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CGRP antagonists for decreasing migraine frequency: New options, long overdue

ABSTRACT

The cornerstone of preventive migraine treatment has long been drugs developed for other diseases such as epilepsy, depression, and hypertension. But a new set of drugs is available for preventing migraine attacks: erenumab, galcanezumab, fremanezumab, and eptinezumab. These monoclonal antibodies target calcitonin gene-related peptide (CGRP) or its receptors, each a key molecule in the pathophysiology of migraine.

KEY POINTS

Migraine is common, affecting nearly 40 million people in the United States.

In clinical trials, CGRP antagonists have been superior to placebo and similar in efficacy to current prophylactic treatments in terms of reducing the frequency of headaches.

These agents have long half-lives, permitting monthly or even quarterly dosing, and favorable side effect profiles compared with currently available oral therapies. This may improve adherence.

The new drugs are an exciting new frontier in headache medicine that is long overdue. However, the approach to migraine management must remain a combination of finding effective treatment and implementing patient-specific lifestyle changes for the best possible outcome.

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THE CORNERSTONE OF PREVENTIVE migraine treatment has long been drugs intended for other diseases—epilepsy, depression, and hypertension. But in 2018, the US Food and Drug Administration (FDA) approved 3 new drugs—erenumab, galcanezumab, and fremanezumab—specifically for decreasing the frequency of migraine attacks. A fourth, eptinezumab, was approved February 22, 2020. These monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptors are the first preventive medications to target the pathophysiology of migraine.

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The new drugs represent an exciting new frontier in headache medicine that is long overdue. Although they don't seem to be more effective than current drugs, they have long half-lives, permitting monthly or even quarterly dosing, and fewer adverse effects, which may improve adherence. In addition, they carry no contraindications for patients with liver disease, kidney disease, stroke, or coronary artery disease. They also have no known significant drug-drug interactions. Their primary disadvantage is cost (about $700 per month), although insurance may pay for them, and the manufacturers have assistance programs (**Table 1**).

NEED FOR MORE OPTIONS

Headache disorders, treated as early as 1200 BCE by the ancient Egyptians, affect nearly half of the world's adult population.[1,2] In the United States alone, migraine affects nearly 40 million people and is one of the most common complaints ad-

TABLE 1

Current calcitonin gene-related peptide (CGRP) antagonists

Drug	Mechanism	Dosing and frequency[a]	Most common adverse effects[a]	Average wholesale price and Pharmaceutical Assistance Program[a]
Erenumab	CGRP receptor antagonist	Migraine: 70 or 140 mg subcutaneously, monthly	Injection site erythema or pain, 5%–6% Constipation, 3%	$690 per month (regardless of dose) If commercial insurance plan does not cover or requires prior authorization, patients are eligible for 12 doses over 24 months with a $5 copay card per month; maximum benefit $2,700 annually
Fremanezumab	CGRP ligand antagonist	Migraine: 225 mg monthly or 675 mg every 3 months subcutaneously	Injection site reaction, 45%	$690 per 225-mg syringe Patients with commercial insurance plan are eligible for 12 months of treatment with a $0 copay card; there is no annual maximum benefit; with electronic coupon, copay is $20
Galcanezumab	CGRP ligand antagonist	Migraine: 240 mg, then 120 mg per month subcutaneously Cluster headache: 300 mg at onset of cluster period, then monthly until end of cluster headache	Injection site reaction, 18%	$690 per 120-mg autoinjector If commercial insurance plan does not cover or requires prior authorization, patients are eligible for a $0 copay card; maximum coverage is $4,900 annually As of 2020, this benefit is available only after prior authorization is approved by insurance
Eptinezumab	CGRP ligand antagonist	100 mg/mL or 300 mg/mL via infusion every 90 days	Nausea, 1.6% Fatigue, 1.4%	$1,495 per infusion ($5,980 per year)

[a] Information from product package inserts and personal communication with Cleveland Clinic Adherence Specialty Pharmacy.

dressed by primary care physicians, emergency physicians, and neurologists. It is associated with decreased function in an otherwise healthy and productive demographic group[3–5] and is the leading cause of healthy life-years lost as a result of disability from ages 15 to 49.[6]

