Narrative Review

Advances in CGRP Monoclonal Antibodies as Migraine Therapy: A Narrative Review

Suruchi Aditya, Aditya Rattan[1]

Department of Pharmacology, Dr. Harvansh Singh Judge Institute of Dental Sciences, Panjab University, Chandigarh, India, [1]Cardiology Clinic, Heart Line, Panchkula, Haryana, India

Abstract

Migraine is a potentially disabling disorder, yet it remains underdiagnosed and undertreated. The release of the neuropeptide calcitonin gene-related peptide (CGRP) in the trigemino-cerebrovascular system plays a vital role in the evolution of migraine. It enhances peripheral sensitization by mediating neurogenic inflammation and also influences central sensitization. The majority of the drug classes available for migraine prophylaxis are nonspecific and associated with numerous side effects and drug interactions. Anti-CGRP monoclonal antibodies (mAb) are an innovative therapeutic class that fulfills the need for more efficacious and tolerable preventive therapy. While erenumab is a mAb to the CGRP receptor, eptinezumab, fremanezumab, and galcanezumab bind to the CGRP molecule. They decrease the number of headache days and improve disability. Upper respiratory tract infection, nausea, constipation, pain at the site of injection, and fatigue are the associated side effects. CGRP mAbs are an excellent advancement in translational research and are a promising addition in migraine therapy. This article discusses the recent advances in the development of the CGRP mAbs.

Keywords: Anti-CGRP antibody, CGRP, calcitonin gene-related peptide receptors, eptinezumab, erenumab, fremanezumab, galcanezumab, headache, migraine, monoclonal antibodies

Address for correspondence: Dr. Suruchi Aditya, Department of Pharmacology, Dr. Harvansh Singh Judge Institute of Dental Sciences, Panjab University, Chandigarh, India.
E-mail: suruchiaditya@rediffmail.com

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INTRODUCTION

Migraine, an important cause of disability, is a significant public health concern affecting >1 billion people worldwide.[1] The prevalence of migraine has been reported to largely vary across countries and epidemiological studies from 2.6% to 21.7%.[2] Being aged 25–55 and female gender are reported to be predisposing factors of migraine.[3] The burden of migraine is also found to be increasing among students and veterans.[4,5] More than half of migraineurs are functionally impaired to a severe degree and the resultant lost productivity at work, home, and social context contributes to substantial socioeconomic burden.[6]

The moderate to severe unilateral throbbing headache, worsened by movement is a characteristic attribute. Other features are nausea, appetite loss, vomiting, photophobia, sensitivity to noise and hypersensitivity to certain smells. Bilateral headache and pain involving the face or the whole body have also been observed.[7] Alcohol, certain foods, seasonal changes, light, noises, smells, stress, menstruation,

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and delayed meals trigger and/or aggravate migraine attacks.[8] A few migraineurs experience aura, defined as characteristic visual disturbances that precede, accompany, or follow the pain. Sensory aura comprises tingling and numbness that may spread over the limbs and face.[7]

Migraine is categorized as episodic or chronic. According to the International Headache Society, a patient with ≤14 headache days in a month is labeled to have episodic migraine (EM), while ≥15 headache days per month for >3 months with ≥8 headaches that fulfill the criteria for migraine classify for a label of chronic migraine (CM).[9]Progression to CM may be accelerated by concomitant low socioeconomic status, obesity, medication overuse (MO), unsuccessful treatment, comorbid pain, female gender, and stress.[10]

The pathophysiology of migraine is regarded as a genetically predisposed hypersensitivity of the central nervous system (CNS) to triggers, both inside and outside the brain. Functional changes observed in the brain of CM patients are hyperexcitability of the cortex, sensitization of the trigemino–thalamic area, and flawed descending pain modulation.[11] Recent evidence disproves the vascular hypothesis, which claims that headache is caused by dilation of blood vessels (dural and extracranial). Vasodilatation is now considered as a consequence rather than the cause.[12] Migraine is a neurovascular disorder, with a central role of the trigeminovascular system (TVS) in the causation of pain.

