < 0.001$[b]	MSMD 70 mg—1.1 days, 140 mg—1.6 days, placebo—0.2 days $P < 0.001$*	MPFID Physical impairment score 70 mg + 4.2 140 mg + 4.8 Placebo + 2.4 $P < 0.001$ Everyday activities score 70 mg + 5.5 140 mg + 5.9 Placebo + 3.3 $P < 0.001$	Nasopharyngitis, upper respiratory tract infections, injection-site pain, sinusitis, arthralgia, nausea, fatigue, back pain	Anti-erenumab: 35 (8.0% 70 mg, 3.2% 140 mg) Anti-erenumab neutralizing: 1 (70 mg)
NCT02066415 Phase 2 [52••]	Prevention of CM	70 mg SC Q4W ($n = 188$) 140 mg SC Q4W ($n = 187$) Placebo ($n = 281$)	MMD 70 mg—6.6, 140 mg—6.6, Placebo—4.2 $P < 0.0001$	MSMD 70 mg—3.5 140 mg—4.1 Placebo—1.6 $P < 0.0001$	Not measured	Injection-site pain, upper respiratory tract infection, nausea	Anti-erenumab binding 70 mg: 11 140 mg: 3 Anti-erenumab neutralizing 70 mg: 0 140 mg: 0

[a] One patient was transiently positive for neutralizing antibodies at week 4 but found negative at each subsequent visit

[b] For both erenumab doses

Table 2 A summary of CGRP antagonizing drugs in development

Drug name	Antibody	Current clinical phase	Indication	Half-life	Pharmaceutical company
Eptinezumab (ALD403) [54•]	IgG_1	Phase 3 trials: PROMISE studies	Chronic migraine	31 days	Alder Biopharmaceuticals
Fremanezumab (TEV-48125) [55•]	IgG_2	Phase 3 trials: HALO Program	Episodic migraine	40–53 days	Teva Pharmaceuticals
Galcanezumab (LY29517) [56•]	IgG_4	Phase 3 trials: EVOLVE studies REGAIN study	Episodic & chronic migraine; cluster headaches	28 days	Eli Lilly and Company

around 32 days and linear pharmacokinetics for dosages between 1 and 1000 mg. The double-blind, placebo-controlled trials demonstrated no increases in adverse effects, ECG, or lab changes between injection and placebo groups [57]. Beyond no apparent indication for safety concerns for the biologic injection, there was also preliminary data that showed that the injection could play a preventative role in patients with a high monthly frequency of migraine days [54•]. Multiple phase 3 trials are being prepared for full publication. The first trial, PROMISE I, had preliminary results showing statistically significant reductions in migraines across a 3-month time period while the second trial, PROMISE II, enrolled 1050 subjects with data expected by the end of CY2018 [58].

Fremanezumab (TEV-4815, LBR-101, RN-307) is another fully humanized IgG2 antibody that is undergoing regulatory review by the FDA. In comparison to eptinezumab, it is directed at patients who are suffer from episodic migraines—migraines that occur at a frequency of less than 15 times per month. During the phase 1 trials, the injection was first tested in primates to determine its effect on systolic and diastolic blood pressure as well as relevant ECG parameters. No statistically significant differences were found between a treatment and a placebo group [59]. The same study then tested the antibody with prolonged injections into adult females and found similar, negligible results between the placebo and treatment groups in heart rate, blood pressure, and relevant ECG parameters. The half-life of this drug was shown to range from 40 to 53 days during this human testing [60]. The individual studies were combined and a more comprehensive review was published restating key findings from both studies and setting the stage for phase II trials [61]. During the phase II trials, 297 eligible patients tested different dosages (225, 675, 900 mg) against a placebo to determine ideal efficacy, which was graded based on both 50, 75, and 100% response rates and sustained response rates. In the cases of both 50 and 75% acute reduction in migraines, there were statistically significant differences in the placebo versus treatment groups. On the contrary, the 100% reduction was small in all groups and fell within the margin of error. Further, the sustained response rates were disappointing with 24 to 33% of patients on fremanezumab seeing a 50% reduction in migraine frequency and 18% of placebo patients seeing the same reduction. Notably, a low, insignificant number of patients in both treatment and placebo groups saw sustained reduction of 75 to 100% [55•]. Lastly, the phase III trial randomized 1130 patients in the HALO program on a quarterly, monthly, or placebo dosing schedule and saw somewhat better results with 38 to 41% of patients receiving fremanezumab treatments seeing a 50% reduction in average headaches per month versus 18% in the placebo group. The trial group noted that long-term durability and safety still needed to be completed and submitted their findings to the FDA for approval while continuing phase III and IV trials [62].

Galcanezumab (LY2951742) is another fully humanized CGRP antibody also for which phase 3 trials have also been completed. It is currently undergoing regulatory review for its indications for both episodic and chronic migraine. Results from these trials were presented at the 2017 American Headache Society conference [58]. The original phase 1 safety trials showed the injection to be well tolerated in single doses between 1 and 600 mg and consecutive doses of 150 mg with a half-life of 28 days. Further, no safety concerns were noted and no adverse cardiovascular effects were reported [63]. The phase 2 trials considered 218 subjects randomized from 2012 to 2013 across 35 separate American locations. These trials demonstrated a 75% response rate in 49% of treated subjects versus 27% of placebo subjects, lacking any difference in adverse effects [57]. Moving toward phase 3 data, the EVOLVE-1 and EVOLVE-2 trials looked at a large global sample size of patients with episodic migraines over the course of 6 months in 120-mg, 240-mg, and placebo dosages administered once a month. A 50% reduction was seen in 61% of the treatment patients as opposed to a 38% in the placebo group with further significant differences in the 75 and 100% reduction rates as well [56•]. The REGAIN study used a similar design over a 3-month period in a domestic setting to look at chronic migraine as opposed to episodic migraine and found similar positive results [57].

Conclusions

Migraine disorder is a highly prevalent headache condition that is frequently debilitating and severely limiting of normal daily activity. As a result of a complex and poorly understood

mechanistic pathophysiology, clinical treatment options for patients suffering from both episodic and chronic migraines have been limited, often leading to refractory cases. Recent breakthroughs in our understanding of the role of CGRP in mediating migraine headaches has led to the development of a novel class of CGRP antagonist biologics that promise significant improvement over conventionally used pharmacotherapy. With the FDA approval of Aimovig™ for clinical use and further medications undergoing development, the future looks bright for patients suffering from migraine headaches.

Compliance with Ethical Standards

Conflict of Interest Ivan Urits, Mark R. Jones, Kyle Gress, Karina Charipova, Jacob Fiocchi, and Omar Viswanath declare no conflict of interest. Dr. Kaye is a speaker for Depomed, Inc. and Merck, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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