Migraine is considered as one of the most debilitating neurological disorders but the success of the anti-calcitonin gene-related peptide (CGRP) therapies marks a new era in the treatment of migraine and has paved way for further research into the exact pathophysiology of migraine. Here, the authors discuss their literature review on the anti-CGRP therapies to examine the pathophysiology of migraine, with a focus on the possible role of CGRP and the safety and efficacy of monoclonal antibodies targeting it.
prophylaxis. Key words used to search included migraine, pathophysiology, calcitonin gene-related peptide, monoclonal antibodies. The search with no restrictions on the dates of the articles, showed:

- 36 837 peer-reviewed published articles listed for migraine
- 14 856 peer-reviewed published articles listed for calcitonin gene-related peptide
- 9267 peer-reviewed published articles listed for the combined keywords migraine and pathophysiology
- 1063 articles for the combined key words calcitonin gene-related peptide and migraine
- 353 peer-reviewed published articles listed for the combined keywords calcitonin gene-related peptide and monoclonal antibodies
- 152 articles for the combined key words calcitonin gene-related peptide, monoclonal antibodies and migraine

In the study, the research team included randomised controlled trials in which anti-CGRP therapies were used as monotherapy in patients with episodic or chronic migraine, meta-analyses and review articles. In addition, the research team used no geographic restrictions in the search.

**Discussion**

**Migraine pathophysiology**

Wolff in the 1940s postulated the vasogenic theory of migraine that suggested that migraine triggers primarily cause vasoconstriction followed by vasodilation of the meningeal vessels. The ischaemia induced by the initial vasospasm causes the perception of aura and the rebound vasodilation leads to the stimulation of the meningeal nociceptors, which are sensory afferents of the trigeminal ganglion innervating the meninges and meningeal vasculature. The activated trigeminal afferents relay impulses to higher centers causing generation of the characteristic headache of migraine. This theory, however, has been largely disproved since then with some researchers going as far as to say that vasodilation is neither sufficient nor necessary to cause migraine pain, as later experiments demonstrated that there was no correlation between the phases of migraine and alterations in blood flow and that cerebral blood flow could be normal or even reduced during the headache phase.

Debunking of the vasogenic theory by further experimentation paved the way for the current, widely supported neurogenic or neurovascular theory of migraine. According to this theory, migraine triggers cause an initial neuronal dysfunction, which is followed by a cascade of events culminating in a typical episode of migraine. What this dysfunction actually is has remained elusive to researchers and continues to be the most confounding aspect about migraine till date. However, several theories about the primary neuronal dysfunction have been put forward. One such theory is that of cortical sensory depolarisation/depression (CSD). Initially described by Leao, CSD is a slow-spreading wave of neuronal depolarisation that is associated with an initial phase of cerebral hyperperfusion followed by prolonged hypoperfusion. BOLD fMRI studies done in migraineurs experiencing visual aura have shown cerebrovascular changes typically seen in CSD. In addition to this, magnetoencephalography (MEG) studies have provided straightforward evidence by detecting alterations in the magnetic field of the cortex (induced by CSD) in patients going through a visual aura, consolidating the association between CSD and aura.

The fact that CSD is the physiological correlate of migraine aura has been well established. However, how crucial it is in generating migraine pain is still a topic of debate. Researchers in support of this theory have described that CSD causes an efflux of molecules such as potassium, glutamate, ATP, H+ ions, NO, etc, which are responsible for activating the trigeminal sensory afferents. Activated nociceptors carry pain impulses to the second-order neurons in the trigemino-innocervical complex (which includes the trigeminal nucleus caudalis in addition to the dorsal horn of C1 and C2 spinal cord) that transmit impulses to higher centers such as the brainstem, thalamus, basal ganglia, periaqueductal grey and the cortex, which leads to the manifestation of pain and accompanying symptoms of migraine. The activated afferents also release vasoactive peptides such as CGRP locally causing meningeal vasodilation and neurogenic inflammation, which may also contribute to some extent to the pain. Hence, the neurogenic theory makes it clear that vasodilation occurs secondary to neuronal dysfunction and is not the primary cause of migraine pain.

