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Calcitonin-Gene-Related Peptide (CGRP) Monoclonal Antibodies in Migraine Prevention; Literature Review

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ABSTRACT

Migraine is one of the most common disabling disorders worldwide that influence the patient functionality and quality of life. Current preventive therapy has succeeded in preventing and decreasing migraine days; however, unwanted adverse effects are considered a serious issue and can lead to discontinuation of the medication. The calcitonin-gene-related peptide is a neuropeptide that plays a major role in migraine pathogenesis, and inhibiting this peptide is thought to achieve a therapeutic role in migraine prevention. This literature review aims to review the role of this peptide in migraine pathogenesis and the implementation of monoclonal antibodies in migraine preventive therapy. A relevant articles were collected from the PubMed database, using the following Mesh words: Calcitonin-gene-related peptide, migraine, migraine prevention. Calcitonin-gene-related peptide monoclonal antibodies seem to have a significant therapeutic role in migraine prevention. Few side effects were reported, of which infection was the common reported one. The long-term safety profile has not been evaluated up to our knowledge. Therefore, a long-term safety assessment would be required in addition to comparison with the standard migraine preventive therapy.

Keywords: *CGRP antagonist, Calcitonin-gene-related peptide, Chronic migraine, Migraine prevention, Aura*

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INTRODUCTION

Migraine is considered the second disabling disorder and the second most reported cause of absence for non-manual employees. Almost more than one-third of migrainous patients have equal to or more than four monthly attacks, for which one-fourth of them are labeled as chronic migrainous (Kernick, 2020). Chronic migraine greatly influences psychosocial functioning and is associated with an increased risk of medical and psychiatric illness (Smitherman *et al*., 2013; Kernick, 2020). Migrainous headache is commonly affecting females with a female to male ratio of almost 3: 1. It has been suggested that nearly one in every four women will suffer from migraine, and the prevalence heights in early to middle adulthood and decreased considerably consequently. Moreover, headache is among the top 20 reasons for clinic consultation and the top 5 reasons for emergency department consultation (Smitherman *et al*., 2013).

Episodic migraine is defined by the occurrence of migrainous attacks less than 15 days monthly. In contrast, chronic migraine is characterized by migrainous headaches on at least 15 days per month (Manack *et al*., 2011). Apart from head pain, migraine is associated with other distressing symptoms, such as photophobia, phonophobia, vomiting, visual symptoms, dyspepsia, autonomic manifestations, and cervical pain (Schuster & Rapoport, 2017). The diagnosis of migraine

headaches is usually clinical, and laboratory tests or imaging are requested to exclude other causes of headaches. While the exact incidence of chronic migraine in the general population has not been studied, the American Migraine Prevalence and Prevention (AMPP) estimated that chronic migraine incidence among people with episodic migraine is 2.5% annually. Further, the estimated prevalence in the general population is 2% (Manack *et al*., 2011).

Risk factors for chronification of episodic migraine headaches are classified into three categories; nonmodifiable, modifiable, and putative. Nonmodifiable risk factors, such as elder age, female gender, Caucasian race, poor educational level, and socioeconomic status, and genetic factors (Manack *et al*., 2011). Modifiable factors include the frequency of attacks, overweight, drug overuse (Opiates and barbiturates), snoring, life stressors, depression, and anxiety (Bigal *et al*., 2008; Manack *et al*., 2011). Putative factors, which being tested, such as proinflammatory status and prothrombotic states (Manack *et al*., 2011). People with episodic migraine progress to chronic migraine at an estimated rate of 2.5% every year, of which the medications used to abort migraine attacks play a significant role in transformation into chronic migraine, especially in men or who have a high frequency of attacks (Bigal *et al*., 2008).

