

CALCITONIN GENE-RELATED PEPTIDE INHIBITORS: A NEW CLASS OF DRUG FOR MIGRAINE TREATMENT

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ABSTRACT

Migraine is a chronic primary headache disorder that affects around 15 % of world population. It is usually felt as a throbbing pain on one side of the head. Many people also have symptoms such as nausea, vomiting and increased sensitivity to light or sound. Migraine is a common health condition, affecting around one in every five women and around one in every 15 men. They usually begin in early adulthood. Drugs that are currently taken for prophylaxis are not specific for migraine but include antiepileptic drugs, β - blockers and antidepressants. Since these drugs are not migraine-specific, it may cause mild to serious side effects. So the use of older and current drugs for migraine prevention is limited by its inadequate efficacy, tolerability and patient adherence. A new class of drugs – calcitonin gene-related peptide inhibitors – has recently been developed as a targeted therapy for migraine. Calcitonin gene-related peptide (CGRP) is a neurotransmitter produced by neurons in the brain. Studies showed that CGRP level increases during migraine attacks and have a major role in the pathology of migraine. Human studies also showed that people who suffer from migraines are more sensitive to CGRP levels, and high CGRP triggers migraine-like headaches within hours. Recent research on migraine is targeted on CGRP therapies such as CGRP receptor antagonist, CGRP antibodies and CGRP receptor antibodies. US-FDA on May 17, 2018 approved a new drug Erenumab- aooe which is a human immunoglobulin G2 (IgG2) monoclonal antibody that has high affinity to CGRP receptor. CGRP-related therapies offer promising improvements over existing medications. Because they are designed specifically to act on the trigeminal pain system. They are more specific, targeted and they seem to have few or no adverse effects. So this new class of targeted drug will be a boon to migraine sufferers who are intolerable with other conventional drugs.

KEYWORDS: CGRP, Erenumab, Headache, Migraine, Monoclonal antibody.**INTRODUCTION**

Headaches are among the most common reasons that patients seek medical attention. Diagnosis and treatment are based on careful clinical approach to understand the anatomy, physiology and pharmacology of the nervous system pathways that mediate the various headache syndromes,^[1] Headache can be classified as primary or secondary. Primary headache such as migraine, tension-type headache, cluster headache often results in considerable disability and decrease in the patient's quality of life. Secondary headache are seen in association with cases such as systemic infection, head injury.^[1,2]

Migraine is a chronic primary headache disorder that affects almost 15% of world population,^[3] It is a chronic, complex neurological disorder that manifests as recurrent attacks of moderate to severe headache pain lasting 4–72 h. The headache is typically unilateral, has a pulsating quality, is aggravated by routine physical activity and is

associated with nausea and/or sensitivity to light and sound.^[2]

The brain of the migraineur is sensitive to environmental and sensory stimuli. Headache is initiated or amplified by various triggers resembling bright lights, sounds or alternative sensory stimulation- hunger, stress, workout, air pressure changes, hormonal fluctuations during menstruation, lack of or excess sleep and alcohol or alternative chemical stimulation. The triggering factors may vary from person to person.^[1]

The U.S. Food and Drug Administration on 17 May 2018 approved Erenumab-aooe for the preventive treatment of migraine in adults. The treatment is given by once-monthly self-injections. Erenumab is the first FDA-approved preventive migraine treatment in a very new category of drugs that act by blocking the activity of calcitonin gene-related peptide receptor.^[4]

Older Treatment Options for Migraine

Drugs that are currently taken for the prophylaxis are not specific for migraine but include drugs indicated for other disease such as antiepileptic drugs, β - blockers, and antidepressants. Since these drugs are not migraine-specific, it causes mild to serious side effects. So the use of older and current drugs for migraine prevention is limited by its inadequate efficacy, tolerability and patient adherence.^[5]

- Pain killers should not be overused, as overuse can cause rebound headaches and toxicity.
- Triptans can also cause medication overuse headache. They have the potential to cause the spasm of blood vessels. It should not be used if a person has a heart attack, stroke or peripheral vascular disease.
- Preventive medicines too can have unwanted side effects. These medications do not work immediately and may take weeks to month to get their full effect.

Pain Relieving Medications	Preventive Medications
Pain relievers (Acetaminophen, Ibuprofen)	Beta blockers (Propranolol, Metoprolol) Calcium channel blocker (Flunarizine)
Triptans (Sumatriptan, Rizatriptan, Almotriptan, Naratriptan, Zolmitriptan, Frovatriptan, Eletriptan)	Tricyclic anti-depressants (Amitriptyline)
Ergot derivatives (Ergotamine and Caffeine combination drugs, Dihydroergotamine)	Anti-seizure medications (Sodium Valproate, Topiramate)
Anti- nausea medications (Chlorpromazine, Metoclopramide or Prochlorperazine)	Onabotulinumtoxin A
Glucocorticoids (Prednisone, Dexamethasone)	NSAID (Naproxen)

CGRP and Migraine

CGRP is a member of calcitonine family of peptide which exist in two forms - α -CGRP and β -CGRP. α -CGRP consist of 32 amino acid. It is formed by the tissue-specific splicing of mRNA transcribed from the calcitonin - CGRP gene (*CALCA*) is located in chromosome 11. CGRP is produced in both peripheral and central neurons. It is a potent vasodilator and can function in the transmission of pain.

