Review Article

Calcitonin Gene-related Peptide Inhibitors: A Shift in Paradigm in the Therapy of Migraine

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Received: 21-05-2019; **Revised:** 28-06-2019; **Accepted:** 05-07-2019.

ABSTRACT

Migraine being one of the prevalent chronic neurological disorder with high socioeconomic impact. The current therapy includes drugs which were developed for other conditions and there was a void in the development of targeted therapy. Calcitonin gene-related peptide (CGRP), a neuropeptide is associated with transmission of nociceptive signals through the trigeminovascular pathway is also responsible for the pathogenesis of migraine. Blocking CGRP by CGRP receptor antagonists and monoclonal antibodies (mAb) targeting CGRP or its receptor seems to be a promising therapeutic strategy in the treatment of migraine. The gepants like telcagepant, ubrogepant, rimegepant and atogepant act by antagonizing the CGRP receptor have proven to be effective in reducing the attacks of migraine but are yet to be approved by FDA. CGRP mAbs like erenumab, galcanezumab and fremanezumab and eptinezumab acts on CGRP ligand and/or receptor has emerged as an effective therapy in the prophylaxis of migraine with being well tolerated gives them an edge over the earlier drugs. Monthly administration of these mAbs further boosts the patient compliance. With the safety data from the trials, these drugs seem to be good enough, yet long term safety data are required to establish them as the future in the treatment of migraine.

Keywords: Migraine; CGRP; Gepants; CGRP antagonist; Monoclonal antibody.

INTRODUCTION

Migraine is one of the most common incapacitating neuronal disorder which presents with severe throbbing pain or a pulsing sensation, usually on one side of the head.[1] The International Headache Society diagnoses a migraine attack by its defining pain and number of attacks (at least 5, lasting 4-72 hours if left untreated) with additional symptoms like nausea and/or vomiting, sensitivity to both light and sound.[2] Migraine is quite a common neurological condition with an estimated prevalence of 15% in the western world and 14.12- 14.7% in India.[3,4,5] Women are comparatively more likely to get affected by migraine as compared to men.[6] It leads to a huge social burden worsening the quality of life as well as an impact on the financial condition of the patient.[7,8] Migraine is also classified on the basis of frequency and chronicity of attacks into episodic and chronic migraine. When the attacks of headache are for <15 days per month it is said to be episodic migraine whereas, episodic migraine can worsen and convert to chronic migraine when the frequency of attacks increases to ≥15 days per month for 3 consecutive months.[9] The pathophysiology involving this debilitating disorder is complex and not clear and as per the prevailing concept, it was thought to be a vascular disorder because triptans which act via vasoconstrictive property were found to be effective in migraine.[10] The severity of headache and frequency determines the strategy of treatment either can be managed by triptans or NSAIDS or if a persistent one needs prophylactic treatment to prevent further attacks.[11] Since the present therapies available do not completely ascertain a cure or absolute remission for migraine so there is always a need for newer targets and therapies to curb this disease condition.[12,13] Calcitonin gene-related peptide (CGRP) has been seen to have a proven role in the pathogenesis of migraine.[14,15] Hence, this article reviews the CGRP as a potential target, mechanism of action, various drugs acting through this pathway, pros and cons and molecules in the pipeline.

CALCITONIN GENE-RELATED PEPTIDE (CGRP)

CGRP is a 37-amino acid neuropeptide which is present both in central as well as peripheral nervous system especially in sensory C fibers and have been found to have a role in pain and inflammation.[16,17,18] CGRP is also found in the trigeminal ganglion, pseudounipolar neurons and even in dorsal root ganglia.[19] The fibers involved in pain transmissions like unmyelinated C fibers and small myelinated Aδ fibers are associated with CGRP and are co-expressed with 5-HT_{1B} and 5-HT_{1D} receptors.[20] The smooth muscle cells of the dural artery, trigeminal ganglia, thalamus, hypothalamus, brain stem, and cortex have receptors for CGRP. In humans, CGRP exists in α and β isoforms synonymously also known as CGRP I and II.[21] The main isoform expressed in the sensory neurons and the trigeminovascular system is αCGRP whereas, β isoform is transcribed from a different gene and is present in the enteric nervous system responsible for inhibiting gastric acid secretion.[22,23]

CGRP Receptor

The CGRP receptor is a G protein-coupled receptor that consists of three subunits i.e., Calcitonin-like receptor (CLR), Receptor activity-modifying protein (RAMP1), Receptor component protein (RCP).[24] The unit which forms the functional subunit is called calcitonin receptor-like protein (CLR). CLR alone is nonfunctional unless it forms a heterodimer with Receptor activity-modifying protein 1 (RAMP1) to form the CGRP receptor.[25] RAMPs are of three types: RAMP1, RAMP2 and RAMP3 and the affinity of the receptor are determined by the type of RAMP it is associated with.[26] Dimerization of CLR and RAMP2 forms AM1 receptor whose ligand is adrenomedullin. Similarly, RAMP3 with CLR forms AM2 receptor which has a partial affinity for CGRP.[21,27] The third component of the receptor i.e., RCP has no role in any alteration of CGRP binding but is crucial for signal transduction inside the cell.[28,29]