Regarding the pathophysiology of migraine, it recently proposed that the trigeminovascular pathway plays a significant role in migraine pathogenesis. The trigeminal afferent neurons provide innervation to the pain-sensitive structures in the head. They are responsible for sensory signals to the trigeminal cervical complex (TCC), then projections to several brain nuclei responsible for headaches and correlated symptoms. During a migrainous attack, the trigeminovascular system is being abnormally stimulated, resulting in vasodilatation, neurogenic inflammation, peripheral and central pain sensitization, leading to chronic head pain (Bigal *et al*., 2008). While the trigeminovascular system is the primary pain-signaling system of the visceral brain, most agents were produced to target the 5-HT1B/D and 5-HT1F receptors (triptans and ditans), resulting in suppression of the trigeminovascular system activation (Schoenen *et al*., 2020).

Therapeutic approaches usually target migraine abortion and preventive therapy to limit the frequency and intensity of headaches. Ordinarily, once-daily pills have been the standard prevention for migraine; nonetheless, these pills are often associated with adverse outcomes, resulting in patient's noncompliance (Schuster & Rapoport, 2017). The Federal Drug Administration (FDA) has approved six orally preventive medications; however, a new agent that targets the calcitonin-gene-related peptide (CGRP) and receptors has been developed for migraine prevention (Yuan *et al*., 2019).

RESULTS AND DISCUSSION

The role of CGRP in migraine pathogenesis

Calcitonin is a hormone released by the parathyroid glands in response to calcium regulation, where the processing of the RNA transcription of the calcitonin gene produces CGRP (Maasumi *et al*., 2018). CGRP is a 37-amino acid neuropeptide encoded on chromosome 11 and classified into two isoforms in the human body, αCGRP and βCGRP (Taylor, 2018; Hargreaves & Olesen, 2019). CGRP is broadly expressed in the central and peripheral neurons; αCGRP is highly expressed in the sensory nervous system and βCGRP in the central nervous system (Hargreaves & Olesen, 2019). αCGRP is the predominant peptide in the dural and trigeminal ganglia, responsible for regulating the cardiovascular system, vasodilatation, neurogenic inflammation, mast cell degranulation, and modulating nociceptive input-sensory pain signaling (Taylor, 2018; Spindler & Ryan, 2020). CGRP receptor is a member of the B G-protein-coupled receptors (GPCRs) family (Taylor, 2018; Hargreaves & Olesen, 2019). The GPCRs are the abundant family of cell-surface receptors which account for 1% of the individual genome. They contribute to mediating neurotransmission, hormones, and local messenger function (Taylor, 2018).

Stimulating the trigeminal ganglion that innervates the meningeal vessels leads to neuropeptides release, including CGRP, substance P, neurokinin A, and pituitary adenylate cyclase-activating peptide (PACAP). Further, the CGRP, PACAP, and substance P are excreted in response to sensory innervation of the meninges. Several studies have found that CGRP increases migraine attacks and may induce migraine-like headaches. CGRP is also found in tiny, unmyelinated C fibers in most sensory nerves, particularly the trigeminal system (Maasumi *et al*., 2018). Additionally, CGRP is a potent vasodilator where it demonstrates a vasodilatory effect in middle cerebral arteries in vitro, pial arterioles in situ, and intracranial arteries by CGRP binding to smooth muscle cells receptors, suggesting the potential role of CGRP in brain circulation during the migrainous attack (Edvinsson *et al*., 2018; Maasumi *et al*., 2018; Hargreaves & Olesen, 2019).

Besides, CGRP leads to neuronal inflammation, resulting in hyperexcitability of the brain in addition to mediating pain signal transmission in the brain by enhanced post-synaptic neuron firing when CGRP binds to its receptor (Edvinsson *et al*., 2018; Hargreaves & Olesen, 2019). Hypothetically, prolonged stimulation of trigeminal neurons through CGRP could participate in the sensitization of central second-order sensory neurons, leading to the potential conversion of episodic migraine into chronic migraine (Hargreaves & Olesen, 2019).