Drugs that have long been used in migraine prophylaxis[7] have many adverse effects and need to be taken daily, which can lead to nonadherence; more than 80% of patients stop taking them within 1 year.[8]

CGRP IS A KEY MOLECULE IN MIGRAINE

Migraine is a multifactorial disorder with complex interactions between multiple predisposing genetic and modulating nongenetic factors.[9]

The current understanding of migraine is that a wave of neuronal and glial depolarization activates meningeal nociceptors innervated by the trigeminovascular system. When these perivascular afferent fibers are activated, the signal travels through the trigeminal ganglion to neurons in the trigeminocervical complex, using CGRP as the prominent neurotransmitter. This leads to symptoms such as cutaneous allodynia, neck pain, photophobia, phonophobia, and osmophobia. Once this signal reaches the visual cortex, it alters visual perception, resulting in double vision, change in color saturation, and blurred vision.[9]

The discovery that using a peripherally active biologic, onabotulinumtoxinA, could be effective in migraine prophylaxis led to further investigation of the mechanism of action.[10] It

is now understood that onabotulinumtoxinA inhibits CGRP release from peripheral neuronal C fibers and does not cross the blood-brain barrier.[11]

CGRP, discovered in 1982, is a large molecule.[8] It binds 2 major receptors: calcitonin receptor-like receptor and receptor activity-modifying protein 1.[12] This leads to signaling that can cause vasodilation or release of neurotransmitters or cytokines, in turn causing neurogenic inflammation and increased neuronal excitability.[12]

CGRP receptors are found at all of the known central and peripheral sites involved in migraine pathogenesis, including the hypothalamus and parabrachial nucleus, and CGRP levels are elevated during migraine attacks and lower between attacks.[12] Studies in animals first showed that stimulation of the trigeminal ganglion was associated with increased blood flow and release of CGRP, which could be inhibited by sumatriptan or dihydroergotamine.[11] Studies in humans showed that sumatriptan, in addition to relieving migraine, lowered CGRP levels in the internal jugular vein.[13] CGRP has also been shown to induce migraine-like symptoms after intravenous infusion.[14]

These observations led researchers to develop drugs that target and block either the CGRP ligand itself or the receptors upon which it acts.

CGRP ANTAGONISTS: A NEW CLASS OF DRUGS

The first CGRP antagonists to be studied were small molecules, with names ending in the suffix "-gepant." These so-called gepants block CGRP receptors, and 6 were found to be effective in acute treatment of episodic migraine.[15–20] However, their development was discontinued due to reports of hepatotoxicity.

Next to be developed were monoclonal antibodies targeting CGRP. These agents are metabolized by the reticuloendothelial system and, as a result, bypass hepatic metabolism; to date, no adverse effects on the liver have been reported.[10,21] Further, the current injectable antibodies are not thought to be contraindicated in patients with coronary artery, cerebrovascular, peripheral vascular, or kidney disease.[10]

DEFINITIONS

Episodic migraine is defined as having fewer than 15 headache days per month fulfilling diagnostic criteria for migraine.[22]

Chronic migraine is defined as headaches on 15 or more days per month for 3 months or more in a patient with a preexisting diagnosis of migraine. Of the total headache days, at least 8 days per month should meet migraine criteria.[22]

EFFICACY OF CGRP ANTAGONISTS

Clinical trials of the monoclonal antibodies (**Table 2**)[23–33] have found them to be superior to placebo and similar in efficacy to current prophylactic treatments for episodic and chronic migraine.[34] Roughly half of patients receiving these drugs achieved at least a 50% reduction in the number of headache days per month, compared with roughly one-fourth of patients receiving placebo. The new drugs have also been shown to be tolerable and safe, with no significant effects on blood pressure or peripheral vasoconstriction.[35]

Erenumab

Unlike galcanezumab and fremanezumab, erenumab targets the canonical CGRP receptor rather than the CGRP ligand itself.