The main point of contention against CSD being the generator of migraine headache is that two-thirds of migraineurs do not experience aura. It is plausible that CSD does occur even in patients experiencing migraine without aura, wherein it begins in a clinically inconspicuous cortical region causing migraine pain without any prior aura symptoms. However, imaging studies have revealed no alterations in the regional cerebral blood flow characteristic of CSD during an episode of migraine without aura.
postulated that some similar cortical phenomena or glial waves may play a role in migraine without aura. Alternatively, some researchers propose that the origin of migraine headache takes place in the brainstem, as apparently several regions in the brainstem remain active during the premonitory phase of a migraine episode. In support of this, PET studies have demonstrated increased regional cerebral blood flow in various brainstem nuclei during a migraine episode. Whether this brainstem activation is causal to the pathophysiology of migraine or is secondary to nociceptive impulses relayed by the trigeminovascular system, is still a matter of debate. Further research needs to be conducted to obtain conclusive evidence to determine the origins of migraine headache as well as the reason for increased susceptibility of certain individuals to these processes.

**Involvement of CGRP in migraine**

Calcitonin gene-related peptide is a 37 amino acid neuropeptide that is present virtually throughout the human body and found extensively in the CNS, PNS, cardiovascular and gastrointestinal systems. It is one of the most potent vasodilators in the human body and is found in two isoforms, α-CGRP and β-CGRP. α-CGRP is predominantly found in the sensory neurons (C and Aδ fibres) of the trigeminal ganglion whereas β-CGRP is mainly expressed in the motor neurons of enteric nervous system. CGRP receptors have multiple components, which include the calcitonin receptor-like receptor (CLR), the receptor activity-modifying protein (RAMP), along with a receptor component protein (RCP). CGRP receptors are highly expressed in the trigeminovascular system and have been demonstrated in various sites such as the cell body of neurons and satellite glial cells of the trigeminal ganglion, meningeal mast cells as well as in the meningeal vasculature. The significance of CGRP in the pathogenesis of migraine cannot be disputed, as is evident by numerous experiments. Historically, elevated levels of CGRP demonstrated in internal as well as external jugular venous blood during an episode of migraine and its normalisation following administration of sumatriptan with alleviation of pain, hinted at the possibility of CGRP being crucial to the generation of migraine headache. Furthermore, studies showed that IV infusion of CGRP in susceptible individuals triggered a headache akin to a classic migraine attack. More recently, the development of anti-CGRP drugs and their tremendous efficacy in the treatment and prophylaxis of migraine has helped in consolidating all the data obtained from previous research. Despite all this evidence, speculation still surrounds the exact role that CGRP plays in the pathogenesis of migraine.

**Figure 1. Involvement of CGRP in the pathogenesis of migraine**

[Image of neurogenic inflammation, peripheral sensitisation, and central sensitisation processes involving CGRP in the trigeminal ganglion and surrounding tissues.]
the pathogenesis of migraine. Hence, the mechanism by which anti-CGRP therapies are effective in treating migraine remains ambiguous at the moment. Several theories have been proposed regarding the role of CGRP in migraine, which shall be discussed here.

CGRP is apparently responsible for the development of peripheral and central sensitisation, characteristic of migraine.20 Peripheral sensitisation is the development of hyperexcitability of the meningeal nociceptors, which is brought about by a considerable reduction in their response threshold due to which even minor innocuous stimuli produce an exaggerated response.31 This is manifested clinically as the exacerbation of headache on bending or coughing (raised intracranial tension) and the typical throbbing sensation observed in migraine.31 It has been suggested that CGRP promotes neuronal-glial signalling in the trigeminal ganglion, thereby inducing peripheral sensitisation.18 CGRP released from neurons of the trigeminal ganglion acts in a paracrine manner by activating the adjacent satellite glial cells, which release inflammatory mediators perpetuating the state of sensitisation.32 Central sensitisation occurs at the level of the second-order neurons of the TCC, where CGRP causes sensitisation of the NMDA receptors and reduces the response threshold for glutamate, which is released in conjunction with CGRP.24 Central sensitisation may also take place at supraspinal regions such as the thalamus, which probably causes the extensive allodynia associated with migraine.33

CGRP (a potent vasodilator), released from trigeminovascular neurons, is responsible for dilatation of the meningeal vessels, plasma protein extravasation (indirectly via release of substance P) and mast cell degranulation, which causes release of numerous proinflammatory mediators promoting neurogenic inflammation, which may further stimulate the meningeal nociceptors perpetuating the pain.26 (Figures 1 and 2).