While the trigeminal sensory system had shown to play a pivotal role in primary headache disorder, the identification of CGRP in the trigeminovascular system in 1985 directly implied that this peptide might play a crucial role in migraine pathogenesis. Soon after, the existence of CGRP in the human body's trigeminal ganglion and cerebral arteries was confirmed. Impressively, younger people (20-40 years) were observed to have high peptide levels, which decreased with time. These findings drew attention to CGRP's role in aborting and preventing migraine attacks. Furthermore, CGRP levels were found to be elevated in other attacks of primary headache disorders, including cluster headache and chronic paroxysmal headache (Charles & Pozo-Rosich, 2019).

On the other hand, these two conditions were observed to have a high level of vasoactive intestinal peptide (VIP) in addition to CGRP. Further trials of migrainous patients had shown elevated CGRP levels in plasma, saliva, and cerebrospinal fluid (CSF) specimens. High CSF CGRP levels indicated the central release of CGRP from the trigeminal nerves, as shown in rats (Edvinsson *et al*., 2018). Further, the relation between CGRP and headache was observed from various clinical trials when exogenous CGRP was given intravenously in patients predisposed to migrainous attacks. As a result, intravenous CGRP induced a lasting,

migraine-like headache, which suggests the causal relation of CGRP in migraine (Charles & Pozo-Rosich, 2019).

Consequent pharmacological studies have shown that the triptans contribute to CGRP release inhibition in the meninges, which supports the possible beneficial effect of CGRP modulation in migraine therapy (Hargreaves & Olesen, 2019). Several trials revealed a similar elevation of CGRP levels in individuals with cluster headaches, which declined following therapeutic oxygen and sumatriptan. CGRP is also elevated after the trigeminal ganglion stimulation in animal and human samples and after the superior sagittal sinus stimulation in animal samples. A study in 2018 reported that CGRP infusion quickly induced attacks of cluster headache in individuals who have active episodic cluster headache or chronic cluster headache, but not those in the remitting phase of episodic cluster headache (Charles & Pozo-Rosich, 2019). Consequently, various agents have been developed to target the CGRP molecule or the CGRP receptors. They are classified into two main classes; 1) monoclonal antibodies (mAbs) and 2) small molecules, which are referred to as gepants (Chiang & Schwedt, 2020). Nonetheless, this literature review is focused on CGRP monoclonal antibodies specifically.

CGRP monoclonal antibodies in migraine prevention

CGRP monoclonal antibodies characterized a high selectivity and long half-life compared to gepants. There are four available approved mAbs in the United States: erenumab, fremanezumab, galcanezumab, and eptinezumab. The first three are given subcutaneously by injection and received FDA approval in 2008, while eptinezumab is administered by intravenous route and received FDA approval in 2020. Galcanezumab, eptinezumab, and fremanezumab target the CGRP ligand, whereas erenumab targets the CGRP receptors. Moreover, CGRP mAbs are absorbed through the lymphatic system into the bloodstream, and it can take up to days to reach the blood due to its slow drainage properties. The CGRP mAbs highest concentration reaches on days 5 to 7 by the subcutaneous route and 3 hours by the intravenous route (Chiang & Schwedt, 2020).

Erenumab is a fully human mAbs that binds to the CGRP receptors with high specificity and potency (Chiang & Schwedt, 2020). It has been approved to treat episodic migraine and CM for 70 or 140mg once monthly. Several trials have approved the efficacy of erenumab in patients with episodic and chronic migraine patients. Erenumab 70 and 140mg showed to significantly reduce monthly migrainous attacks in comparison to placebo (Lai & Huang, 2020; El Gazzar *et al*., 2021). Common side effects include injection-site pain, upper respiratory tract infection, and nausea (Khan *et al*., 2019; Lai & Huang, 2020). A review of four trials of erenumab has shown a similar vascular safety profile when compared to placebo. Patients who received CGRP mAbs reported an improvement in quality of life and disability (Lai & Huang, 2020). In patients with episodic migraine prevention, erenumab 70mg use significantly reduced migraine days following treatment compared to placebo with a net reduction of 1.1 days in favor of erenumab. The most frequent side effects were nasopharyngitis, fatigue, and headache (Khan *et al*., 2019; Miri & Vezvaei, 2021).

