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The Role of CGRP Monoclonal Antibodies in the Treatment of Acute Cluster Headache

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Abstract

This article discusses the role of Calcitonin Gene-Related Peptide antagonists available on the market in treating cluster headaches. All the treatments discussed in this article focus on either abortive, preventive, or transitional care. These therapies include Monoclonal Antibodies (Galcanezumab, Fremanezumab, Erenumab), high-flow oxygen, triptans (sumatriptan, zolmitriptan), Octreotide, non-invasive vagus nerve stimulation (vagus and sphenopalatine nerves), and other medications like dihydroergotamine, lidocaine, and capsaicin. We reviewed many studies from The United States since 2015; analytical methods were utilized. Moreover, we found that some of the treatment options for CH can vary depending on efficacy and route of administration and according to categories of therapy (acute or preventive). Every treatment has a specific and unique mechanism of action, indications, contraindications, and side effects. Therefore, the recommendation of one particular treatment should be considered in the success of the treatment of Cluster Headaches. Monoclonal Antibodies against CGRP have a unique role and are considered a first alternative in treating acute CH.

Keywords: Cluster headache; Monoclonal antibodies; Galcanemunab; Erenumab; Fremanezumab; Triptans; Octreotide; Dihydroergotamine

Abbreviations: CH: Cluster Headache; CGRP: Calcitonin Gene-Related Peptide; eCH: episodic Cluster Headache; cCH: chronic Cluster Headache; CM: Chronic Migraine

Introduction

Cluster headache (CH) is an intense headache disorder associated with the V cranial nerve that affects 1 for every 1.000 people in the United States, being the most common of the headache disorders. The condition is characterized by unilateral

pain, episodes of high pain lasting between 15 and 180 minutes, and autonomic symptoms such as lacrimation and agitation. The severity of the disease depends on the patient's lifestyle, age, and gender. Cluster headaches are caused by abnormal activity of the autonomic nervous system, which plays an essential role in the initial stages of an attack [1,2]. In terms of treatment, monoclonal antibodies are usually the first alternative, specifically monoclonal antibodies against CGRP, which is an indispensable transmitter of the trigeminal system, reducing the likelihood of subsequent episodes. However, there is evidence that CH is difficult to identify, which delays the diagnosis of the condition.

Additionally, the treatment for patients with CH is often suboptimal, which is particularly disappointing since effective treatments are available to stop and prevent attacks.s. On the other hand, the treatment of CH is associated with positive outcomes [2]. The present article examines research from the U.S. since 2015 regarding the treatment with monoclonal antibodies for cluster headaches. Previous studies, indications and contraindications, mechanisms of action, and side effects are discussed.

Monoclonal Antibodies

Galcanezumab

Different pharmacotherapies are currently available for preventing cluster headaches (CH). However, these treatments are not always practical. As of June 2019, the United States has approved the use of galcanezumab (Emgality), previously used to treat chronic migraines, as a treatment for episodic cluster headaches (eCH).). studies have demonstrated that galcanezumab is ineffective in treating chronic cluster headaches (cCH). Calcitonin Gene-Related Peptide (CGRP) is associated with the pathophysiology of migraine and CH. GRP is a vasodilator, primarily released from unmyelinated C-fibers innervating meningeal and cerebral vasculature. GRP binds to its receptor on myelinated Aδ-fibers and vascular smooth muscle cells. Consequently, CGRP dilates arteries and may activate nociceptive fibers and provoke the release of other pain neurotransmitters [3]. Galcanezumab, a humanized monoclonal antibody, binds to the CGRP ligand and blocks its binding to the receptor, thus, preventing it [2]. The research study "Efficacy of galcanezumab in patients with episodic cluster headaches and a history of preventive treatment failure" demonstrated that treatment with galcanezumab decreased the frequency of weekly cluster headaches compared to the administration of a placebo [4,5].

Galcanezumab is administered subcutaneously in the arm, thigh, or abdomen, either with a pre-filled syringe or an auto-injector, due to its enormous size, low permeability through cell membranes, and instability in the gastrointestinal tract. The recommended dose is 300 mg subcutaneously at the onset of the cluster period and 300 mg once a month until the end of a cluster period. The most common side effects were injection site reactions, headache, nasopharyngitis, dermatitis, and diarrhea [6].

