

Erenumab: A novel calcitonin gene-related peptide receptor antagonist developed specifically for migraine prevention

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Abstract

Headaches and migraines continue to be a leading cause of suffering and disability. As per the Global Burden of Disease Survey conducted in 2010, the exact magnitude of the disease still is underestimated. Migraine alone continues to rank seventh as a cause of disability. Various therapeutic modalities exist and newer classes of medications are currently being trialed to provide effective treatment to this population of patients. Erenumab, a calcitonin gene-related peptide receptor inhibitor, is a recent addition to this armamentarium and has been approved by the FDA for use in 2018. It has shown modestly improved outcomes according to the current trials. However, long-term outcomes and adverse effects still are under research. The following article elaborates on the current literature and evidence on this novel drug.

Keywords: Calcitonin gene-related peptide receptor antagonist, Erenumab, migraine

Introduction

Hippocrates described the occurrence of migraine attacks as headaches including the visual disturbances during its aura and the relief from vomiting. The origin of the word “migraine” comes from the Greek word “hemicrania,” which meant “half the skull.” The word hemicrania in relation to migraine-like headaches was later established by the Greek physician; Galen of Pergamon. It was not until 1988 that the International Headache Society (IHS) comprehensively classified migraine along with other headache disorders.^[1]

Migraine affects around 1 in 7 people and is the third most common disease in the world, just behind dental caries and tension-type headaches.^[2] In terms of its global burden as a disease, it is ranked among the top 10 and second only to stroke in its number of associated disability-adjusted life

years, among all the neurological disorders.^[3,4] Its prevalence in Indian setting remains understudied due to lack of available studies and enough data and owing to the variations in population groups in different parts of the country. Ray *et al.*^[5] estimated the prevalence of migraines to be about 14.12% in the eastern part of the country and Kulkarni *et al.*^[6] estimated it as high as 25.2% in a southern Indian state.

As per the IHS, migraine is defined as^[1] episodic headache (that can last from 4–72 h) with two of the following:

1. Unilateral pain
2. Throbbing
3. Aggravation of movement
4. Pain of moderate or severe intensity.

And one of the following:

- 1) Nausea or vomiting
- 2) Photophobia or phonophobia.

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/joacp.JOACP_3_19

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How to cite this article: Garg S, Vij M, Edward N, Vij B. Erenumab: A novel calcitonin gene-related peptide receptor antagonist developed specifically for migraine prevention. *J Anaesthesiol Clin Pharmacol* 2020;36:104-9.

Submitted: 03-Jan-2019 **Revised:** 07-Apr-2019 **Accepted:** 24-May-2019
Published: 18-Feb-2020

While chronic migraine has been defined as 15 or more headache days per month with at least 8 migraine days,^[1] it is known to affect 5–8% of persons with migraine. Episodic migraine is defined as fewer than 15 migraine days or headache days per month, with or without aura and accounts for more than 90% of persons with migraine.^[1]

As migraine is thought to have a polygenetic etiology with environmental modifiers, there has been a paucity of specific therapeutic directions. Until recently, the management of migraine involved a complex multipronged approach of abortive, preventive, and bio-behavioral therapies.

Numerous pharmacological preventive therapies have been used such as beta blockers, valproate, and topamax, which have relatively stronger evidence for use as compared to serotonin antagonists, calcium channel blockers.^[7] However, an optimal prophylactic treatment option remains elusive. A newer drug, erenumab, which is a calcitonin gene-related peptide receptor (CGRP) antagonist, was recently approved by the FDA on May 17, 2018, which projects a promising role in the preventive therapy of migraine and related disability.^[8]

Erenumab

Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody that has high-affinity binding to the CRGP. It has been developed by utilizing recombinant DNA technology in Chinese hamster ovary cells. It has an estimated molecular weight of 150 kDa and is made up of 2 heavy chains (each containing 456 amino acids) and 2 light chains (each containing 216 amino acids).