Calcitonin-like gene receptor peptide (CGRP), the body's strongest vasodilator, is abundant in the neurons of trigeminal ganglia (TG) and the trigeminal nerve.[13] It is stored in vesicles at nerve terminals and released from perivascular sensory afferent nerves, dural mast cells, Schwann cells, and satellite glia in the TVS.[14] After its release, it is carried to the jugular vein through the sagittal sinus.[15] Research by Goadsby and Edvinsson led to notable findings confirming that CGRP is a critical molecule in migraine, shifting the focus away from substance *P* or neurokinin A.[16] During migraine attacks, the levels of CGRP increase in the cranial circulation and saliva.[16] Blood levels of CGRP during the interictal period are significantly higher, suggesting that it may be used as a biomarker for disease activity.[17] In migraine patients, intravenous infusion of recombinant human CGRP 2 μg/min over 20 min can start a headache that is very similar to a spontaneous attack.[18] Raised CGRP serum concentrations can be brought to baseline levels with the use of triptan.[16] The most convincing reasoning for the assertion is that anti-CGRP therapeutics (ligand and receptor antagonists) are effective in both the acute and preventive treatment of migraine.[19]

US Food and Drug Administration (FDA) has approved four CGRP mAbs –erenumab, fremanezumab, galcanezumab (in 2018), and eptinezumab (in 2020)–offering a novel therapeutic option for chronic migraineurs. Aptly called disease-modifying migraine drugs, they represent the first disease-specific preventive migraine therapies.[19]

This narrative review presents an update on the role of CGRP in migraine and CGRP antibodies along with their clinical studies in the prevention of migraine. For the collection of relevant studies, Medline (through PubMed), EMBASE, Cochrane databases, Medscape, Scopus, and clinicaltrials.gov were searched using the search terms "migraine", "CGRP", "monoclonal antibodies (mAbs) to CGRP", "erenumab", "eptinezumab", "fremanezumab", "galcanezumab" and "pathophysiology of migraine". Journal articles published in English from 2010 to 2021 that discussed the role of CGRP in the pathogenesis of migraine, CGRP antibodies, and their clinical trials, were screened.

CURRENT PHARMACOTHERAPY OF MIGRAINE AND ITS DRAWBACKS

Pharmacological treatment aims to reduce headache severity and frequency and manage comorbidities. The choice of pharmacological agent is based on the migraine headache frequency (EM or CM), degree of impairment, history of drugs used in the past, tolerability, comorbid diseases, and patient bias.[20]

At present, nonsteroidal anti-inflammatory drugs, triptans, antiemetics, and combinations of analgesics are recommended for the treatment of acute attack. All medications used in acute cases may lead to the complication of MO headache or rebound headache, which has a frequency of ≥15 days in a month while using the anti-migraine drug for ≥10 days per month for 3 months.[21] Clinicians discourage the use of barbiturates and ergotamine-related drugs due to the risk of side effects and/or dependence.[15] Opioids prevent reversal of central sensitization, are pro-nociceptive, and affect triptan effectiveness.[22] Moreover, the use of polytherapy to treat comorbidities such as cardiovascular and psychiatric diseases may hinder the actions of anti-migraine drugs.[23]

Drug classes available for prophylaxis are calcium channel blockers (flunarizine, verapamil), antidepressants (tricyclic antidepressant: amitriptyline), antiepileptic

drugs (topiramate, sodium valproate, divalproex sodium), antihypertensives (beta blockers-metoprolol, propranolol, timolol), and onabotulinum toxin A. Topiramate has side effects that limit its long-term use.[24,25] Onabotulinum toxin A is administered to 31–39 sites every 12 weeks.[25] These classes of medications were originally developed for other conditions and have multiple therapeutic targets.[9] The majority of these drugs have drawbacks of modest efficacy, poor tolerability, and inconsistent response.[15] Approximately 40% of persons who have EM would benefit from prophylactic therapy; however,<15% of the patients continue its regular use.[24] Poor adherence due to adverse events and tolerance are grave issues that point to an unmet need for specific prophylactic agents.[26] Acknowledging previous ineffective attempts of treatment, patients with "refractory" migraine form a complex subset for whom finding a suitable medication is a challenge. The European Headache Federation labels the failure to respond to three drug classes as resistant migraine, and the failure of all drug classes with established evidence in migraine as refractory migraine.[27]

ROLE OF CGRP IN THE PATHOPHYSIOLOGY OF MIGRAINE

Calcitonin, α and β CGRP, amylin, adrenomedullin, and adrenomedullin 2 make up the CGRP family. β CGRP differs from α CGRP by 1 to 3 amino acids in different species and is expressed exclusively in the enteric sensory neurons.[28] CGRP receptors are heteromers, comprising the calcitonin receptor-like receptor (CLR), receptor activity-modifying protein 1(RAMP1) and the receptor component protein. CGRP binds in a pocket made by heteromers CLR and RAMP1.[29]

In the CNS, CGRP is expressed in the neurons of the cerebral cortex, hippocampus, substantia nigra, cerebellum, brainstem, thalamic and hypothalamic nuclei. CGRP and its receptor largely have a common distribution, but their expression is also discrete in many areas.[14,30] It is intriguing to note that while CGRP-expressing neurons are small to medium in diameter (C fibers), its receptors (colocalized CLR and RAMP1) are found on larger neurons, myelinated Aδ fibers, and satellite glial cells.[30] In conformity with the differential location of CGRP and its receptors, it was observed that CGRP antibody fremanezumab selectively inhibited the myelinated Aδ fibers but not the C fibers.[31] Whether this difference in site of action contributes to any differential effect between antibody to the peptide and antibody to the receptor remains to be clarified.