Fremanezumab

Recent Clinical Trials show excellent data indicating that monoclonal antibodies such as Fremanezumab (Ajovy) have high specificity for their target, have a longer half-life, and promising safety and toxicity profiles [7]. In previous double-blind and placebo-controlled trials, Fremanezumab demonstrated efficacy with favorable safety and tolerability in both Episodic Migraine (EM) and Chronic Migraine (CM) patients. For example, in two 12-week phases 3 HALO EM and HALO CM trials, Fremanezumab significantly reduced the monthly average number of migraine days and the monthly number of headache days of at least moderate severity compared with patients receiving placebo [8]. n HALO long-term safety study, both quarterly and monthly, was well tolerated and demonstrated improvement in monthly migraine days, headache days, and headache-related disability for up to 12 months in patients with migraine [8]. In a 12-week, randomized, double-blind period of the phase 3 FOCUS trial, Fremanezumab demonstrated efficacy and tolerability as a quarterly or monthly migraine preventative treatment in adults with EM or CM and documented prior inadequate response to 2 to 4 migraine preventive medication classes [8]. fremanezumab has been approved by the FDA in the United States since 2018 after multiple studies showed that it was well-tolerated, safe, and effective in treating migraines [9]. In addition, like other monoclonal antibodies, Fremanezumab is degraded into small peptides and amino acids by enzymatic proteolysis, not by cytochrome p450 enzymes, so it does not generate toxic metabolites. As a result, the risk of hepatotoxicity or drug interactions is low. framanezumab has a long half-life of approximately 31 days, allowing less frequent injections [9].

Fremanezumab is a fully-humanized IgG2 monoclonal antibody that selectively binds ALFA- CGRP and BETA-CGRP. It blocks the calcitonin gene-related peptide CGRP, a neuropeptide that is increased in migraine, thereby preventing activation of the trigeminovascular pain pathway [9]. fremanezumab is currently approved in adults and is administered subcutaneously in the abdomen, thigh, or upper arm. The recommended dosage is 225mg monthly or 675mg quarterly (three consecutive injections of 225 mg each [9]. No specific maternal toxicities exist, patterns of significant congenital disabilities, or increased reporting of spontaneous abortion. Here is still a limited number of adverse reactions. Continuous surveillance is still required during pregnancy and lactating women [7]. The most common side effects reported in clinical trials were injection site reactions, including pain, erythema, and induration at the injection site. Serious adverse effects such as cardiovascular, hepatotoxicity, or hypersensitivity were rare and occurred at rates similar to placebo groups [9].

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Erenumab

Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody with high-affinity binding to the CRGP. Erenumab antagonizes the CGRP function through the competitive blockade with high affinity and specificity. In addition, it antagonizes the accumulation of cAMP, which has been shown in both in vivo and in vitro studies [10]. AMP through CGRP stimulation in neuroblastoma cells in human in vitro studies, Erenumab potently and competitively inhibited [125I]-CGRP binding to the canonical CGRP receptor. Furthermore, it fully antagonized CGRP-stimulated cAMP accumulation in human SK-N-MC neuroblastoma cells. Erenumab is a fully human monoclonal antibody that selectively and potently binds to the canonical CGRP receptor [11].

Erenumab, available in doses of 70 mg and 140 mg injections, is a newly FDA-approved injectable drug administered monthly in dosages of 70 mg or 140 mg. It is available in 70-mg single-use pens for self-administered subcutaneous injection [11].

Formulation of this drug (AIMOVIG™) has been recently approved in the United States to prevent migraine in adults. It also received a positive opinion in the European Union on May 31, 2018. Most migraine patients in clinical practice present with one or more comorbidities such as fibromyalgia, pelvic pain, and low back pain. Whether this medication is a practical approach to these conditions is still unclear and needs further research. In addition, it is used to prevent episodic migraine headache attacks [12]. Injection site reactions (pain, erythema, and pruritus) are the most common adverse effects experienced by 5% to 6% of patients. Erenumab costs about $600 for 70 mg per month and $1,200 for 140 mg per month, making it similar in price to other calcitonin gene-related peptide antagonists on the market [12].