CGRP is a neuropeptide that, along with its receptor, is present in both central and peripheral neurons.^[9,10] The peptide equally impacts the neuronal modulation of nociceptive signaling and vascular activity. These actions are enabled predominantly by its location in dorsal root and trigeminal ganglions, and it is these two-fold actions that make its role in causing migraine plausible.^[11]

CGRP levels have been shown to surge excessively during a migraine and return to normal with headache relief. Inhibition of the effects of CGRP could theoretically attenuate compensatory vasodilation in ischemic-related conditions. This knowledge of contribution of CGRP in the pathophysiological processes fundamental to migraine disorders led to the development of CGRP antagonists (the “-gepants”) and four different antibodies targeting the CGRP receptor, namely erenumab or targeting CGRP itself (fremanezumab, eptinezumab, and galcanezumab).

The role of CGRP in migraine has been further elucidated in phase 2 and phase 3 clinical trials of small-molecule

CGRP-receptor antagonists in acute migraine and is further supported by phase 2 and phase 3 trials of monoclonal antibodies targeting the CGRP pathway, which suggests that the pathway could be a target for preventive migraine treatment.^[12]

Erenumab is a fully human monoclonal antibody that selectively and potently binds to the canonical CGRP receptor. A subcutaneous injection (SC) formulation of this drug (AIMOVIG™) has been recently approved in the United States for the prevention of migraine in adults,^[8] and it has also received a positive opinion on 31 May 2018 in the European Union.^[13]

Pharmacodynamics properties of Erenumab

Mechanism of action

Erenumab antagonizes the CGRP function through competitive blockade with high affinity and specificity. It thereby antagonizes the accumulation of cAMP. This has been shown in both *in vivo* and *in vitro* studies. cAMP through CGRP stimulation in neuroblastoma cells in human *in vitro* studies [Figures 1 and 2]. In, *in vitro* studies, erenumab potently and competitively inhibited [125I]-CGRP binding to the canonical CGRP receptor and fully antagonized CGRP-stimulated cAMP accumulation in human SK-N-MC neuroblastoma cells.^[10]

It does not have any reported activity on other calcitonin family receptors (e.g., adrenomedullin, calcitonin, and amylin), even at a higher concentration of 10 μM. The levels of CGRP increase throughout the duration of pain due to migraine and slowly come back to normal levels when pain diminishes. CGRP-R acts on cerebral blood vessels, which are thought to be responsible for the development of migraines. Erenumab reduces the number of monthly migraine attacks by blocking CGRP-R receptors on blood vessels. It has also been seen to inhibit capsaicin-induced increases in dermal blood flow in *in vivo* studies in monkeys.^[10] When administered subcutaneously, in healthy volunteers or patients of migraine, subcutaneous injection of erenumab 140 mg

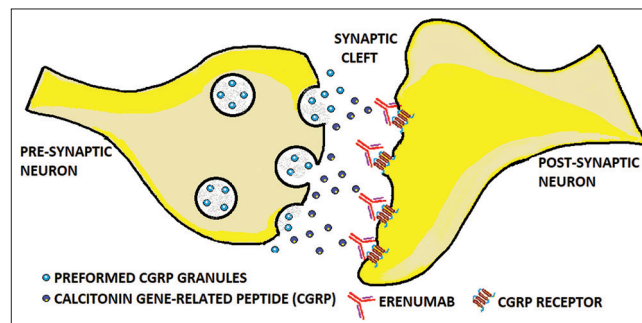


Figure 1: Mechanism of Action of Erenumab

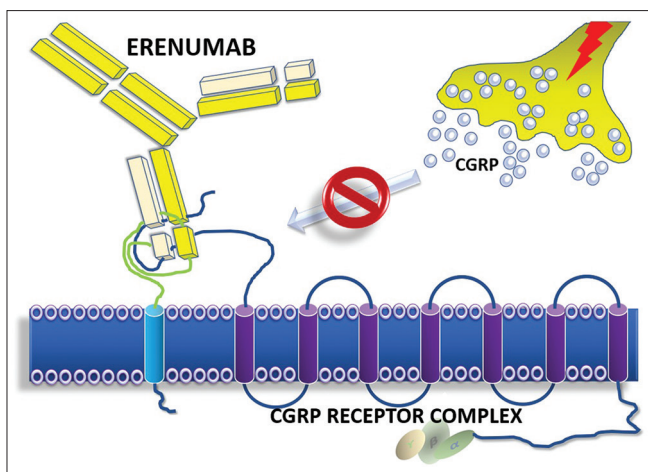


Figure 2: Erenumab competitively blocks the CGRP receptor thereby antagonizing the CGRP receptor functions

inhibited capsaicin-induced increase in dermal blood flow by 74.6–94.6%. When given multiple doses, these were significantly inhibited at day 8 compared with placebo. Apparent erenumab dose dependency was not observed in this pharmacodynamic assay.^[11]