The TVS, abundant in CGRP, consists of sensory pseudounipolar neurons of the TG with first-order afferent neurons innervating the pial and dural meningeal vessels, and efferent projections synapsing with second-order neurons in the trigeminal nucleus caudalis.[32] During activation of the TVS, CGRP leads to neurogenic inflammation in the meningeal vasculature and mast cell degranulation resulting in peripheral sensitization, which is an enhanced afferent activity of nociceptive neurons to a stimulus.[33] It is responsible for intracranial hypersensitivity (patient experiences pain aggravation on physical exertion due to fluctuations in intracranial pressure) and the throbbing headache.

Russo *et al.* have proposed that CGRP enhances neural sensitization through CGRP-triggered feedback loops.[34] Firstly, endogenously generated nitric oxide (NO) can form nitroxyl (HNO) with hydrogen sulfide, to cause CGRP release from trigeminal dural fibers.[35] Secondly, CGRP increases purinergic P2X3 gene expression in nociceptive TG neurons, furthering CGRP release.[36] Finally, CGRP can induce its own synthesis in TG neurons by paracrine and autocrine mechanisms.[13] In addition, studies point to a role of the neuron–glia interplay: the release of CGRP activates the satellite glia cells, which release proinflammatory cytokines and results in a positive feedback loop.[32,37]

The information from the second-order neurons is relayed to the third-order neurons in the posterior thalamus and hypothalamus. Thalamocortical projections convey the craniovascular nociceptive signals to neurons in the cortical regions such as visual, motor, auditory, and somatosensory.[32] Long-term changes suggest that CGRP may activate transcription factors and pronociceptive proteins, ultimately enhancing nociception.[29] It was shown to induce long term potentiation in the anterior cingulate cortex, where it enhanced synaptic transmission through glutamate N-methyl D-aspartate receptors.[38] It has been proposed that peripherally situated CGRP leads to distant amplification of central neuronal circuits, leading to a decreased capability to control the pain.[15] Central sensitization of nociceptive signals leads to autonomic, cognitive, and affective symptoms.[39] It may lead to cutaneous allodynia when even a non-noxious stimuli is perceived as painful; in migraineurs, pain can be evoked by light touch during brushing hair or taking bath.[39] More corroborative evidence will unravel the role of antidromic release of CGRP in mediating central sensitization. The complex interplay between meningeal vasculature, meningeal milieu, and trigeminal afferents sustains the sensitization but the role of CGRP in modulating the ascending transmission of nociceptive signaling in migraine remains to be elucidated.

CGRP ANTAGONISTS

The actions of CGRP can be blocked using many approaches such as non-peptide CGRP inhibitors called "gepants" and mAbs. The site of action of both gepants and mAbs is outside the blood-brain barrier.[15]

Gepants

Olcegepant and telcagepant, were associated with liver toxicity on repeated use.[26] Safety data for ubrogepant, atogepant, and rimegepant do not disclose notable risk for hepatotoxicity. Ubrogepant (oral) and rimegepant (orally disintegrating tablets) were approved by the FDA for the treatment of acute migraine in 2019 and 2020, respectively.

CGRP monoclonal antibodies

mAbs directed at CGRP molecule (eptinezumab, fremanezumab, and galcanezumab), and mAbs for CGRP receptor (erenumab) are in clinical use.[19,40,41]

CLINICAL STUDIES WITH MONOCLONAL ANTIBODIES

Erenumab

Erenumab, a CGRP receptor blocker, is a humanized IgG2 mAb that has been found to have an early-onset efficacy. In one trial, patients who received erenumab (140 mg) reported a ≥50% decrease in the migraine days/week in the first week of use.[42] In a study from Italy, treatment with erenumab for 1 month reduced the monthly migraine days (MMDs) in patients with CM by 12.2 days, in addition to resulting in reduced use of medication, intensity of pain, and disability.[43] Two phase III randomized controlled trials (RCTs) have evaluated the efficacy of subcutaneously administered erenumab (70 mg and 140 mg monthly) in the prevention of EM and found ≥50% reduction in MMDs in a significant proportion of patients [Table 1].[44,45] A Phase IIIb trial (LIBERTY) that included EM patients with a history of 2–4 preventive drug failures verified the superiority of erenumab 140 mg.[55] In a real-world audit in patients with medically refractory CM, 62% of the patients obtained a 50% reduction in MMD at 6 months with the use of erenumab140 mg.[27] In a retrospective analysis, patients unresponsive to or with contraindications to six preventive medications (five orally administered drugs [beta-blockers, flunarizine, topiramate, amitriptyline, valproate] and onabotulinum toxin A) showed a reduction of 4.7 MMD over three treatment cycles.[56] In the subset of patients with MO, the use of erenumab lead to a reduction of 6.6 MMDs compared with reduction of 3.5 MMDs with placebo in a 3-month study.[57] In the interim safety analysis of a 5-year open-label study, erenumab was found to be a safe drug.[58]