Current First-line Therapy

High-flow oxygen

High flow oxygen has been recommended to treat a severe acute Cluster headache attack. It is one of the most critical first lines in managing this disease. Many studies have shown excellent results in treating CH with oxygen inhalation. The mechanism of action is s still unclear why oxygen exhibits such good efficacy in treating CH. However, some dates have mentioned that the vasoconstrictive effect of oxygen exists, and oxygen therapy should be adequate for CH [13]. Goadsby and Edvinsson reported associations between hyperoxia and neuropeptides. After oxygen treatment, the results indicated a significant reduction of calcitonin gene-related peptide concentration in the jugular vein, suggesting hyperoxia's possible effect on trigeminal afferents [14]. Therefore, the administration of High-flow oxygen inhalation *via* a non-rebreather mask during CH attacks has been recommended; Petersen et al. investigated the different effects of three mask types and found that the demand valve oxygen or O2ptimask maybe is the best option compared to the simple mask. A 6-15 L/min flow rate has a more pleasing effect [13].

Cluster headache therapy can be divided into two categories: acute and preventive. Acute therapy is a symptomatic treatment of headaches and other symptoms associated with cluster headache attacks. On the other hand, preventive therapy reduces the frequency and intensity of cluster headache attacks. Some side effects of high flow oxygen include a dry or bloody nose, visual disturbance, barotraumas, and oxygen toxicity [15]. High-flow oxygen therapy can be administered at a different flow rate (6-15 L/min), low-flow rate (6-7 L/min) has a positive response in 56%-75% of the patients, in a high flow rate (12-15 L/min), the response was reported in more 78% of the patients [16].

Triptans: Sumatriptan/Zolmitriptan

Cluster headaches can be managed based on three stages: abortive, preventive, and transitional treatment [17,18]. Abortive treatment is the first and fast-acting treatment used in cluster attacks, which includes triptans, such as sumatriptan and zolmitriptan [17,18,19]. The abnormal serotonin (5-hydroxytryptamine) metabolism plays an essential role in the pathophysiology of cephalgia, arterial and venous dilation, or neurogenic dural plasma leak. Sumatriptan is a selective agonist of 5-hydroxytryptamine-like receptors (5-HT1B/1D), preventing plasma extravasation from dura mater and constricting blood vessels [19]. Arrow blood vessels prevent pain signals from being sent to the brain and block the release of certain natural substances such as calcitonin gene-related peptide, substance P, and neurokinin A [19,20]. Indications for triptans are migraines and cluster headaches [19].

Sumatriptan is approved by Food and Drug Administration (FDA) and can be administered orally, intranasally, and subcutaneously, whereas zolmitriptan is only given intranasally [18,19]. Oral presentations of sumatriptan tablets are 25mg, 50mg, and 100mg. Sumatriptan nasal spray formulations are available in 5mg, 10mg, and 20mg. he subcutaneous dose of sumatriptan is 6mg with available presentations of 3mg, 4mg, and 6mg [21,17,18,19]. Zolmitriptan nasal spray formulations are 5 and 10 mg [17,18]. Although adverse reactions are frequent and usually dose-dependent, the most common side effects depend on the route of administration. Oral sumatriptan treatment causes chest pain, hypertension, nausea, vomiting, abdominal pain, peripheral vascular ischemia, and splenic or renal infarction [19]. Subcutaneous administration may cause transient erythema at the injection site, drowsiness, hypo- or hypertension, and palpitations [18,19]. Finally, nasal spray formulations cause palpitations, increased or decreased blood pressure, and taste disturbances [17,18,19]. The most frequent contraindications are ischemic heart disease, cerebrovascular syndromes, hepatic failure, peripheral vascular diseases, and concomitant use of ergotamine (derivatives) or MAO inhibitors [21,18,19].