Role of CGRP in Migraine

The pathophysiology of this disorder is yet to be understood properly but the most common theory which is acknowledged is considering migraine as a vascular disorder. The dilation of cerebral and meningeal arteries in the brain is held responsible for the pain associated with migraine.[30] CGRP has been shown to have a potent vasodilatory effect on intracranial arteries.[23] Literature reveals that the cerebral and dural arteries have a proportionately elevated level of expression of CGRP receptors which supports the fact that CGRP is associated with the pathogenesis of migraine.[31,32] At present, there is a shift of ideology and the trigeminovascular pathway is gaining popularity in the pathogenesis of migraine.[33] CGRP has been found to be associated with transmission of nociceptive signals from the trigeminal ganglion to the brainstem, other regions of the brain and also form plexus around intracranial arteries.[21,34] When activated the trigeminal nociceptive endings releases CGRP which is further associated with induction of vasodilatation, edema, and recruitment of inflammatory cells which culminate into neurogenic inflammation and pain.[22,35] It has been seen that while the patient has migraine attacks, there is a rise in the CGRP levels when measured from the external jugular vein.[36] Whereas, triptans on administration during a migraine attack has been shown to lessen the levels of CGRP in serum which were further correlated with the clinical improvement of the patient.[37] In view of such significance of the CGRP pathway in migraine antagonism of the CGRP receptor has turned out to be a potentially effective target in the pharmacotherapy of this disorder.

CGRP as a Target

Antagonism of CGRP receptor has been an appealing target for the treatment of migraine. The first CGRP receptor antagonist to be discovered was olcegepant.[38] It was a potent compound which had a large molecular weight and low bioavailability hence was developed as an intravenous (I.V.) infusion which further turned out to be a major limitation.[39] Due to this limitation, the IV preparation was never a popular option for treatment of migraine which led to the development of orally viable form later on.[40]

Telcagepant was the next molecule to be developed which was more potent oral drug and was found to be effective in the clinical trials but the development was later stopped because of the reports of liver toxicity.[41,42,43] Ubrogepant is an orally active CGRP antagonist undergoing trials and has given positive results when compared with placebo for acute migraine.[44] Rimegepant and Atogepant are similar CGRP receptor antagonist which are been found efficacious and are currently under clinical trials for the treatment of acute migraine.[45,46] These CGRP antagonists which are synonymously also called “Gepants” have shown to be promising for the treatment of acute migraine but are still to prove their efficacy in the prophylaxis of migraine.[21]

CGRP Monoclonal Antibodies

With the advancement of drug discovery and development of target-based therapies monoclonal antibodies (mAbs) has gained popularity in the therapy of various diseases. Presently, mAbs are being tried in numerous neurological disorders and migraine is one of them. Cranial blood vessels are not the sole cause in migraine pathogenesis but other neurological structures like trigeminal ganglion and nucleus caudalis are also relevant and are not fully protected by the blood-brain barrier.[47,48] Monoclonal antibodies target the smooth muscle cells on blood vessels and neurons and the structures located outside the blood-brain barrier.[48] Till date, four mAbs against CGRP or its receptor have been developed and out of which three have been approved by the Food and Drug Administration (FDA).

Erenumab is the first mAb to be approved for the preventive treatment of migraine by FDA in May 2018.[21] It is a fully human IgG2 monoclonal antibody against CGRP receptor produced using Chinese hamster ovary (CHO) cells. Structurally, it has two heavy chains containing 456 amino acids in each of them and two lambda subclass light chains containing 216 amino acids each.[49] Erenumab is recommended at a dosage of 70 mg subcutaneously (SC) once monthly. However, in some patients, the dose can be escalated to 140 mg monthly to achieve remission from this chronic condition.[49] The median peak serum concentrations after a single dose of erenumab in healthy adults were obtained in approximately 6 days with an estimated absolute bioavailability of 82% and the effective half-life was estimated to be 28 days.[49,50] The common adverse effects(ADRs) associated with erenumab are injection site reactions, constipation, non-serious cases of rash, pruritus, cramps and muscle spasms.[49,50]

Galcanezumab is the second mAb to be approved by FDA in Sept 2018 for the preventive treatment of migraine.[51] Galcanezumab is a humanized IgG4 mAb generated in CHO cells specific for CGRP ligand and is specifically designed to selectively bind to the human CGRP entities directly.[52]

Structurally, it is made of two identical immunoglobulin kappa light chains and two gamma heavy chains. Galcanezumab is recommended in the dosage of 240 mg SC once as a loading dose which can be taken as self-administered two consecutive injections of 120 mg each then followed by 120 mg once-monthly doses.[52] It takes about five days to reach maximum concentration and the elimination half-life is approximately 27 days.[52] Injection site reactions and hypersensitivity reactions like rash, urticaria, and dyspnea are the reported ADRs.[52]