**Anti-CGRP monoclonal antibodies**

The evolution of anti-CGRP antibodies has been a revolutionary step with monumental implications in the field of migraine (Table 1). The site of action of these drugs still remains doubtful but it has been proposed that as monoclonal antibodies are large molecules that cannot cross the blood-brain barrier (BBB), they probably have a peripheral rather than central site of action in the nervous system.34 Potential sites would be the dura mater and the trigeminal ganglion (both of which are devoid of the BBB) where prominent actions of CGRP such as neurogenic inflammation and peripheral sensitisation may be inhibited by the anti-CGRP monoclonal antibodies.20,34 However, some researchers are of the opinion that the blood-brain barrier gets disrupted during an episode of migraine34 and hence it is possible that even a region in the central nervous system can be the target of anti-CGRP therapies, but no conclusive evidence has been obtained to support this theory.

**Erenumab**, previously known as AMG 334, is an FDA-approved completely human monoclonal antibody targeting the CLR/RAMP1 subunits of the CGRP receptor.35 The ARISE trial was a phase 3 trial to assess variation in the number of monthly migraine days (MMD) brought about by administration of 70mg erenumab versus placebo in 577 patients (age range 18–65 years) suffering from episodic migraine (4–14 migraine days/month). Patients were randomised to either placebo or 70mg erenumab SC administered monthly for 12 weeks. Assessment was done at weeks 9–12. The change in MMD for the erenumab 70mg group was –2.9 days whereas for the placebo group it was –1.8 days (difference 1.0 day and \( p < 0.001 \)). The 50% responder rate for erenumab was 39.7% and for placebo it was 29.5%. (\( p = 0.010 \)). Adverse events most frequently encountered in either groups were URTI and injection site pain.36

Another phase 3 trial for the prophylaxis of episodic migraine, the STRIVE trial, compared the efficacy of monthly 70mg and 140mg subcutaneous erenumab injections with placebo administered...
randomly to a population of 955 patients for six months. Mean change in the number of monthly migraine headache days (MHD), assessed at months 4–6 was higher for both the active groups being –3.2 days for 70mg group and –3.7 days for the 140mg group versus placebo –1.8 days (p<0.001 for either dose of erenumab as compared with placebo). The proportion of people experiencing a 50% reduction in the number of migraine headache days/month for the 70mg, 140mg and placebo groups were 43.3%,