There are 2 available doses, 70 mg and 140 mg, which patients give themselves once a month at home using a preloaded subcutaneous autoinjector.[10]

In episodic migraine. Three trials looked at 50% responder rates and mean decrease in monthly migraine days with use of erenumab in patients with episodic migraine (**Table 2**).[23–25] Results were reliably better with erenumab than with placebo, including in groups with so-called refractory migraine for whom 2 to 4 oral preventive therapies had failed.[25]

In chronic migraine, the results were similar.[26] Adverse effects noted included injection site pain (reported by 4% of patients receiving active treatment), constipation (4% of those on 140 mg), and muscle spasm (4% of those on 140 mg).[26]

Erenumab received FDA approval for prevention of migraine on May 17, 2018.

Fremanezumab

Fremanezumab targets the CGRP ligand rather than the receptor. It can be taken as a

The CGRP antagonists are an exciting new frontier in headache medicine

TABLE 2

Efficacy of calcitonin gene-related peptide antagonists in clinical trials of migraine prevention

Authors	Treatment	No. of patients	Baseline migraine days per month	Decrease in migraine days from baseline	50% response rate
Tepper et al[26]	Erenumab 70 mg monthly	191	17.9	6.6	40%
	Erenumab 140 mg monthly	190	17.8	6.6	41%
	Placebo	286	18.2	4.2	23%
Dodick et al[24]	Erenumab 70 mg monthly	282	8.1	2.9	40%
	Placebo	288	8.4	1.8	30%
Reuter et al[25]	Erenumab 140 mg monthly	121	9.2	1.8	30%
	Placebo	125	9.3	0.2	14%
Goadsby et al[23]	Erenumab 70 mg monthly	317	8.3	3.2	43%
	Erenumab 140 mg monthly	319	8.3	3.7	50%
	Placebo	319	8.2	1.8	27%
Dodick et al[27]	Fremanezumab 225 mg monthly	290	8.9	4.0	48%
	Fremanezumab 675 mg quarterly	291	9.2	3.0	44%
	Placebo	294	9.1	2.6	28%
Silberstein et al[28]	Fremanezumab 675 mg, then 225 mg monthly	379	12.8	4.6	41%
	Fremanezumab 675 mg quarterly	376	13.2	4.3	38%
	Placebo	375	13.3	2.5	18%
Stauffer et al[29]	Galcanezumab 120 mg monthly	213	5.6	4.7	62%
	Galcanezumab 240 mg monthly	212	5.7	4.6	61%
	Placebo	433	5.8	2.8	39%
Skljarevski et al[30]	Galcanezumab 120 mg monthly	231	9.1	4.1	59%
	Galcanezumab 240 mg monthly	223	9.1	4.2	57%
	Placebo	461	9.2	2.3	36%
Detke et al[31]	Galcanezumab 240 mg, then 120 mg monthly	278	19.2	4.8	28%
	Galcanezumab 240 mg monthly	277	19.4	4.6	28%
	Placebo	558	19.6	2.7	15%
PROMISE-1[32]	Eptinezumab 30 mg every 12 weeks	219	8.7	4.0	50.2%
	Eptinezumab 100 mg every 12 weeks	223	8.7	3.9	49.8%
	Eptinezumab 300 mg every 12 weeks	224	8.6	4.3	56.3%
	Placebo	222	8.4	5.4	37.4%
PROMISE-2[33]	Eptinezumab 100 mg every 12 weeks	356	16.1	7.7	57.6%
	Eptinezumab 300 mg every 12 weeks	350	16.1	8.2	61.4%
	Placebo	366	16.2	5.6	39.3%

monthly subcutaneous injection of 225 mg or as a quarterly injection of 675 mg.

In episodic migraine. A phase 3 trial in episodic migraine showed a decrease in mean monthly headache days and increases in the 50% responder rate and 75% responder rate with either dose compared with placebo ($P < .0001$).[27]

In chronic migraine. The same trial also compared fremanezumab and placebo in patients with chronic migraine.[36] The number of days with headache of moderate to severe intensity was reduced by 4.2 days in the placebo group and by 6 days in both a group receiving 225 mg monthly and a group receiving 675 mg quarterly.[28] In a separate study,[37] investigators found that patients noted an improvement as early as 1 week from initiation of therapy in both dose regimens.

Fremanezumab received FDA approval for prevention of migraine on September 14, 2018.

