

## CGRP, Current Focus in Migraine

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### Abstract

Migraine commonly affects all aspects of the life of a migraineur which includes their personal and family life, occupational (or academic) aspects and leisure time. The condition affects not only the patient, but also the family, employers and co-workers and society at large. CGRP or calcitonin gene related peptide is a specific target which is now a target for therapy for migraine prophylaxis. The receptors are found all over the central nervous system such as brainstem, cerebral cortex and even the meninges. The newer medications are four monoclonal antibodies and smaller molecules - the gepants. Anti CGPR monoclonal antibodies may reduce the drop out from therapy since the side effect profile is not significant. Besides, the frequency of medication is monthly or quarterly. And the onset of action is in days. The response rate is good. This therapy promises to bring relief to a large segment of patients who had no relief so far from the traditional and less traditional therapies.

**Keywords:** Migraine; CGRP; Gepants; Monoclonal Antibodies; Ubrogепant; Rimegepant; Atogepant; Galcanezumab; Eptinezumab; Erenumab

### Introduction

Migraine commonly affects all aspects of the life of a migraineur which includes their personal and family life, occupational (or academic) aspects and leisure time. The condition affects not only the patient, but also the family, employers and co-workers and society at large. The healthcare system and burden is significant in any system- developed nations or developing nations alike. The impairment includes not only the duration of migraine, but also the interictal period and migraine free periods (because of the migraineurs need and anxiety to avoid the migraine triggers). The quality of life is therefore significantly affected. The cognitive effects are also getting evaluated and specially affect the language aspects, memory (visual and verbal), attention and executive functions [1,2].

### Discussion

Preventive migraine medications are a significant part of therapy as they can not only reduce the frequency but can also reduce the severity and duration of attack by increasing the potency of the therapy for acute episodes of migraine. Yet, the preventive therapy remains grossly underutilized. Among patients who are initiated on prophylaxis, there is lack of compliance to the therapy. The commonest causes of drop out from the therapy include a long duration of onset of efficacy of therapy and frequent medications not to mention the adverse effects associated [3,4].

Strategies for oral prevention include the following:

1. Start with lowest possible dose and titrate slowly.
2. Reach a therapeutic dose.
3. Give an adequate trial of therapy.

4. Optimize drug selection by considering co morbidities.
5. Set realistic goals and expectations such as:
  - a. 50% reduction in attack frequency.
  - b. Decrease in attack severity and/or duration.
  - c. Improved response to acute therapy.
  - d. Benefits may not occur till 8 weeks to 6 months to fully accrue [5].

Guidelines for the migraine prophylaxis have been included by various neurological societies. Some of the chief guidelines include:

1. Severely impaired quality of life, business duties etc, school attendance etc. HIT 6, MIDAS, SF 36, SF 12, MSQ, WHO DAS are some of the common scales used.
2. 2 or more attacks per month. Others include 1 attack per week, or more than 4 days per month. Beyond this point, headache frequency usually increases.
3. A disabling aura.
4. Ineffective treatment for acute episodes.
5. Severe accompanying symptoms.
6. Chronic migraine.
7. When migraine attacks significantly interfere with patient’s daily routine despite treatment of acute episodes.
8. Problems with acute therapy such as contraindications to therapy, failure of the therapy, adverse effects of the therapy, overuse of the medications (more than 10 days per month). Frequent use of acute medicines causes medication overuse headache. Acute therapy often limited to 2 headache days per week on a regular basis.
9. The preference of patients sometimes if the attacks impaired ability to function.
10. Certain conditions of migraine regardless of frequency of attacks need prophylaxis. These include, hemiplegic migraine, migraine with brain stem aura, migraines with prolonged aura, and migrainous infarctions [6,7].

Success of prevention is defined as a decrease in frequency of migraine attacks per month by at least 50% within 3 months [7].

In assessing a patient who presents with migraine a clinician needs to assess the days of migraine, the days in between the pain days and pain free days. The clinician needs to know the way in which a migraine is affecting the patient’s life. As the treatment progresses, the focus should be on disability, impact of migraine and how the treatment improves quality of life. The reduction in the number of headache days should be monitored too (Table 1) [8].

<b>Traditional Migraine Prophylaxis Medications</b>	<b>Monoclonal Antibodies for Migraine Prophylaxis</b>
Not specific to migraine.	Specific to migraine.
Oral formulation.	Subcutaneous or intravenous preparation.
Dose titration needed.	No dose titration needed.
Daily medication intake required.	Monthly or Quarterly intake needed.
Slow onset of action (months).	Fast onset of action (days).
Lower cost.	Higher costs.
Adverse effects common-weight changes, mood changes, drowsiness, fatigue, dizziness, and sexual dysfunction.	Adverse effects are not usual.

**Table 1:** Differences between the prophylaxis medications- traditional and monoclonal antibodies.

CGRP or calcitonin gene related peptide is a specific target which is now a target for therapy for migraine prophylaxis. The receptors are found all over the central nervous system such as brainstem, cerebral cortex and even the meninges. The activation of CGRP and its release leads to neurogenic inflammation and meningeal vessel dilatation [9].