<table>
<thead>
<tr>
<th>Drug/trial/ double blind phase</th>
<th>Study size and age group</th>
<th>Type of Migraine</th>
<th>Dosage</th>
<th>Primary endpoint/ time point</th>
<th>Primary endpoint efficacy</th>
<th>50% responder rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab/ ARISE/12 weeks</td>
<td>577 (18–65 years)</td>
<td>Episodic migraine (4–14 days/ month)</td>
<td>70mg sc Monthly injections</td>
<td>Change in monthly MHD (weeks 9–12 )</td>
<td>(70mg) –2.9d (Placebo) –1.8d (p&lt;0.001)</td>
<td>39.7% 29.5% (p=0.010)</td>
</tr>
<tr>
<td>Erenumab/ STRIVE/6 months</td>
<td>955 (18–65 years)</td>
<td>Episodic migraine (4–14 days/ month)</td>
<td>70mg, 140mg SC Monthly injections</td>
<td>Mean change in monthly MHD (months 4–6)</td>
<td>(70mg) –3.2d (140mg) –3.7d (Placebo) –1.8d (p&lt;0.001 for each dose vs placebo)</td>
<td>43.3% 50.0% 26.6% (p&lt;0.001 for each dose vs placebo)</td>
</tr>
<tr>
<td>Galcanezumab/ EVOLVE-1/ 6 months</td>
<td>858 (18–65 years)</td>
<td>Episodic migraine (4–14 days/ month)</td>
<td>120mg, 240mg sc Monthly injections</td>
<td>Mean change in monthly MHD (months 1–6)</td>
<td>(120mg) –4.7d (240mg) –4.6d (Placebo) –2.8d (p&lt;0.001 for each dose vs placebo)</td>
<td>62.3%, 60.9%, 38.6% (p&lt;0.001 for each dose vs placebo)</td>
</tr>
<tr>
<td>Galcanezumab/ EVOLVE-2/ 6 months</td>
<td>915 (18–65 years)</td>
<td>Episodic migraine (4–14 days/ month)</td>
<td>120mg, 240mg sc Monthly injections</td>
<td>Mean change in monthly MHD (months 1–6)</td>
<td>(120mg) –4.3d (240mg) –4.2d (Placebo) –2.3d (p&lt;0.001 for each dose vs placebo)</td>
<td>59.3% 56.5% 36% (p&lt;0.001 for each dose vs placebo)</td>
</tr>
<tr>
<td>Galcanezumab/ REGAIN/3 months</td>
<td>1113 (18–65 years)</td>
<td>Chronic migraine (≥15 days/month)</td>
<td>120mg, 240mg sc Monthly injections</td>
<td>Mean change in monthly MHD (months 1–3)</td>
<td>(120mg) –4.8d (240mg) –4.6d (Placebo) –2.7d (p&lt;0.001 for each dose vs placebo)</td>
<td>27.6% 27.5% 15.4% (p&lt;0.001 for each dose vs placebo)</td>
</tr>
<tr>
<td>Fremanezumab/ 12 weeks</td>
<td>1130 (18–70 years)</td>
<td>Chronic migraine (≥15 days/month)</td>
<td>675 mg sc quarterly (single dose) 675/225/225mg sc</td>
<td>Mean change in average no. of headache days/ month (weeks1–12)</td>
<td>(Quarterly) –4.3d (Monthly) –4.6d (Placebo) –2.5d (p&lt;0.001 both regimens vs placebo)</td>
<td>38% 41% 18% (p&lt;0.001 for both regimens vs placebo)</td>
</tr>
<tr>
<td>Fremanezumab/ 12 weeks</td>
<td>875 (18–70 years)</td>
<td>Episodic migraine (6–14 days/ month)</td>
<td>675 mg sc single dose (quarterly) 225mg sc monthly</td>
<td>Mean change in monthly MHD (weeks 1–12)</td>
<td>(Single dose) –3.4d (Monthly) –3.7d (Placebo) –2.2d (p&lt;0.001 both regimens vs placebo)</td>
<td>44.4% 47.7% 27.9% (p&lt;0.001 both regimens vs placebo)</td>
</tr>
<tr>
<td>Eptinezumab/ PROMISE-1/12 weeks</td>
<td>888 (Efficacy analysis)</td>
<td>Frequent episodic migraine (≤14 days)</td>
<td>30mg, 100mg 300mg iv infusion (Single infusion, quarterly dosing)</td>
<td>Change in monthly MHD (weeks 1–12)</td>
<td>(30mg) –4.0d (100mg) –3.9d (300mg) –4.3d (Placebo) –3.2d</td>
<td>50.2% 49.8% 56.3% 37.4%</td>
</tr>
</tbody>
</table>

Abbreviations: sc= subcutaneous; MHD= Migraine headache days; CGRP= calcitonin gene-related peptide; d= days; iv= intravenous
50% responder rate = proportion of people experiencing ≥50% reduction in the number of monthly migraine headache days
50.0%, 26.6% (p<0.001 for either dose of erenumab vs placebo) hence demonstrating a prominently greater 50% responder rate in both of the active groups. Most common side-effects were nasopharyngitis and upper respiratory tract infections across all groups, with the 70mg erenumab group reporting a higher incidence of pain at the injection site.37