Pharmacokinetics properties of erenumab

As a result of binding to the CGRP-R receptor, erenumab exhibits non-linear kinetics. Nevertheless, at therapeutic doses, following subcutaneous dosing every 4 weeks, the pharmacokinetics of erenumab exhibit predominantly linear kinetics, owing to saturation of binding to CGRP-R. After administration of 140 mg subcutaneous doses every 4 weeks, less than 2-fold accumulation was detected in serum concentrations, which subsided to a steady state by 12 weeks of initial dosing. In healthy volunteers, a single 70 mg dose produced a C_{max} of 6.25 $\mu\text{g/ml}$ after 6 days and an area under the concentration-time curve (AUC) from time zero to time of last measurable concentration (AUC_{last}) of 171 day $\cdot\mu\text{g/ml}$. In patients with migraine, a single 140 mg dose produced a C_{max} of 9.93 $\mu\text{g/ml}$ after 11 days and AUC_{last} of 367 day $\mu\text{g/ml}$.^[14]

Absorption

The median peak serum concentrations were attained in 4 to 6 days subsequent to a single subcutaneous dose of 140 mg or 70 mg administered to healthy adults, whereas the estimated absolute bioavailability was 82%.

Distribution

Following a single 140 mg intravenous dose, the mean (SD) volume of distribution during the terminal phase (V_z) was estimated to be 3.86 (0.77) liters.

Biotransformation and elimination

Erenumab is predominantly eliminated using a non-specific proteolytic pathway. At higher concentrations, the elimination

is basically through a non-specific, non-saturable proteolytic pathway, whereas at lower concentrations, the elimination is majorly through saturable binding to target (CGRP-R). Erenumab was detectable in serum levels 30 to 160 days post-dose, with doses of ≥ 70 mg resulting in detectable levels at ≥ 100 days post-dose.^[15] Erenumab has an effective half-life of 28 days.^[8]

Dosing and route of administration

The drug is administered in dosages of 70 mg, once a month, however, some patients may benefit from 140 mg a month dosing. It is administered subcutaneously into the abdomen, thigh, or upper arm.

Aimovig is available in a single dose pre-filled autoinjector formulation, with a strength of 70 mg/ml, available in one or two per pack.

Special populations

On the basis of population pharmacokinetics analysis, the pharmacokinetics of erenumab was not affected by age, gender, race, or in either episodic or chronic migraine subtypes. However, there is still lack of clear evidence for certain patient population groups. Patients with hemiplegic migraine and who had cardiovascular and cerebrovascular events were excluded from the trials. There is no clarity if it could be used in pregnant or lactating patients either as these patients were not included either. Another area that would need further research would be acceptable to have patients on concomitant botox and aimovig therapy. The current trials only enrolled patients after 4 months of use of last Botox therapy.

Patients with renal impairment

Patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) have not been studied. Population pharmacokinetic analysis of integrated data from the erenumab clinical studies did not reveal a difference in its pharmacokinetics in patients with mild or moderate renal impairment relative to those with normal renal function.

Patients with hepatic impairment

There have been no studies performed in patients with hepatic impairment. Erenumab, as a human monoclonal antibody, is not metabolized by cytochrome P450 enzymes, and hepatic clearance is not a major clearance pathway for erenumab.

Erenumab exposure increased more than dose proportionally after SC administration of single 1 to 70 mg doses and approximately dose proportionally at higher doses (70 to 210 mg) in a phase I study in healthy volunteers ($n = 49$) and patients with migraine ($n = 12$).

Clinical efficacy and safety

Conduct of various phase I, II, and III trials that have successfully demonstrated the efficacy of erenumab in this regard have led to this fruition [Table 1].

Sun *et al.* conducted a multicenter, randomized, double-blind, placebo-controlled, phase 2 trial,^[16] compared three doses of erenumab, 7, 21, and 70 mg and concluded that the 70 mg dosing might be a potential therapy for prevention of episodic migraine.