Galcanezumab is a humanized mAbs that binds to the CGRP ligand. IT received FDA approval for migraine prevention in adults as a once-monthly injection subcutaneously (Chiang & Schwedt, 2020). It incompletely antagonizes CGRP, resulting in fast target engagement and disengagement. This could facilitate a notable level of CGRP to be free to be engaged with the receptor (Edvinsson, 2018). Galcanezumab's efficacy in migraine therapy has been studied in various phase 3 clinical trials. The use once-monthly 120 or 240mg once-monthly subcutaneous injection was compared with placebo, resulting in a significant reduction of monthly migraine attack days (Lai & Huang, 2020). The most reported side effects include injection-site reaction, skin rash, pruritis, upper respiratory tract infection, sinusitis, and abdominal pain with careful consideration to the cardiovascular safety profile (Khan *et al*., 2019; Lai & Huang, 2020). In phase 2 clinical trial of galcanezumab efficacy in preventing episodic headache, where participants were randomized to receive subcutaneous galcanezumab 150mg or placebo every two weeks for a total of 12 weeks. As a result, the net reduction in per month migraine attack days was 1.2 days in favor of galcanezumab. Furthermore, galcanezumab was associated with a reduced number of headache days, migraines number, possible migraine headache days, and migraine attacks number (Khan *et al*., 2019).

Fremanezumab is a 95% humanized and 5% murine antibody that acts by bindings to the CGRP ligand and received FDA approval in 2018 for migraine prevention therapy. The recommended frequency is either monthly or every 3 months (Chiang & Schwedt, 2020). Once-monthly subcutaneous injection of fremanezumab was provided a beneficial effect on both chronic and episodic migraine. The injection is administered safely under the skin, and the patient can learn to self-inject in the future without visiting the clinic (Tepper, 2016). The efficacy of fremanezumab in subjects with high-frequency episodic migraine was evaluated in the randomized control trial. As a result, the number of migraine days was significant>50% reduced when compared to placebo. In a trial of subjects with chronic migraine, fremanezumab was significantly associated with reduced the mean number of headache days. The most frequent side effect was injection-site reactions and pruritis (Dodick, 2019; Damanhouri *et al*., 2021).

Eptinezumab is a humanized antibody that binds to α and β forms of human CGRP with high selectivity and potency (Dodick, 2019). Eptinezumab received FDA approval in 2020 for migraine preventive therapy in adults, and the recommended dosage is 100mg and 300mg (Lai & Huang, 2020). In a randomized clinical trial evaluating the efficacy of eptinezumab on monthly migraine days compared to placebo, the net reduction in monthly migraine days was 1.0 days in favor of the eptinezumab. The most frequent side effects include upper respiratory tract infection and urinary tract infection, and three patients have developed six critical side effects (Khan *et al*., 2019). A two pivotal phase 3 trials evaluated the efficacy of 30mg, 100mg, 300mg of eptinezumab or placebo in subjects with episodic migraine; as a result, the primary endpoint (reduction of monthly migraine headache days) was achieved in >75% over 1-12 weeks in the eptinezumab groups compared to placebo (Dodick, 2019).

CONCLUSION

Migraine is a complex disorder that affects the patient psychosocial functioning and quality of life. The calcitonin-gene-related peptide is a neuropeptide that is found to have an

essential key in migraine pathology. Monoclonal antibodies have been developed subsequently to target that neuropeptide, resulting in a significant reduction in migraine days in both episodic and chronic migraine. Nonetheless, certain adverse outcomes have been reported, of which infection was the most frequently reported. Clinical trials comparing calcitonin-gene-related peptides with the standard preventive therapy would be warranted in the future.

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