**Galcanezumab**, previously known as LY2951742, is an FDA-approved humanised monoclonal antibody that has high affinity and specificity for the CGRP ligand. EVOLVE-1 was a phase 3 trial in which a study population of 858 adults (age 18–65 years), suffering from episodic migraine (4–14 migraine headache days/month), were randomised (2:1:1) to placebo, 120mg or 240mg galcanezumab SC administered monthly for six months. Evaluations were performed during the entire treatment course. The primary endpoint efficacy criterion was satisfied by both doses of galcanezumab. A considerably greater decline in the monthly migraine headache days (MHD) was perceived in the 120mg (−4.7 days) and 240mg (−4.6 days) galcanezumab groups compared with −2.8 days with placebo (p<0.001 for either dose of galcanezumab vs placebo). Injection site pain was the most frequent side-effect, with the active groups reporting a higher frequency of injection site reactions, erythema and pruritis.38

Another phase 3 trial involving galcanezumab, EVOLVE-2, had a slightly higher study population of 915 patients with episodic migraine, who were randomised (2:1:1) to placebo, 120mg or 240mg galcanezumab SC administered monthly for a period of six months. The primary endpoint was a mean change in the monthly migraine headache days, which was substantially higher compared with placebo for both the galcanezumab 120mg (−4.3 vs −2.3 days; difference 2 days, p<0.001) and 240mg doses (−4.2 vs −2.3 days; difference 1.9 days, p<0.001). Injection site reactions, erythema and pruritis were more frequently reported in the galcanezumab-treated group.39

The REGAIN study, yet another phase 3 trial involving galcanezumab, differed from the previous two EVOLVE trials in that it was conducted in chronic migraineurs (≥15 headache days/month). Some 1113 patients suffering from chronic migraine were randomised (2:1:1) to receive placebo, 120mg or 240mg galcanezumab SC monthly for three months. The least squares mean change in the monthly migraine headache days was higher for the both the galcanezumab 120mg (−4.8 days) and 240mg (−4.6 days) groups as compared with placebo (−2.7 days) (p<0.001 for either dose of galcanezumab as compared with placebo). Injection site reactions were commoner in the galcanezumab treated groups.40

**Fremanezumab**, previously known as TEV-48125, is an FDA-approved humanised monoclonal antibody against the CGRP ligand. A phase 3 trial was performed to establish the efficacy of fremanezumab in the prophylaxis of chronic migraine (≥15 headache days/month) as compared with placebo. In a double-blind phase of 12 weeks, 1130 patients aged 18–70 years were randomised (1:1:1) to fremanezumab 675mg SC single dose (quarterly dosing regimen), fremanezumab 675mg, 225mg and 225mg SC at baseline, 4 weeks and 8 weeks respectively (monthly dosing regimen) or placebo. The least-squares mean reduction in the average headache days/month was prominently higher with both the quarterly (−4.3 days) and monthly (−4.6 days) dosing regimens of fremanezumab as compared with placebo (−2.5 days) (p<0.001 for both dosing regimens vs placebo). Injection site induration and erythema were more common with the fremanezumab-treated group as compared with placebo.41

A randomised controlled trial to ascertain the efficacy of fremanezumab in the prevention of episodic migraine (6–14 headache days/month) was undertaken with a study population of 875 patients for a double-blind phase of 12 weeks. Two dosing regimens of fremanezumab 675mg SC quarterly (single dose) and 225mg SC monthly, were tested against placebo. The mean change in monthly MHD was the primary end point estimated over the 12-week double-blind phase. Both dosing regimens of fremanezumab proved to be superior than placebo with the mean reduction in MHD being −3.4, −3.7 and −2.2 days for the fremanezumab 675mg single dose, fremanezumab 225mg monthly dose and placebo, respectively (p<0.001 for both dosing regimens vs placebo). Injections site reactions, pain, induration were commoner among the fremanezumab-treated group.42