A randomized, phase II, double-blind, placebo-controlled, study^[17] conducted by Tepper *et al.* provided, class 1b evidence that erenumab either in 70 or 140 mg dosing could be a potential new preventive therapy in patients with chronic migraine. They included adults aged 18–65 years with chronic migraine, a total of 667 patients. This was a multi-center trial and enrolled patients from multiple centers in North America and Europe.

Patients were divided into three groups randomly. They received subcutaneous placebo, erenumab 70 mg or erenumab 140 mg, given every 4 weeks for 12 weeks. It was concluded that erenumab 70 mg and 140 mg reduced monthly migraine days (MMD) vs. placebo (both doses –6.6 days vs. placebo –4.2 days; difference –2.5, 95% CI –3.5 to –1.4, $P < 0.0001$). The most frequent adverse events were injection-site pain, upper respiratory tract infection, constipation, and nausea.

Goadsby and colleagues^[12] conducted their trial (STRIVE) on a group of 955 patients and randomly assigned them to three groups being administered either a 70 or 140 mg dosing of erenumab or a placebo. The treatment was given

subcutaneously and monthly over a period of 6 months. The mean number of MMD at baseline was 8.3 in the overall population; by months 4 through 6, the number of days was reduced by 3.2 in the 70 mg erenumab group and by 3.7 in the 140 mg erenumab group, as compared with 1.8 days in the placebo group ($P < 0.001$ for each dose vs. placebo). The number of days of use of acute migraine-specific medication treatment days (MSMD) was reduced by 1.1 days in the 70 mg erenumab group and by 1.6 days in the 140 mg erenumab group, as compared with 0.2 days in the placebo group ($P < 0.001$ for each dose vs. placebo). A significant improvement in physical impairment scores and everyday activities was also reported with this trial.

ARISE^[18] is a phase 3, randomized, double-blind, placebo-controlled study conducted by Dodick *et al.*, which included 577 adults with episodic migraine and were randomized to placebo or 70 mg erenumab. They showed that patients treated with erenumab 70 mg SC once monthly experienced a least-squares mean reduction from baseline of 2.9 days in MMD after 3 months compared with a 1.8 day reduction in the placebo group ($n = 288$; $P < 0.001$); MMD at baseline were 8.1 and 8.4 days for erenumab and placebo recipients, respectively. 39.7% (erenumab) and 29.5% (placebo) of patients received a >50% reduction in monthly migraine days (OR: 1.59 (95% CI: 1.12, 2.27) ($P = 0.010$). Migraine-specific medication treatment days were reduced by -1.2 (erenumab) and -0.6 (placebo) days, ($P = 0.002$). The LIBERTY trial^[19] conducted by Reuter *et al.*, evaluated the efficacy of erenumab in patients who had failed 2–4 other prophylactic migraine treatments; At week 12, 30.3% of patients treated with erenumab 140 mg SC achieved a $\geq 50\%$ reduction in MMD compared with 13.7% for placebo (odds ratio: 2.73; $P = 0.002$). Significant

Table 1: Clinical drug trials for erenumab

Authors	Study design	Type of trial/ number of patients	Patients included	Dosing
Sun <i>et al.</i> , 2016	Phase II multicenter	Randomized placebo controlled 267 patients	1) Episodic migraine, with or without aura, for at least 12 months prior to the study 2) Prior failure to ≤ 2 classes of prevention treatments	Subcutaneous monthly placebo Subcutaneous monthly erenumab: 7, 21 and 70 mg
Tepper <i>et al.</i> , 2017	Phase II multicenter	Randomized placebo controlled 667 patients	1) Chronic migraine, with or without aura, for at least 12 months prior to the study Patients with prior failure to ≤ 3 classes of migraine prevention treatments	Subcutaneous monthly placebo Subcutaneous monthly erenumab: 70 and 140 mg
Goadsby <i>et al.</i> , 2017	STRIVE, Phase III	Randomized placebo controlled 955 patients	1) Episodic migraine, with or without aura, for at least 12 months prior to the study 2) Prior failure to ≤ 3 classes of migraine prevention treatments	Subcutaneous monthly placebo Subcutaneous monthly erenumab: 70 and 140 mg
Dodick <i>et al.</i> , 2018	ARISE, Phase III S	Randomized placebo controlled 577 patients	1) Episodic migraine, with or without aura, for at least 12 months prior to the study 2) Prior failure to ≤ 2 classes of prevention treatments	Subcutaneous monthly placebo Subcutaneous monthly erenumab: 70 mg
Reuter <i>et al.</i> , 2018	LIBERTY, Phase III	Randomized placebo controlled 246 patients	1) Episodic migraine, with or without aura, for at least 12 months prior Prior failure with 2–4 migraine prophylaxis treatments	Subcutaneous monthly placebo Subcutaneous monthly erenumab: 140 mg