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Other Treatments

Octreotide

Octreotide is a synthetic octapeptide that resembles somatostatin. Somatostatin is a peptide hormone that has an inhibitory role in regulating multiple physiological functions, including pituitary, pancreatic and gastrointestinal hormone secretion [22]. For example, the hypothalamus inhibits the secretion of thyroid-stimulating hormone, growth hormone, adrenocorticotropic hormone, and prolactin. In addition, it inhibits the release of insulin, glucagon, gastrin, and other gastrointestinal peptides [23]. Octreotide exerts its biological effects vía specific somatostatin receptors (SSTs) expressed on target tissues stated previously. Live human receptor subtypes have been discovered and numbered SST 1 through 5; these receptors are known to be G-protein-coupled. Octreotide does not bind to SST 1 or 4. However, Octreotide has shown a high, low, and moderate affinity for SST2, SST3, and SST5. This drug is absorbed poorly from the gastrointestinal tract and thus administered intravenously (IV) or subcutaneously. V and subcutaneous doses have proven to be bioequivalent through specific radioimmunoassay [23].

Due to somatostatin's overall effects throughout the body, Octreotide is utilized for multiple therapeutic purposes such as carcinoid tumors, gastrointestinal peptide tumors, glucagonomas, acromegaly, esophageal variceal bleeding, malignant bowel obstruction, and very recently, it has been studied as second-line treatment in patients with cluster headaches. A randomized, placebo-controlled trial of 100 μg subcutaneous octreotide was well tolerated by patients with cluster headaches and a reasonable second-line alternative for those with failed response or contraindications to triptans [23]. There are no known contraindications of Octreotide, except if the patient has an allergic reaction to the drug. The most common side effects include nausea, abdominal cramps, diarrhea, flatulence, and fat malabsorption. These side effects may start after drug injection, and severity is dose-dependent; they resolve spontaneously within 7-14 days despite the continuous treatment [23]. Octreotide was one of the first biologically stable somatostatin analogs to be synthesized in 1979 and approved by the FDA; its use in the clinical setting continues, and researchers continue to find a new use for this medication [24].

Non-invasive Vagal Nerve Stimulation

Neuromodulation is a non-invasive treatment that stimulates the central or peripheral nervous system. The goal is to modify the pain and other mechanisms implicated in headaches. The nucleus tractus solitarius, the primary nucleus of the vagus nerve, appears to receive dural nociceptive afferents. Physiological studies have shown an effect of vagal afferent on non-cranial nociceptive pathways. In addition, vagal stimulation can modify the pial blood flow. One proposed mechanism is a depletion in the glutamate levels of neuronal firing in the spinal trigeminal nucleus secondary to continuous vagus stimulation. No cardiac side effects were reported in any of the studies, probably due to the pulse wave of vagal nerve stimulator devices specifically designed to activate A- and B-myelinated fibers. A portable transcutaneous non-invasive device that stimulates the cervical portion of the vagus nerve has been created (Gamma Core R). the non-invasive vagus nerve stimulation is administered by placing the device on the neck, which produces a mild electrical current that is transmitted to the vagus nerve through the skin. This treatment has shown a high safety and tolerability rate in primary headaches. The FDA approved it for acute treatment of migraine and episodic cluster headaches as effective and cheaper, contributing to the improved quality of life for patients [25]. Non-invasive vagal nerve stimulation is well tolerated and has minimal adverse effects, such as short-term discomfort at the site of device application. They stimulate their bodies to treat themselves, and don" t need pharmacologic intervention [26].

Sphenopalatine ganglion (SPG) stimulation: the sphenopalatine ganglion is a principal outflow pathway for the facial nerve cranial dilator system. It is a sensitive nicotinic ganglion that contains vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activated peptide (PACAP), and nitric oxide synthase. Through this, the primary basis is to develop canonical cranial autonomic symptoms such as lacrimation, conjunctival injection, aural symptoms, and periorbital edema. Therefore, a miniaturized implantable neurostimulator was developed containing a lead with six electrodes implanted in the pterygopalatine fossa close to the SPG and anchored to the zygomatic process of the maxilla. It is controlled remotely by the physician or the patient, who can adjust the intensity based on the voltage at which deep paresthesias are evoked behind the nose's root, indicating correct activation. SPG stimulation's most common side effects were sensory disturbances and pain due to surgical implantation. This treatment is still under investigation and has not yet been approved by the FDA [26,27].