Eptinezumab

Eptinezumab, a humanized IgG1 mAb that targets both the α and β isoforms of CGRP, is the only CGRP mAb that is administered intravenously quarterly.[59]

Two Phase III RCTs have assessed the efficacy of eptinezumab as a prophylactic treatment for both EM and CM and significant reductions in the number of MMDs and ≥50% reduction in MMDs were noted [Table 1].[46,47] In the trial that included EM patients, eptinezumab 100 mg and 300 mg reduced the probability of experiencing migraine on the first day after infusion by >50%.[46] In a 1 year, open-label safety study, the use of eptinezumab 300 mg in patients with CM reduced migraine-associated disability and improved functionality.[60]

Fremanezumab

Fremanezumab is a humanized IgG2 mAb that can bind to both the α and β isoforms of CGRP. Trials have evaluated its use in the prevention of EM at 225 mg (subcutaneous) monthly and 675 mg quarterly (single high dose; placebo at weeks 4 and 8)[48] and in the prevention of CM at 675 mg quarterly (placebo at weeks 4 and 8) and 225 mg monthly (with a one-time high dose of 675 mg at start) and found significant reductions in the number of MMDs and ≥ 50% reduction in MMDs [Table 1].[49] In the FOCUS trial, fremanezumab was effective in migraineurs unresponsive to up to four classes of preventive agents. A notable improvement in depressive symptoms for patients with comorbid depression was observed.[50] In a long-term study with fremanezumab, in the EM group, more than one-third of patients had a ≥75% reduction in MMD, while one-fifth attained 100% reduction.[51]

Galcanezumab

Galcanezumab is a humanized IgG4 mAb that binds to both the α and β forms of CGRP.[40] Trials have demonstrated the effectiveness of subcutaneous monthly doses of 120 mg (with a single loading dose of 240 mg) and 240 mg as a prophylactic therapy for both EM and CM [Table 1].[52-54,61] In a year-long study, galcanezumab was found to improve functional impairment and reduce disability.[62,63] In patients with EM or CM with a documented failure of two to four preventive medications, galcanezumab group reported 4.1 fewer MMDs from baseline compared with one fewer than baseline with placebo.[64]

Ongoing phase 3 and phase 4 studies are evaluating the efficacy and safety of the mAbs in children, concomitant depression, vestibular migraine, and cluster headache.[65]

Table 1: Phase 3 clinical trials with calcitonin gene related peptide

Antibody	Name of trial	Number of patients	Setting	Dose of drug	Duration of trial	Primary end point (decrease in MMDs)	Secondary endpoint (% of patients with ≥50% reduction in MMDs)
Erenumab	STRIVE[44]	577	EM	70 mg	3 months	2.9*	39.7*
				Placebo		1.8	29.5
	ARISE[45]	955	EM	70 mg	3 months	3.2*	43.3*
				140 mg		3.7*	50*
				Placebo		1.8	26.6
Eptinezumab	PROMISE-1[46]	888	EM	30 mg	3 months	4.0*	50.2*
				100 mg		3.9*	49.8*
				300 mg		4.3*	56.3*
				Placebo		3.2	37.4
	PROMISE-2[47] Months 4-6	1072	EM	100 mg	3 months	8.1*	60.7*
				300 mg		8.8*	63.4*
				Placebo		6.1	44.5
Fremanezumab	HALO EM[48]	875	EM	Monthly	3 months	3.7*	47.7*
				Single		3.4*	44.4*
				High dose		2.2	27.9
				Placebo			
	HALO CM[49]	1130	CM	Monthly	3 months	4.6*	41*
				Quarterly		4.3*	38*
				Placebo		2.5	18
	FOCUS[9,50] (EM/CM patients with inadequate response to 2-4 classes of medications)			Monthly	12 weeks	4.1*	34*
				Quarterly		3.7*	34*
				Placebo		0.6	9
	HALO LTS[9,51]		EM	Monthly	12 months	8.0	68
				Quarterly		7.2	66
			CM	Monthly		5.1	57
				Quarterly		5.2	53
Galcanezumab	EVOLVE-1[52]	1671	EM	120 mg	6 months	4.7*	62.3*
				240 mg		4.6*	60.9*
				Placebo		2.8	38.6
	EVOLVE-2[53] Phase 2b	915	EM	120 mg	6 months	4.3*	59.3*
				240 mg		4.2*	56.5*
				Placebo		2.3	36
	REGAIN[54]	1113	CM	120 mg	3 months	4.8*	27.6*
				240 mg		4.6*	27.5*
				Placebo		2.7	15.4