improvements were also seen with erenumab 140 mg in terms of MMD (mean improvement of 1.61 days vs. placebo; $P = 0.004$) and MSMD (mean improvement of 1.73 days vs. placebo; $P < 0.001$).

Lattanzi *et al.*^[20] in their recently published systematic review discuss erenumab with regards to the above-mentioned trials, their limitations, and outcomes. Their analysis suggests that all the conducted trials were associated with a greater reduction in MMD and MSMD either with the monthly dose of 70mg or 140mg. Further, subgroup analyses demonstrated that erenumab was effective in reducing MMD and MSMD either in patients with episodic or with chronic migraine, at any dose and any time point. The mean reduction in MMD with erenumab at the 7 mg and the 21 mg doses were not significantly different from those with placebo.

Phase III EMPOWER studies are in progress. A recent meta-analysis by Dr Zhu^[21] has analyzed eight randomized controlled trials, including 2,292 patients and concluded that not only do the CGRP antagonists help reduce the MMD significantly but also help reduce the acute migraine-specific medication intake. The adverse events were similar between the CGRP monoclonal antibody group and placebo group.

Sussman *et al.*^[22] have suggested that the use of erenumab may be a cost-effective approach to prevent monthly migraine days among patients with chronic migraine vs. onabotulinumtoxin A.

Adverse Effects

There were no major concerns noted with the safety profile with the medication across all the trials. The occurrence of cardiovascular events throughout the double-blind treatment phase of the trials was low and did not differ between the erenumab and placebo groups with either dose. There were no significant changes noted in the serum chemistry, hematology laboratory values, ECG findings, and vital signs.^[20]

Adverse reactions occurring with an incidence of $\geq 2\%$, and at least a 2% greater incidence than with placebo, in patients treated with erenumab during the first 3 months of the phase III STRIVE and ARISE trials, and one phase II trial included injection site reactions (6 and 5% of erenumab 70 [$n = 787$] and 140 mg [$n = 507$] once monthly recipients, respectively, compared with 3% of placebo recipients [$n = 890$]), constipation (1 and 3%, respectively, vs. 1%), and cramps/muscle spasms (< 1 and 2%, respectively, vs. $< 1\%$). Few (1.3%) patients treated with erenumab in these three studies discontinued double-blind treatment because of adverse events.^[8] With the exception

of the LIBERTY trial, there was an overall incidence of 4.3–8.0% of anti-erenumab-binding-antibodies noted. This was noted to be of infrequent occurrence.

Further research areas

A high proportion of migraine patients in clinical practice present with one or more comorbidities such as fibromyalgia, pelvic pain, and low back pain. Whether the use of this medication is an effective approach toward these conditions is still unclear and needs further research. Humanized monoclonal antibodies binding the CGRP ligand such as fremanezumab, galcanezumab, and eptinezumab are currently under investigation trials and are expected to be introduced soon. In addition, erenumab being a specific CGRP antagonist, drugs acting at other targets of CGRP warrant looking at other medications for the plausible treatment of headaches.

Conclusion

Erenumab, available in doses of 70 mg and 140 mg injections, is newly FDA approved injectable drug used for the prevention of episodic migraine headache attacks. It is a novel addition to the pharmacological armamentarium. There is a need for search for newer options as the currently available medications are either limited by their suboptimal efficacy and tolerability or associated with significant drug interactions. CGRP antagonists such as erenumab seem to be a positive stride in this regard. Various trials done so far report good efficacy and safety and have not reported significant adverse effects. However, larger follow-up studies including larger number of patients need to be done and further research needs to be done to further elucidate the efficacy of this drug. There are no reliable studies on Erenumab about its safety during pregnancy or while breastfeeding or for pediatric use at this point.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Brinder Vij is on advisory board of Amgen and is on speaker Bureau as well for Aimovig with Amgen Pharmaceuticals.

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