The peripheral release of CGRP from trigeminal nerve fibers leads to the sensitization of trigeminal nociceptors. Like that, the release of CGRP within the trigeminal nucleus caudalis could also facilitate activation of nociceptive neurons and glial cells. Altogether CGRP has a major role in the development of persistent pain, central sensitization and other events characteristic of migraine pathology.^[6]

CGRP receptors are expressed by multiple cells of different types. They are seen within the nervous, cardiovascular, and immune systems. The CGRP receptor is a heteromeric receptor composed of G protein-coupled receptor called calcitonin receptor-like receptor (CALCRL) and a receptor activity-modifying protein (RAMP1).

Preclinical reports suggests that, during a migraine attack primary sensory neurons in the trigeminal ganglion get activated and release CGRP. This CGRP binds to and activates CGRP receptors located in the menigeal vessels and causes vasodilation. Studies have further explained the role of CGRP in the pathophysiology of migraine. Activation of primary sensory neurons in the trigeminal vascular system in humans can cause the release of CGRP. During some migraine attacks, increased concentrations of CGRP can be found in both saliva and plasma drawn from the external jugular vein.

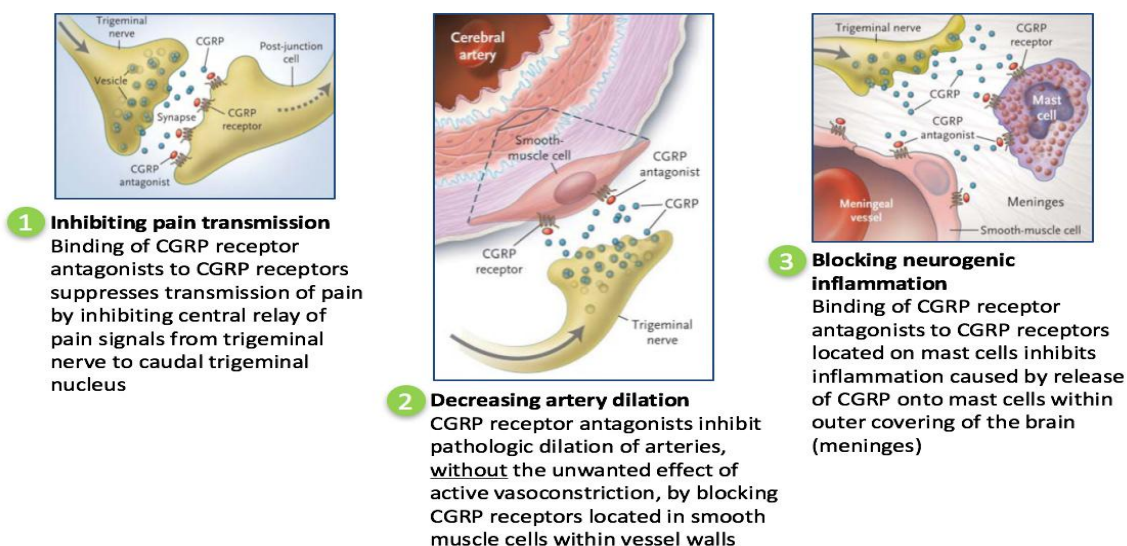
Furthermore, intravenous administration of alpha-CGRP is able to induce headache in individuals susceptible to migraine.^[7] So current researchers is target on CGRP blocking as a primary method for migraine treatment.

CGRP class of drugs can be categorized into 3 types

1. CGRP receptor antibody
2. CGRP antibody
3. CGRP receptor antagonists (gepants)

Mechanism of Action of Cgrp Blocking Drugs

1. Binding of CGRP receptor antagonists to CGRP receptors located on mast cells would inhibit inflammation caused by trigeminal nerve release of CGRP onto mast cells within the meninges and block neurogenic inflammation (Fig 1).
2. By blocking the CGRP receptors, CGRP receptor antagonists would inhibit the pathologic dilation of intracranial arteries without the unwanted effect of active vasoconstriction.
3. Binding of CGRP receptor antagonists to CGRP receptors would suppress the transmission of pain by inhibiting the central relay of pain signals from the trigeminal nerve to caudal trigeminal nucleus.^[8]



Source Durham PL. *N Engl J Med* 2004 350:1073-1075

Fig. 1: Mechanism of action of CGRP drugs.^[6]

CGRP Receptor Antibody: Erenumab

Erenumab is a fully human monoclonal antibody developed to block the pathway of calcitonin gene-related peptide (CGRP). The treatment showed promise in a phase II study in patients with episodic migraine and in a phase II study of patients with chronic migraine, according to Peter Goadsby, MD, Ph.D., Professor of Neurology at the University of California, San Francisco School of Medicine. Phase III study included 955 participants to examine whether erenumab would be an effective preventive treatment for episodic migraine. The investigators then randomized patients in groups of equal size to placebo, 70 mg of subcutaneous erenumab, or 140 mg of subcutaneous erenumab. The treatment period lasted for six months.