Galcanezumab

Galcanezumab also targets the CGRP ligand. It is given subcutaneously once a month with an autoinjector or prefilled syringe in a recommended monthly dose of 120 mg after an initial loading dose of 240 mg.

In episodic migraine. Two 6-month trials compared galcanezumab monthly injections of galcanezumab 120 mg, galcanezumab 240 mg, and placebo.[29,30] Both studies demonstrated a reduction of migraine days and an increase in 50% responder rate superior to placebo.[36] Interestingly, about 17% of patients had a 100% reduction in mean migraine days. This was seen most commonly in the last 3 months of the trials and was statistically significant compared with placebo ($P < .001$).[10]

In chronic migraine. In a phase 3 trial, galcanezumab showed a significant decrease in mean monthly migraine days compared with placebo. Also, differences in the 50% and 75% responder rates were statistically significant in each treatment group compared with placebo ($P < .001$). Similar to the episodic migraine trial, 11.5% of galcanezumab recipients in the chronic migraine trial also noted 100% reduction in mean migraine days, again noted most commonly in the last 3 months of the clinical trial ($P < .001$).[31]

This drug received FDA approval for prevention of migraine on September 27, 2018.

Eptinezumab

Eptinezumab, a monoclonal antibody against the CGRP ligand, is given intravenously, whereas the other CGRP monoclonal antibodies are given subcutaneously,

In episodic migraine. In a 3-month phase 3 trial,[32] quarterly infusions of eptinezumab 300 mg significantly reduced the number of mean monthly migraine days. Secondary end points included the 75% responder rate at week 12 (49.8% in the 100-mg arm, $P = .0085$; and 56.3% in the 300-mg arm, $P < .0001$). The clinical trial also demonstrated rapid onset of effect with a reduction in the likelihood of migraine within 24 hours of infusion. Before treatment, 58% of the participants were likely to have a migraine on any given day. This declined by 27% in the placebo group, 51% in those who received 100 mg, and 53% in those who received 300 mg ($P < .0001$ for both doses). At a 300-mg dose given quarterly, the 75% responder rate was maintained for up to 1 year.[10]

In chronic migraine, a phase 3 clinical trial showed a significant reduction in mean monthly migraine days compared with placebo at doses of 100 mg and 300 mg.[33]

This drug received FDA approval February 22, 2020.

The first CGRP antagonists to be studied were small molecules, termed gepants

A PRAGMATIC APPROACH TO ANTI-CGRP DRUG THERAPY

The approach to migraine management must remain a combination of cost-effective first- and second-line treatments, generally reserving CGRP monoclonal antibodies for patients for whom these options fail. All pharmacologic treatments should be accompanied by education and specific lifestyle changes for the best possible outcome.

The Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society[7] in 2012 reviewed the evidence and ranked the migraine preventive therapies available in the United States at that time according to the evidence of their efficacy. **Level A medications**, ie, those rated as having "established efficacy," were:

- The antiepileptic drugs divalproex sodium, sodium valproate, and topiramate

- The beta-blockers metoprolol, propranolol, and timolol
- The tripan frovatriptan (for short-term prophylaxis).

Level B medications, ie, those that are "probably effective," were:

- The antidepressants amitriptyline and vanlafaxine
- The beta-blockers atenolol and nadolol
- The triptans naratriptan and zolmitriptan.

Level C medications, ie, "possibly effective," were:

- The angiotensin-converting enzyme inhibitor lisinopril
- The angiotensin II receptor blocker candesartan
- The alpha-agonists clonidine and guanfacine
- The antiepileptic drug carbamazepine
- The beta-blockers nebivolol and pindolol
- The antihistamine cryptoheptadine.

While no formal guidelines exist for deciding whether anti-CGRP drugs would be appropriate for specific patients, the American Headache Society has offered general recommendations[38,39] based on the frequency of migraine.