Intranasal Medications: Dihydroergotamine, Lidocaine, and Capsaicin

Dihydroergotamine, lidocaine, and capsaicin are treatment options for cluster headaches. However, very little research with significant samples is available to prove its effectiveness over other treatments. dihydroergotamine acts similarly to triptans binding to nonspecific 5-HT receptors. 5HT receptors can cause vasoconstriction and contraction of smooth muscle cells and inhibit the release of neuropeptides like CGRP and substance P [28]. dihydroergotamine can be administered intravenously or intranasally at 1mg [27]. Lidocaine is a local anesthetic that reduces pain perception by blocking voltage-gated sodium channels on the sphenopalatine ganglion, thereby inhibiting the production of an action potential and thus blocking the transmission of nociception [28]. It is administered intranasally at varying dosages and concentrations between 4-10% as drops, sprays, or cotton swabs [28]. Lidocaine can be applied if sumatriptan or oxygen is ineffective or contraindicated. Capsaicin

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is a compound found in chili peppers that is responsible for the sensation of spiciness and belongs to a group of compounds called vanilloids. Capsaicin activates the TRPV1 channel (transient receptor potential vanilloid 1) [28], allowing sodium and calcium ions to pass through the cell, depolarizing nociceptive neurons, thus causing the sensation of spiciness [28]. It is administered intranasally.

Dihydroergotamine is contraindicated in patients with coronary artery and cerebrovascular disease, pregnancy, melanoma, and uncontrolled hypertension [28]. One study showed that when administered intranasally, it had similar effectiveness in aborting attacks as a placebo; however, the intensity decreased. It had a success rate of 57-100% when administered intravenously for three consecutive days. When administered intravenously, 58% reported nausea as a side effect, and 28% reported leg cramping [27]. In another study, 25% of patients reported dihydroergotamine to be effective. 1% of patients reported no or minimal physical and medical complications [28]. A reduction of pain within 3 min was reported in a study in which 0.5-0.8mL and 1mL of lidocaine at 4% were administered ipsilaterally, with only minor local side effects like numbness reported [26]. In one study, 2% of patients reported intranasal lidocaine to be entirely or very effective, with 97% reporting no or minimal physical and medical complications. One study showed a decrease in the frequency of attacks when capsaicin was administered intranasally [28]. Another study showed that 10mm of capsaicin administered on the ipsilateral side of the pain was relieved compared to contralateral administration [27]. In a second study, 5% of patients reported intranasal capsaicin to be entirely or very effective, with 92% reporting no or minimal physical and medical complications [28].

Conclusion

Cluster Headache is a neurological disorder characterized by intense unilateral headaches with cranial autonomic symptoms. Trigeminovascular system activation and release of calcitonin gene-related peptide are vital factors in the cluster headache pathway. Classically, practitioners have approached the treatment for cluster headaches in three phases: abortive, transitional, and preventive. The most well-known first-line abortive agents are high-flow oxygen and triptans. These therapies relieve pain by vasoconstrictive effects and blocking the release of calcitonin gene-related peptides. The abortive therapies include ergotamine, lidocaine, capsaicin, and Octreotide. Preventive treatment is crucial in managing cluster headaches; it is necessary for reducing acute attacks' frequency, severity, and duration. Novel therapies have emerged, and calcitonin gene-related monoclonal antibodies —Galcanezumab, Fremanezumab, and Enerumab— present as alternative modalities for cluster headaches resistant to traditional treatments. Solanezumab, a monoclonal antibody, works by binding to the CGRP ligand and is preferred for those patients with episodic resistant attacks but ineffective for chronic cluster headaches. Fremanezumab is a monoclonal antibody similar to Galcanezumab, with the advantage of a longer life, allowing less frequent injections. Lastly, Enerumab has a slightly different mechanism of action; it acts by binding directly to the canonical CGRP receptor. Calcitonin gene-related monoclonal antibodies are promising therapies for acute cluster headaches, and although already approved, it is wise to keep surveillance and await long-term outcomes. Future research could include the effect of Gepant and Diptans on cluster headaches, two new treatments currently used for migraines.

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