ZAHEER AALIF, AKHTAR OMAR, RAVI NARENDRANATH,
MOHAMMED BILAL MUNEER, TAMAR AKHVLEDIANI

THE EFFICACY OF CGRP ANTAGONISTS IN THE TREATMENT OF MIGRAINE

(Review Article)

USMD Program, Tbilisi State Medical University, Tbilisi, Georgia

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Abstract

Migraine is one of the most common and disabling diseases in the world. The usage of Calcitonin Gene-Related Peptide (CGRP) antagonist drugs has been on the horizon and looks to be a promising treatment option. Growing evidence suggests that CGRP plays a key role in the development of peripheral sensitization and associated enhanced pain. CGRP is involved in the development of neurogenic inflammation and is upregulated in inflammatory and neuropathic pain conditions. Drugs like Erenumab, Rimegepant, Olcegepant and others of the same category have shown significantly fewer side effects along with high therapeutic effects, which makes this group of drugs a useful addition to the existing therapeutic options.

Introduction

With a prevalence of 11.6% worldwide, 13.8% in females, 6.9% in males, the World Health Organization is listing migraine as the fifth most disabling disease in the world. Migraine is one of the top 10 causes of disability that affects work productivity and social functioning, regardless of ethnicity, geography and socioeconomic status [2].

According to the International Headache Society, a migraine is a headache that lasts for 4 to 72 hours and has at least two of the following characteristics: unilateral localization, pulsating quality of pain, moderate to severe intensity, and aggravation by motion. In addition, at least one of the following two symptoms has to accompany the headache: nausea and/or vomiting, or photophobia and/or phonophobia. Typically, migraine is episodic, but some patients experience chronic migraine headaches occurring at least 15 days a month. The migraine headache is almost always preceded by the premonitory phase that can last for hours. Tiredness, gastrointestinal problems, and mood changes are the most commonly reported symptoms, and these can persist for the entire migraine attack. A recovery or postdrome phase, which is characterized by fatigue and continued sensory disturbances, often follows the headache [10].

There have been well-established studies showing acute and prophylactic treatment, and even Botulinum toxin to be effective for migraine, however, because of their considerable side effects (e.g., selective vasoconstriction in case of triptans), these drugs have somewhat restricted use. Hence the need for newer better alternatives [10].

A CGRP receptor is a new therapeutic target for migraine treatment. In the underlying pathophysiology of migraine, the release of the CGRP from trigeminal nerves is now thought to play a central role. Recent studies have shown that the CGRP levels are elevated during a migraine episode and that an infusion of CGRP can in fact trigger a migraine attack. Furthermore, it is seen that the serum level of CGRP in the external jugular vein is elevated in patients with all forms of vascular headaches, including migraine and cluster headaches. In addition, the absence of vasoconstrictor activity may prove to be a major benefit of the use of CGRP receptor antagonists in migraine treatment [4,9,10].

In this article, we have reviewed selected studies that show the efficacy of CGRP antagonists for the prophylaxis and treatment of migraine.

Etiology

The pathophysiology of migraine is associated with the trigeminal innervation of pain-producing intracranial structures. The ophthalmic division of the trigeminal ganglion gives rise to a plexus of largely unmyelinated fibres which surround the large cerebral vessels, venous sinuses and dura mater [5]. The trigeminal branches that innervate cerebral vessels arise from neurons, which are located in the trigeminal ganglion. These cells contain vasoactive substances, namely substance P and calcitonin gene-related peptide (CGRP). A study conducted in 1988 concluded that these vasoactive substances are released in the extracerebral circulation during the activation of the trigeminal nerve ganglion. Migraine is thought to be

caused by the irritation of the trigeminal nerve followed by the increased release of CGRP which has vasodilatory effects on cerebral vessels [6]. Nerves that innervate the cranial vessels consist of myelinated and unmyelinated fibres, which are responsible for the severe pain experienced during a migraine attack. The activation of trigeminovascular systems increases the blood level of CGRP by 85% [11].

The pathophysiological basis of CGRP paves way for the treatment of migraine. Modulation of the release of CGRP from trigeminal ganglions can aid in the treatment of severe migraine.

Andreou et al. report that glutamate plays a role in the pathophysiology of CGRP release. According to this study, receptors with the GluR5 subunit (iGluR5 glutamate receptor) are present on the trigeminal ganglion and could potentially be involved in mediating pain in migraine attacks. Activation of the iGluR5 kainate receptor with its agonist called iodowillardiine causes inhibition of the vasodilation effect that is mediated with CGRP. Therefore, it can be concluded that activation of the glutamate receptors can have a therapeutic effect in migraine attacks [1]. Another interesting way to treat migraine attacks is by directly inhibiting the CGRP receptors via CGRP receptor antagonists. For example, Olcegepant is a highly potent and a very specific antagonist of CGRP receptors [8].

Existing data

Olsen et al. showed that 2.5 mg of Olcegepant had a 66% success rate [9].

Another trial by Goadsby et al. showed a significant reduction of the migraine attack frequency using a monthly dose of 70 or 140 mg of Erenumab Migraine attacks [7].

The knowledge about CGRP receptors in the CNS is limited but their functions on the enteric and peripheral nervous system has been well established. The side effects that have been detected so far have been mild, including paresthesia, nausea, headache, dry mouth and unspecific visual disturbances. However, further observations are needed to evaluate the long-term side effects of these novel medications. [3].

Conclusions

The CGRP plays a major role in the pathogenesis of migraine headaches. CGRP antagonists are effective anti-migraine drugs showing efficacy for both migraine treatment and prophylaxis.

References:

1. Andreou AP. et al. Activation of iGluR5 Kainate Receptors Inhibits Neurogenic Dural Vasodilatation in an Animal Model of Trigeminovascular Activation. Br J Pharmacol Blackwell Publishing Ltd, 2009;157:464–73
2. Chan C, Wei D, Goadsby PJ. Biochemical Modulation and Pathophysiology of Migraine; J Neuroophthalmol 2019;39(4):470-79
3. Deen M, Correnti E, Kamm K. et al. Blocking CGRP in migraine patients - a review of pros and cons. J Headache Pain 2017;18(1):96.
4. Durham PL. CGRP-Receptor Antagonists — A Fresh Approach to Migraine Therapy? N Engl J Med 2004; 350(11):1073–75.
5. Goadsby PJ. Pathophysiology of Migraine. Ann Indian AcadNeurol2012; 15 (Suppl 1): S15–S22.
6. Goadsby PJ, Edvinsson L, Ekman R. Release of Vasoactive Peptides in the Extracerebral Circulation of Humans and the Cat during Activation of the Trigeminovascular System. Ann Neu1988;23(2):193-96;
7. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med 2017; 377(22):2123–32
8. Ho TW,Edvinsson L, Goadsby PJ. et al. CGRP and Its Receptors Provide New Insights into Migraine Pathophysiology. Nat RevNeurol 2010; 6:573–82
9. Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM. Calcitonin Gene-Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine. N Engl J Med 2004; 350(11):1104–10.
10. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. Annu Rev PharmacolToxicol 2015; 55:533–52.
11. Zagami AS, Goadsby PJ, Edvinsson L. Stimulation of the superior sagittal sinus in the cat causes release of vasoactive peptides. Neuropeptides 1990;16(2):69–75.