*Statistically significant difference ($P<0.01$) when compared with placebo. Primary endpoint: Decrease in number of MMD compared with baseline; Secondary endpoint: Percentage of patients who achieved a ≥50% reduction in MMD. MMD - Monthly migraine days; EM - Episodic migraine; CM - Chronic migraine

Advantages and disadvantages of monoclonal antibodies

Excellent patient response and safety profile make anti-CGRP mAbs a great leap forward in migraine therapy. They are the first mechanism-based migraine-specific drugs and have shown fast response and better compliance than other currently used medications. An effective prophylactic anti-migraine drug lowers the headache frequency by ≥50% in 3 months.[21] About 48%–62% patients have shown a >50% reduction in MMD with the use of these mAbs.[40] In one study, patients with a history of a positive response to a triptan at any time had a higher probability to respond to erenumab compared with triptan non-responders.[66] Data from trials in resistant and refractory CM show that mAbs may be more useful in patients with inadequate response, poor tolerability, or contraindications than other prophylactic agents.[27,50,56,64] Another advantage is that the therapeutic effect lasts long after stopping the drug.[67] In addition, CGRP antibodies show a low potential for drug–drug interactions, as there is an absence of hepatic metabolism or renal clearance. They are degraded by proteolysis to smaller peptides and amino acids that does not involve the liver.[68,69] A meta-analysis reported that compared with topiramate, anti-CGRP mAbs showed a stronger placebo and weaker nocebo phenomena in the RCTs in the prophylaxis of EM. The difference between the anti-CGRP mAbs and onabotulinum toxin A in the treatment of CM was not significant.[70]

Parenteral administration carries the disadvantage of requiring the help of medical staff. This can increase the placebo response as well as the risk of initiating an infection. Besides local site reactions, there is also an issue of systemic immunological effects. Although these mAbs do not have a target within the immune system,

antidrug antibodies may decrease effectiveness or start immunoallergic reactions.[17] Favorably, such an effect has not been seen in trials. Use in wound healing is cautioned, as CGRP promotes keratinocytes, helps in increasing revascularization, and decreases macrophage invasion.[41] As CGRP is a multifunctional neuropeptide involved in the maintenance of physiological processes, side effects related to cardiovascular and CNS are being monitored in the post-marketing surveillance. The FDA recently added a label change stating the possibility of development of hypertension or worsening of pre-existing hypertension in patients starting erenumab.[25] Constipation has been commonly reported in recent trials as well as in the real-world experience.[27,67] Long-term risks, especially in comorbid conditions, will be revealed through use in the future.[41] The risks have also not yet been assessed in population subsets such as in children and pregnant and lactating women. Antibodies should not be used in coronary heart disease, ischemic stroke, subarachnoid hemorrhage, or peripheral arterial occlusive disease. They are contraindicated in patients with inflammatory bowel disease, pulmonary hypertension, chronic obstructive pulmonary disease, Raynaud's syndrome, and wound-healing disorders as well as in patients who have received transplantation.[24]

CGRP mAbs are costly, but they provide more migraine-free days and increase health-related quality of life when compared with no treatment.[68] mAbs reduce migraine-related direct and indirect costs, with each migraine-free day having been estimated to save approximate between $130 and $340.[71,72]

CURRENT SCENARIO OF CGRP MONOCLONAL ANTIBODIES IN MIGRAINE THERAPY

American Headache Society guidelines state that mAbs treatment with established dosing may be used in adults demonstrating intolerance or unresponsiveness to at least two well-established prophylactic agents after 6 weeks of treatment initiation.[68] Evaluation of the treatment should be done after 3 months for drugs given monthly and after 6 months for those administered quarterly. In addition, patient feedback on functional ability and quality of life should be taken into consideration.[68] Data regarding interchanging CGRP mAbs in unresponsive patients is inconclusive.[73]

Besides the use of drugs, managing CM involves patient education, lifestyle changes, avoiding MO, and treating associated comorbidities.[11] In patients where most of the available drugs are contraindicated, such as overweight/obese patients with comorbid depression, CGRP mAbs maybe used as the first-line treatment together with onabotulinum toxin A. For others, failure with onabotulinum toxin A maybe a precondition before using CGRP mAbs. Treatment with erenumab for 9 months in onabotulinum toxin A-resistant CM patients has been found to reduce pain and medication use and improve the quality of life.[74] Use of oral rimegepant for the acute treatment of migraine was found to be safe and tolerable in patients concomitantly receiving erenumab, fremanezumab, or galcanezumab as a prophylactic treatment of migraine.[75] Real-world experience will disclose more information on their safety and efficacy, as these mAbs will be combined with drugs of different classes.