Fremanezumab is the third FDA approved mAb for the preventive treatment of migraine which got approved in Sept 2018.[53] It is fully humanized IgG2Δa/kappa mAb generated in CHO cells that specifically bind to CGRP ligand and blocks its binding to the CGRP receptor.[54] Fremanezumab is recommended with two dosage schedule either it can be given 225 mg SC injection monthly or a cumulative dose of 675 mg every 3 months(three consecutive injections of 225 mg each).[54] It takes five to seven days to reach maximum concentration and the elimination half-life is approximately 31 days. The safety and efficacy of fremaneuzumab in pediatric and geriatric patients have not been established in the trials and it currently lacks data regarding its use in pregnancy and lactation.[54] The common ADRs which were reported were injection site reactions and hypersensitivity reactions like rash, pruritus, drug hypersensitivity, and urticaria.[54]

Eptinezumab is a fully humanized IgG1 mAb that selectively binds to CGRP ligand with high affinity to block its interaction with the human CGRP receptor.[55] It is administered intravenously (IV) as an infusion which has an advantage of swift target engagement with 100% bioavailability. A Phase 3 randomized, double-blind, placebo-controlled trial named PROMISE 1 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) was conducted to evaluate the safety and efficacy of eptinezumab for episodic migraine prevention.[56] In this trial total 888 patients were randomized who received either eptinezumab in a dosage of 30, 100, and 300 mg vs placebo once every 12 weeks.[56] PROMISE 1 showed that approximately 50% of patients receiving eptinezumab 30, 100, and 300 mg achieved ≥50% reduction in mean monthly migraine days (MMD) over Weeks 1–12 in patients with episodic migraine and the reduction was significant.[57] Patients experienced a significant reduction in the probability of migraine from day 1 following infusion of eptinezumab. PROMISE 1 met the primary endpoint with statistically significant reductions in MMD. The common adverse effects observed with eptinezumab were upper respiratory tract infection, nasopharyngitis and sinusitis and occurrences of adverse events were similar to placebo groups.[57] PROMISE 2 (PRevention Of Migraine via Intravenous ALD403 Safety and Efficacy 2) is the second Phase 3, randomized, double-blind, placebo-controlled trial which evaluates 1,072 patients for the safety and efficacy of eptinezumab for chronic migraine prevention.[58] In the study, patients received eptinezumab (300 mg or 100 mg), or place every 12 weeks and it showed a significant reduction in mean MMD.[58] The commonly reported ADRs were nasopharyngitis, upper respiratory infection, nausea, and urinary tract infection, arthralgia, dizziness, anxiety, and fatigue.[58] Being a drug, which can be infused IV it has varied advantages like a rapid onset of action, 100% bioavailability, high systemic exposure with even lesser drug dosage and more predictable pharmacokinetics.[59] Presently, the biologics license application for eptinezumab has been submitted to FDA and expected to be approved in the near future.[60] The CGRP targeted therapies are summarized in table no. 1.

Table 1: Summary of monoclonal antibodies acting through CGRP pathway

Drug	Mechanism of Action	Route of administration	Dose regimen	FDA approval
Erenumab	Fully human IgG2 mAb against CGRP receptor	Subcutaneous	70 mg/ 140 mg once monthly	May 2018
Galcanezumab	Humanized IgG4 mAb specific for human CGRP ligand with high affinity to block its interaction with the human CGRP receptor	Subcutaneous	240 mg once as loading dose followed by 120 mg once monthly doses	Sept 2018
Fremanezumab	Fully humanized IgG2Δa/kappa mAb specifically binds to CGRP ligand with high affinity to block its interaction with the human CGRP receptor	Subcutaneous	225 mg monthly, or a cumulative dose of 675 mg every 3 months	Sept 2018
Eptinezumab	Fully humanized IgG1 mAb selectively binds to CGRP ligand with high affinity to block its interaction with the human CGRP receptor	Intravenous infusion	100 mg or 300 mg place every 12 weeks	Yet to be approved

CGRP: Calcitonin gene-related peptide; mAb: Monoclonal antibody; IgG: Immunoglobulin G

Migraine is also found to be associated with various comorbid conditions like depression, anxiety, bipolar disorder and fibromyalgia.[61,62] Hence, we need a few studies which could look at the potential of CGRP in treating migraine along with the associated comorbidities. The cost of these CGRP mAbs are high and hence can be considered a drawback in the therapy of a chronic condition like migraine. Though the data from the trials conducted on various CGRP mAbs have been appealing along with the short-term safety reports still the long-term safety of these mAbs on cardiovascular, cerebrovascular and gastrointestinal systems are extremely essential and are yet to be determined.

CONCLUSION

Migraine being a common and recurrent neurological disorder prophylaxis plays an important role in prevention apart from treating the condition. The gepants under trial have proven their efficacy but few being hepatotoxic in nature newer and target based therapy was the necessity of the hour. The CGRP mAbs like erenumab, galcanezumab and fremanezumab have been approved by the FDA and once monthly administration helps increasing compliance among migraineurs as compared to other existing drugs used for prophylaxis of migraine. The short-term safety profile of these CGRP mAbs as obtained from the trials have been acceptable yet there is a need for long-term safety data for the effective and safe use in therapy episodic or chronic migraine.

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Source of Support: Nil, **Conflict of Interest:** None.