The newer medications are four monoclonal antibodies and smaller molecules - the gepants. They are classified as follows:

1. Small molecules CGRP receptor antagonist- ubrogepant, rimegepant, atogepant.
2. Monoclonal antibodies binding to CGRP- galcanezumab, eptinezumab.
3. Monoclonal antibodies binding to CGRP receptors- erenumab [10].

The gepants (such as telcagepant, olcegepant, MK 3207, ubrogepant, atogepant, BHV 3500) are amongst the first molecules that were created against the CGRP receptors. They are small molecules and may cross the blood brain barrier in minimal amounts. They are useful in the termination of the acute migraine headaches. Hepatotoxicity results if they are tried in daily doses for prophylaxis therapy of migraine. They have a higher side effect profile [11].

Monoclonal antibodies are the other forms of medication that are under evaluation. They have gradually evolved- from murine models to chimeric forms to humanized forms to human antibodies. Their immunogenicity has reduced as they evolved, from being safe in 65% in the chimeric form to more than 95% and 100% respectively in humanized and human antibodies respectively. In humanized forms, neutralizing antibodies may still be triggered. These do not cross the blood brain barrier (Table 2) and this suggests that they act via action on the peripheral activity of these molecules, possibly on trigeminal system or the meninges, both of which are present outside of the blood brain barrier. Trigeminal ganglion is a possible key regulator in headache. The CGRP receptor binding sites and protein expression of CGRP and its receptor are found in the trigeminal ganglion. CGRP is expressed in small or medium sized cells and is thin pearl like fibres among the trigeminal cells. This would also mean a possibly lower incidence of the central nervous system related side effects. It was previously considered that the blood brain barrier may open up temporarily that may allow passage of these antibodies resulting in their effects. However it has been found that blood brain barrier remains unchanged even when there is an episode of migraine headache. They do not result in hepatotoxicity since they are eliminated by the reticular activating system. They are useful in the migraine prophylaxis [10].

Monoclonal Antibodies	Small Molecules
Size of 150 kD.	Size < 1 kD.
Not accumulated in liver.	Liver coenzymes can increase.
Injectable mode of administration.	Oral mode of administration.
Do not enter the cells or the blood brain barrier.	Can enter cells and blood brain barrier.
Half-life 1 - 4 weeks.	Half-life of minutes to hours.
Manufactured in tissue culture.	Chemically synthesized.
Consistent pK variability between individuals.	Variable oral absorption and hepatic elimination.

**Table 2:** Differences between monoclonal antibodies and smaller molecules-gepants.

Eptinezumab, Erenumab, Fremanezumab, Galcanezumab (Table 3) are all useful monoclonal antibodies. They are useful in migraine therapy, both acute and chronic, with and without medication overuse headache. They have a quick onset of approximately 1 week and a significant clinical effect within the first month of onset of therapy. Their safety, tolerability and adverse effect profile is comparable to that of a placebo. They yield a high response rate. They significantly reduce the mean monthly migraine days and reduce the need for acute migraine termination therapy. They can be prescribed with older migraine prophylaxis therapy such as beta blockers. They have a reduced potential for drug-drug interaction [12].

Drug	Type of Antibody	Useful In*	Mechanism	Frequency	Dose	Side effects
Erenumab	Human	EM, CM	Anti CGRP receptor	S/C Monthly	70 or 140 mg	Nasopharyngitis and URTI, fatigue, headache, sinusitis, injection site pain, nausea
Galcanezumab	Humanized	EM, CM, CI M	Anti CGRP	S/C Monthly	120 or 240 mg	URTI, injection site pain
Eptinezumab	Humanized	EM, CM	Anti CGRP	IV Quarterly	100 or 300 mg	URTI, un, fatigue
Remanezumab	Humanized	EM, CM, CI M	Anti CGRP	S/C Monthly, IV Quarterly		Injection site pain, erythema, pruritus, induration

**Table 3:** Comparison of the CGRP monoclonal antibodies.

\*EM: Episodic Migraine; CM: Chronic Migraine; CI M: Cluster Headache.

Some previously used medications like capsaicin and cannabinoids have also been shown to affect CGRP, although indirectly. It suffices to say that while “newer” options (which are the focus of this review) are always beneficial, ‘older’ options should always be considered when possible and beneficial [13].

## Conclusion

Anti CGPR monoclonal antibodies may reduce the drop out from therapy since the side effect profile is not significant. Besides, the frequency of medication is monthly or quarterly. And the onset of action is in days. The response rate is good. While 50% patients yield more than 50% reduction, some super responders show a 75% (in 25% patients) to 100% (in 10 - 15% patients) reduction in migraine days [10]. This therapy promises to bring relief to a large segment of patients who had no relief so far from the traditional and less traditional therapies.

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