CONCLUSION

Migraine is a highly prevalent disabling disease occurring in the most productive years of life. CGRP plays a central role in the neurobiology of migraine headaches. Anti-CGRP mAbs represent the first prophylactic therapy designed specifically for migraine. CGRP mAbs show advantages of fast onset, good patient response, acceptable safety profile, less off-target effects, and long duration of action that allows once a month administration. Considering the limitations of the currently available agents, these injectable biologics offer exciting prospects in migraine prevention.

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REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858.
2. Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? Brain Behav 2018;8:e00950.
3. Pezzini A, Del Zotto E, Giossi A, Volonghi I, Costa P, Dalla Volta G, *et al.* The migraine-ischemic stroke relation in young adults. Stroke Res Treat 2010;2011:304921.
4. Altalib HH, Fenton BT, Sico J, Goulet JL, Bathulapalli H, Mohammad A, *et al.* Increase in migraine diagnoses and guideline-concordant treatment in veterans, 2004-2012. Cephalalgia 2017;37:3-10.
5. Sixsmith E, Starr M. Managing childhood migraine. Aust Fam Physician 2015;44:356-9.
6. Steiner TJ, Stovner LJ, Katsarava Z, Lainez JM, Lampl C, Lantéri-Minet M, *et al.* The impact of headache in Europe: Principal results of the Eurolight project. J Headache Pain 2014;15:31.