During the last three months of treatment, the mean number of monthly migraine days decreased by 3.2 for patients receiving 70 mg of erenumab and by 3.7 for patients receiving 140 mg of erenumab, compared with 1.8 for patients receiving placebo. The difference between the active and control arms was statistically significant. The rate of participants who had a 50% reduction in migraine attacks was 26.6% for controls, 43% for patients receiving the 70-mg dose, and 50% for patients receiving the 140-mg dose.^[6]

US FDA granted the approval as Aimovig to Amgen Ltd. It is injected subcutaneously once in a month. It comes in 2 different types of devices: a single-dose (1 time) prefilled autoinjector or a single-dose (1 time) prefilled syringe with 70 mg of drug.^[9] Erenumab is targeted against CALCRL and RAMP1 in the CGRP binding pocket and fully antagonizes CGRP responses. Clinical trials have shown that erenumab is an effective prophylactic therapy for episodic and chronic migraine.

CGRP Receptor Antagonists: Gepants

Olcgepant was the first non-peptide CGRP receptor antagonist to be discovered. Telcagepant, Ubrogapant, MK-3207, BI 44370 and BMS-927711 were developed subsequently. Currently, Ubrogapant and Rimegepant have shown positive results in phase 2 and phase 3 is ongoing.^[10] If the newer gepants prove to be safe as well as effective, they will provide useful alternatives to triptans, particularly for patients with migraine and cardiovascular risk factors, nonresponders to triptans and patients with triptan-induced medication-overuse headaches.^[11]

Anti-Cgrp Antibody

Several humanized monoclonal anti-CGRP antibodies (Galcanzumab, Eptinezumab and Fremanezumab) are currently undergoing clinical trials and have proved effective for the prevention of episodic and chronic migraine.^[12]

Pros and Cons of Cgrp Blocking

Studies had proved the role of CGRP in migraine pathophysiology. Blocking of CGRP has emerged as a possible mechanism for prevention of migraine attacks. Clinical trials have shown superior efficacy of these drugs. The drugs also have been well tolerated, except in some case of Gepants which showed liver toxicity. The drugs are formulated as monoclonal antibodies and have a high biological half-life. So the frequency of administration of the drug is reduced to once in a month. Also, route of administration is subcutaneous which allow the patient for self-administration.

Since CGRP and its receptors are widely present in the nervous system, they are involved in the various physiological process. Therefore, CGRP blocking may have a risk to cardiovascular patients. CGRP being a vasodilator, long-term blocking and resulted

vasoconstrictions may lead to stroke. In addition, long-term side effects are not known. Animal studies reported that blocking CGRP may induce constipation, imbalance the homeostatic functions of the pituitary hormones or decrease wound healing. But these effects have not been reported in human studies so far.^[13]

Drawbacks

- Even though monoclonal antibodies provide prolonged half-life, the long-term consequence of monoclonal antibodies is yet to be studied.
- Adverse effects from 1 - 10%: Injection site pain (5-6%), Constipation (1-3%), Cramps, muscle spasms (<1 to 3%)
- Unknown risks during pregnancy.
- The price tag is of Erenumab is currently \$575 per injection = \$6,900 per year.
- Any sensitivity to medication could take time to recover due to its long half-life: 28 days.^[14]

CONCLUSION

A migraine is a chronic disorder of the brain with recurrent severe attacks, from one or two times a year to nearly daily. The main feature of these attacks is severe headache. Other common features are nausea, vomiting, sensitivity to light, odors or sounds and are unable to carry on daily activity. The pain relieving medicines and preventive medicines used so far for migraine are not specifically targeted for migraine and therefore they possess various unwanted side effects.

A new class of drug is being introduced to migraine therapy that target the trigeminal sensory neuropeptide - calcitonin gene-related peptide (CGRP) or its receptor. CGRP-related therapies offer wide improvements over existing medications as they're the first to be designed, specifically to act on the trigeminal pain system. They are more specific and they seem to have few or no adverse effects. CGRP receptor antagonists, anti-CGRP antibodies and anti-CGRP receptor antibodies have proved their effectiveness for migraine pain relief.

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