All drug treatments should be accompanied by education and specific lifestyle changes

Patients in whom CGRP antagonists can be considered

- **Those with 4 to 7 migraine days per month** who have been unable to tolerate a 6-week trial of at least 2 oral preventive medications with level A or B evidence (see above).[7,38,39] In addition, patients should also have at least moderate disability on the Migraine Disability Assessment Scale or the Headache Impact Test 6, both of which are used to assess functional impairment secondary to migraine.
- **Those with 8 to 14 headaches per month** who cannot tolerate a 6-week trial of at least 2 oral preventive drugs with level A or B evidence (no need to demonstrate functional impairment).
- **Those with 15 or more headaches per month** (ie, chronic migraine) if at least 2 preventive medications with level A or B evidence have failed or if onabotulinumtoxinA has produced an inadequate response after at least 2 administrations or has caused adverse effects precluding further use.

At this time, not enough data exist on the safety of this class of medications in pregnant patients or children.

The findings from clinical trials suggest that if a patient is going to respond to CGRP monoclonal antibody therapy, it should happen within the first 3 months, often as early as 1 month after starting. If migraines continue unabated in this period, it is reasonable to discontinue the medication.

GEPANTS REVISITED

Gepants have been revisited in clinical trials over the past 5 years for both abortive and preventive treatment.[40]

Ubrogepant for acute migraine treatment

A multicenter, randomized, double-blind, placebo-controlled clinical trial of ubrogepant for the acute treatment of migraine showed a statistically significant improvement in rates of pain freedom 2 hours post-dose at 25 mg (P = .013), 50 mg (P = .020), and 100 mg (P = .003).[41] Adverse effects were similar to those with placebo and included dry mouth, nausea, fatigue, dizziness, and somnolence. There were no observed liver function test elevations as were seen with previous gepant trials.

Ubrogepant received FDA approval on December 23, 2019.

Rimegepant

Rimegepant has also been studied for the acute treatment of migraine in a double-blind, randomized, placebo-controlled trial.[20,21] Patients were randomized to receive placebo, sumatriptan, or rimegepant. The primary outcome was percentage of patients who were free of pain 2 hours post-dose.

Sumatriptan 100 mg and rimegepant 75 mg, 150 mg, and 300 mg were all significantly more effective than placebo (P < .007). Rimegepant was as effective as sumatriptan. No chest discomfort or paresthesias were reported with rimegepant as they were with sumatriptan.

A prospective multicenter, open-label, long-term safety study is under way.

Atogepant

Atogepant, another oral gepant, has been evaluated for prevention of episodic migraine. Mean headache days were reduced by 4.23 days per

month with atogepant 40 mg twice daily, compared with 2.85 days with placebo (P = .0034). There was no evidence of hepatotoxicity.[42]

OTHER TYPES OF HEADACHE

Cluster headache

Episodic cluster headache is defined as cluster headache attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 3 months. Chronic cluster headache, in contrast, is defined as cluster headache attacks occurring for 1 year or longer without remission, or with remission periods lasting less than 3 months.

In June 2019, galcanezumab received FDA approval for treatment of episodic cluster headaches. For treatment, galcanezumab 300 mg is administered as 3 consecutive injections of 100 mg at the onset of a cluster period and then monthly until the end of the cluster period.

In clinical trials,[43–46] galcanezumab significantly reduced mean cluster attack frequency compared with placebo, with more than 70% of patients experiencing at least a 50% reduction in weekly cluster headache attack frequency by week 3. However, while trials showed galcanezumab to be effective in episodic cluster, this was not true for chronic cluster.

Fremanezumab was also not effective in the prevention of chronic cluster headache compared with placebo.[10]

Persistent posttraumatic headache

Data from rodent models of concussion suggest that cephalic tactile pain hypersensitivity improves with administration of murine CGRP antagonists.[47] Fremanezumab is currently being studied for the prevention of persistent posttraumatic headache.[48]

Medication-overuse headache

Patients with medication-overuse headache may also benefit from anti-CGRP monoclonal antibodies. Both erenumab and fremanezumab have shown efficacy in treating the subgroup of chronic migraine patients with medication-overuse headache.[49–51] Erenumab 70 mg led to a reduction of 5.2 migraine days per month, and 140 mg had a reduction of 5.4 days, compared with a reduction of 3.5 days with placebo in patients with medication-overuse headache (P < .001).[48]

Erenumab is also being considered for evaluation in pediatric patients with chronic migraine.[52]

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