**Eptinezumab**, previously known as ALD 403, is a humanised monoclonal antibody targeting the CGRP ligand, yet to be approved by the FDA. A phase 3 randomised controlled trial, PROMISE-1, tested eptinezumab for its efficacy in the prevention of frequent episodic migraine (≥14 headache days/month). This was different from trials of the other monoclonal antibodies as the route of administration chosen was intravenous, in hopes that it would achieve higher efficacy. A total of 888 patients were randomised to 30mg, 100mg, 300mg eptinezumab or placebo single dose (quarterly dosing) administered by intravenous infusion and decrease in the monthly migraine days during a 12-week period was taken as the primary endpoint.
The reduction in monthly migraine days for eptinezumab 30mg, 100mg, and 300mg versus placebo was -4.0d \((p=0.0045)\), -3.9d \((p=0.0179)\), -4.3d \((p=0.0001)\) vs -3.2 days, respectively. PROMISE 2, a phase 3 trial of eptinezumab for the prevention of chronic migraine has also shown promising results by achieving both its primary and secondary targets. All these trials have demonstrated the tremendous efficacy of anti-CGRP monoclonal antibodies in the prophylaxis of episodic as well as chronic migraine. With the exception of eptinezumab, the other monoclonal antibodies have a subcutaneous route of administration, which makes them highly convenient for self-administration. With characteristics such as a monthly or quarterly dosing regimen, target specificity and a very favourable side-effect profile with negligible adverse events reported during all the trials, the use of anti-CGRP monoclonal antibodies will encourage better patient compliance than currently used prophylactic drugs for migraine.

Limitations and considerations
To date, all human studies done on monoclonal antibodies for migraine prevention have been short-term clinical trials. This is a major limitation, as long-term adverse effects caused by prolonged blockade of CGRP are as yet unknown. CGRP is a ubiquitous peptide and mediates various physiological processes; one such process being vasodilation. Antagonism of CGRP-induced vasodilation poses a risk for the development of medication-induced hypertension or inhibition of cardioprotective responses during ischaemia. Therefore, further studies in patients with comorbidities, especially those with cardiovascular risk factors (eg obesity, diabetes, hypertension, etc) need to be undertaken to gauge the safety of the anti-CGRP mAbs in this high-risk group of patients. Additionally, no research has been done regarding the safety of these drugs in pregnancy. Apart from safety concerns, the efficacy of CGRP mAbs in prolonged treatment regimens may also be jeopardised by the production of auto-antibodies against the CGRP mAbs. Despite the fully humanised nature of the CGRP monoclonal antibodies, the risk of development of autoantibodies cannot be completely excluded.

Conclusion
The development of anti-CGRP antibodies has been crucial, especially in context to the current prophylactic treatment available for migraine. Topiramate, an antiepileptic drug, has been used routinely for the prophylaxis of migraine and has demonstrated an efficacy profile similar to that of anti-CGRP mAbs. Various phase 3 trials have shown a significantly greater reduction in the number of monthly migraine days with 100mg/day of topiramate (-1.8 to -2.6 days) as compared with placebo (-1.0 to -1.3 days). However, despite its efficacy, topiramate is characterised by a high incidence of serious side-effects such as memory problems, fatigue, weight loss and anorexia.

Though speculation still surrounds the site of action of the anti-CGRP mAbs, with potential sites being the meninges and trigeminal ganglion, all clinical trials have unanimously demonstrated the mAbs to be extremely efficacious in the prophylaxis of episodic as well chronic migraine by causing a significant decline in the number of monthly migraine days, with negligible side-effects, which make these drugs more suitable than currently used drugs such as topiramate for migraine prophylaxis. The success of these drugs has aided researchers in delving deeper into the pathophysiology of migraine, confirming the key role that CGRP plays in its pathogenesis by initiating important processes such as peripheral and central sensitisation, although a lot more regarding the origins of migraine remains undiscovered. Further research needs to be undertaken to determine the long-term safety as well as efficacy of these drugs, especially in patients with cardiovascular comorbidities and in pregnant women, as women of the reproductive age group form a major bulk of migraine sufferers. Detailed studies determining the exact generator of migraine headache, either CSD or the brainstem, will aid in exploring newer avenues in the treatment of migraine.

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