7. Weatherall MW. The diagnosis and treatment of chronic migraine. Ther Adv Chronic Dis 2015;6:115-23.
8. Hoffmann J, Recober A. Migraine and triggers: Post hoc ergo propter hoc? Curr Pain Headache Rep 2013;17:370.
9. Friedman DI, Cohen JM. Fremanezumab: A disease-specific option for the preventive treatment of migraine, including difficult-to-treat migraine. Emerg Top Life Sci 2020;4:179-90.
10. Agostoni EC, Barbanti P, Calabresi P, Colombo B, Cortelli P, Frediani F, *et al.* Current and emerging evidence-based treatment options in chronic migraine: A narrative review. J Headache Pain 2019;20:92.
11. Andreou AP, Fuccaro M, Lambru G. The role of erenumab in the treatment of migraine. Ther Adv Neurol Disord 2020;13:1756286420927119.
12. Charles A. Vasodilation out of the picture as a cause of migraine headache. Lancet Neurol 2013;12:419-20.
13. Russo AF. Calcitonin gene-related peptide (CGRP): A new target for migraine. Annu Rev Pharmacol Toxicol 2015;55:533-52.
14. Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain 2017;158:543-59.
15. Benemei S, Cortese F, Labastida-Ramírez A, Marchese F, Pellesi L, Romoli M, *et al.* Triptans and CGRP blockade – Impact on the cranial vasculature. J Headache Pain 2017;18:103.
16. Durham PL, Vause CV. Calcitonin gene-related peptide (CGRP) receptor antagonists in the treatment of migraine. CNS Drugs 2010;24:539-48.
17. Cernuda-Morollón E, Larrosa D, Ramón C, Vega J, Martínez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology 2013;81:1191-6.
18. Levin M, Silberstein SD, Gilbert R, Lucas S, Munsie L, Garrelts A, *et al.* Basic considerations for the use of monoclonal antibodies in migraine. Headache 2018;58:1689-96.
19. Martelletti P, Edvinsson L, Ashina M. Shaping the future of migraine targeting calcitonin-gene-related-peptide with the disease-modifying migraine drugs (DMMDs). J Headache Pain 2019;20:60.
20. Silberstein SD. Preventive migraine treatment. Continuum (Minneap Minn) 2015;21:973-89.
21. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
22. Tepper SJ. Opioids should not be used in migraine. Headache 2012;52 Suppl 1:30-4.
23. Pomes LM, Guglielmetti M, Bertamino E, Simmaco M, Borro M, Martelletti P. Optimising migraine treatment: From drug-drug interactions to personalized medicine. J Headache Pain 2019;20:56.
24. Diener HC, Förderreuther S, Gaul C, Giese F, Hamann T, Holle-Lee D, *et al.* Prevention of migraine with monoclonal antibodies against CGRP or the CGRP receptor: Addition to the S1 guideline: Therapy of migraine attacks and prevention of migraine. Recommendations of the Germany society of neurology and the German migraine and headache society. Neurol Res Pract 2020;2:11.
25. Blumenfeld AM. Clinician-patient dialogue about preventive chronic migraine treatment. J Prim Care Community Health 2020;11:2150132720959935.
26. Sacco S, Bendtsen L, Ashina M, Reuter U, Terwindt G, Mitsikostas DD, *et al.* European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain 2019;20:6.
27. Lambru G, Hill B, Murphy M, Tylova I, Andreou AP. A prospective real-world analysis of erenumab in refractory chronic migraine. J Headache Pain 2020;21:61.
28. Hay DL, Garelja ML, Poyner DR, Walker CS. Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. Br J Pharmacol 2018;175:3-17.
29. Messlinger K. The big CGRP flood – Sources, sinks and signalling sites in the trigeminovascular system. J Headache Pain 2018;19:22.
30. Edvinsson L, Grell AS, Warfvinge K. Expression of the CGRP family of neuropeptides and their receptors in the trigeminal ganglion. J Mol Neurosci 2020;70:930-44.
31. Melo-Carrillo A, Strassman AM, Nir RR, Schain AJ, Noseda R, Stratton J, *et al.* Fremanezumab-A humanized monoclonal anti-CGRP antibody-inhibits thinly myelinated (Aδ) but not unmyelinated (C) meningeal nociceptors. J Neurosci 2017;37:10587-96.
32. Bigal ME, Walter S, Rapoport AM. Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. Headache 2013;53:1230-44.
33. Tajti J, Szok D, Majláth Z, Tuka B, Csáti A, Vécsei L. Migraine and neuropeptides. Neuropeptides 2015;52:19-30.
34. Russo AF. CGRP as a neuropeptide in migraine: Lessons from mice. Br J Clin Pharmacol 2015;80:403-14.
35. Dux M, Will C, Vogler B, Filipovic MR, Messlinger K. Meningeal blood flow is controlled by H2 S-NO crosstalk activating a HNO-TRPA1-CGRP signalling pathway. Br J Pharmacol 2016;173:431-45.
36. Panconesi A, Bartolozzi ML, Guidi L. Migraine pain: Reflections against vasodilatation. J Headache Pain 2009;10:317-25.
37. Thalakoti S, Patil VV, Damodaram S, Vause CV, Langford LE, Freeman SE, *et al.* Neuron-glia signaling in trigeminal ganglion: Implications for migraine pathology. Headache 2007;47:1008-23.
38. Li XH, Matsuura T, Liu RH, Xue M, Zhuo M. Calcitonin gene-related peptide potentiated the excitatory transmission and network propagation in the anterior cingulate cortex of adult mice. Mol Pain 2019;15:1744806919832718.
39. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: A disorder of sensory processing. Physiol Rev 2017;97:553-622.
40. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: New drugs, new hope? J Headache Pain 2019;20:37.
41. Deen M, Correnti E, Kamm K, Kelderman T, Papetti L, Rubio-Beltrán E, *et al.* Blocking CGRP in migraine patients – A review of pros and cons. J Headache Pain 2017;18:96.
42. Schwedt T, Reuter U, Tepper S, Ashina M, Kudrow D, Broessner G, *et al.* Early onset of efficacy with erenumab in patients with episodic and chronic migraine. J Headache Pain 2018;19:92.
43. Barbanti P, Aurilia C, Egeo G, Fofi L. Erenumab: From scientific evidence to clinical practice-the first Italian real-life data. Neurol Sci 2019;40:177-9.
44. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, *et al.* A controlled trial of erenumab for episodic migraine. N Engl J Med 2017;377:2123-32.
45. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, *et al.* ARISE: A phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38:1026-37.
46. Saper J, Lipton R, Kudrow D, Hirman J, Dodick D, Silberstein S, *et al.* Primary results of PROMISE -1(Prevention of Migraine via intravenous eptinezumab safety and efficacy-1) trial: A phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for prevention of frequent episodic migraines (S20.001). Neurology 2018;90 15 Suppl:S20.
47. Kudrow D, Lipton R, Silberstein S, Cady R, Schaeffler B, Biondi D, *et al.* Eptinezumab for prevention of chronic migraine: Results of 2 infusions in the phase 3 PROMISE -2(Prevention of Migraine via intravenous eptinezumab safety and efficacy-2) trial (P2.10-006). Neurology 2019;92 15 Suppl:P2.10-006.
48. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, *et al.* Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized clinical trial. JAMA 2018;319:1999-2008.
49. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, *et al.* Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 2017;377:2113-22.
50. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, *et al.*

Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): A randomised, double-blind, placebo-controlled, phase 3b trial. Lancet 2019;394:1030-40.
51. Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R, *et al*. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. Neurology 2020;95:e2487-99.
52. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. JAMA Neurol 2018;75:1080-8.
53. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia 2018;38:1442-54.
54. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e2211-21.
55. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, *et al*. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: A randomised, double-blind, placebo-controlled, phase 3b study. Lancet 2018;392:2280-7.
56. Raffaelli B, Kalantzis R, Mecklenburg J, Overeem LH, Neeb L, Gendolla A, *et al*. Erenumab in chronic migraine patients who previously failed five first-line oral prophylactics and onabotulinumtoxina: A dual-center retrospective observational study. Front Neurol 2020;11:417.
57. Tepper SJ, Diener HC, Ashina M, Brandes JL, Friedman DI, Reuter U, *et al*. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. Neurology 2019;92:e2309-20.
58. Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick D, Rippon GA, *et al*. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia 2019;39:1455-64.
59. Macone A, Tepper SJ. Calcitonin gene-related peptide: The new era of migraine therapy. Future Drug Discov 2019;1:FDD14.
60. Spierings E, Biondi D, Hirman J, Horblyuk R, Cady R. Reduced Impact of Headaches after Migraine Preventive Treatment with Eptinezumab in Patients with Chronic migraine: Results from the PREVAIL Open-label Safety Study. Philadelphia, PA: American Headache Society Annual Meeting; 2019.
61. Förderreuther S, Zhang Q, Stauffer VL, Aurora SK, Láinez MJ. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: Data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. J Headache Pain 2018;19:121.
62. Ford JH, Foster SA, Stauffer VL, Ruff DD, Aurora SK, Versijpt J. Patient satisfaction, health care resource utilization, and acute headache medication use with galcanezumab: Results from a 12-month open-label study in patients with migraine. Patient Prefer Adherence 2018;12:2413-24.
63. Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, *et al*. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. BMC Neurol 2018;18:188.
64. Mulleners WM, Kim BK, Láinez MJ, Lanteri-Minet M, Pozo-Rosich P, Wang S, *et al*. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): A multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol 2020;19:814-25.
65. Novel Insight In to Migraine Pathophysiolgy and Galcanezumab Mechanisms of Action. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04271202. [Last accessed on 2021 Feb 18].
66. Frattale I, Caponnetto V, Casalena A, Assetta M, Maddestra M, Marzoli F, *et al*. Association between response to triptans and response to erenumab: Real-life data. J Headache Pain 2021;22:1.
67. Raffaelli B, Mussetto V, Israel H, Neeb L, Reuter U. Erenumab and galcanezumab in chronic migraine prevention: Effects after treatment termination. J Headache Pain 2019;20:66.
68. American Headache Society. The American headache society position statement on integrating new migraine treatments into clinical practice. Headache 2019;59:1-18.
69. Raffaelli B, Reuter U. The biology of monoclonal antibodies: Focus on calcitonin gene-related peptide for prophylactic migraine therapy. Neurotherapeutics 2018;15:324-35.
70. Kokoti L, Drellia K, Papadopoulos D, Mitsikostas DD. Placebo and nocebo phenomena in anti- CGRP monoclonal antibody trials for migraine prevention: A meta-analysis. J Neurol 2020;267:1158-70.
71. Akhtar A. The role of anti-calcitonin gene-related peptide in migraine and its implication in developing countries: A reasonable option to consider despite higher cost. Cureus 2019;11:e4796.
72. Hou M, Xing H, Cai Y, Li B, Wang X, Li P, *et al*. The effect and safety of monoclonal antibodies to calcitonin gene-related peptide and its receptor on migraine: A systematic review and meta-analysis. J Headache Pain 2017;18:42.
73. Robbins L. CGRP monoclonal antibodies for chronic migraine: Year 1 of clinical use. Pract Pain Manag 2020;19:58-62.
74. Talbot J, Stuckey R, Crawford L, Weatherby S, Mullin S. Improvements in pain, medication use and quality of life in onabotulinumtoxinA-resistant chronic migraine patients following erenumab treatment – Real world outcomes. J Headache Pain 2021;22:5.
75. Berman G, Croop R, Kudrow D, Halverson P, Lovegren M, Thiry AC, *et al*. Safety of rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. Headache 2020;60:1734-42.