

The Most Promising Targeted Preparation for the Treatment of Migraine from the Pathophysiological Mechanism: Aimed at CGRP Drugs

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Abstract: Migraine is a common disorder of brain dysfunction. At present, there are four theories: trigeminal neurovascular theory, vascular dysfunction theory, neurogenic inflammation theory, and diffusion inhibition theory, which provide new ideas for the treatment of migraine. In recent years, the study of CGRP (calcitonin gene-related peptide) receptor antagonists and CGRP-targeted antibodies has made breakthroughs in the treatment of migraine. By blocking or inhibiting the effects of CGRP, these drugs can effectively reduce the attack frequency and pain degree of migraine, with good efficacy and safety. New migraine prophylactic drugs, such as CGRP receptor monoclonal antibodies and small molecule CGRP receptor antagonists have been developed and approved, and some anti-CGRP drugs have shown good efficacy and safety in clinical trials, making anti-CGRP drugs a new and effective clinical treatment for migraine, providing more options and hope for the treatment of migraine. This paper explores the mechanism of action, efficacy and safety of anti-CGRP drugs. With the continuous development of science and technology, it is believed that more drugs will appear in the future, bringing more treatment options for migraine patients.

1. Introduction

Migraine is a common disorder of brain dysfunction that may cause serious health problems. Symptoms of the disease include moderate to severe pulsing-like pain, recurrent attacks associated with nausea or vomiting, and fear of acoustic and optical stimulation. At an acute onset, migraine can develop a risk of disability, while chronic migraine affects the quality of life of millions of people.

In recent years, the continuous introduction of new drugs has brought breakthroughs in the treatment of migraine. Currently, CGRP receptor antagonists and CGRP-targeted antibody drugs have become new hotspots in the treatment of migraine, where CGRP is released to cause headache and other migraine symptoms in combination with the corresponding receptor. Therefore, in

response to the mechanism of CGRP, scientists have developed new drugs, such as CGRP receptor antagonists and CGRP-targeted antibody drugs, to treat migraine by blocking or inhibiting the effects of CGRP. It shows good efficacy in clinical practice, and in addition, the safety of these drugs is widely recognized, with relatively few adverse reactions and well tolerated by patients. Besides the therapeutic effect, CGRP mba also has excellent preventive effects. This paper mainly discusses the use of anti-CGRP drugs in the treatment and prevention of migraine attacks and discusses its mechanism of action, efficacy, and safety.

2. Current Understanding of Migraine Pathomechanism

The mechanism of migraine is a complex and diverse field, and its findings have important implications for the development of new drugs and treatments. At present, there are four main theories about the mechanism of migraine: trigeminal neurovascular theory, vascular dysfunction theory, neurogenic inflammation theory, and diffusion inhibition theory. These theories have their own unique theoretical system and scientific basis, but there are also some controversies and unsolved points. Based on the existing studies of migraine pathophysiology, we will deeply explore the principle of migraine attack and the mechanism of action of drug treatment.

2.1. Trigeminal Neurovascular Theory

Mainly include migraine attacks and the trigeminal nerve vascular system (TGVS) pain pathway activation, its main conduction pathway from the meningeal trigeminal nerve vascular network, after the trigeminal ganglion and the trigeminal neck complex of secondary neuron synapses (TCC), secondary neurons rise from TCC to thalamic cortical neurons, and further projection to the brain nucleus, such as blue loculeus (LC), periaqueductal gray matter (PAG) and hypothalamic [1]. Activation of the TGVS pain pathway releases neuropeptides at the level of the dura mater, such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activated polypeptide (PACAP), as well as in response to nociceptive neuronal stimulation innervating the dura mater.

Moreover, the release of CGRP from the peripheral terminals also triggers a cascade of events, including increased nitric oxide synthesis and sensitization of the trigeminal nerve, which is shown in Figure 1. CGRP secreted by the trigeminal ganglion interacts with neighboring neurons and satellite glia to maintain peripheral sensitization and can drive central sensitization in second-order neurons. The characteristic beat pain in migraine occurs by sensitizing the central trigeminal vascular neurons in the trigeminal neck complex (TCC) and thalamic nuclei.

We have currently developed some drugs or treatments to control or relieve the onset of migraine by regulating the level of CGRP, to inhibit the synthesis and release of CGRP, or to reduce the activity of CGRP in vivo by other ways, which has become a new way to treat migraine, to achieve the purpose of pain relief.

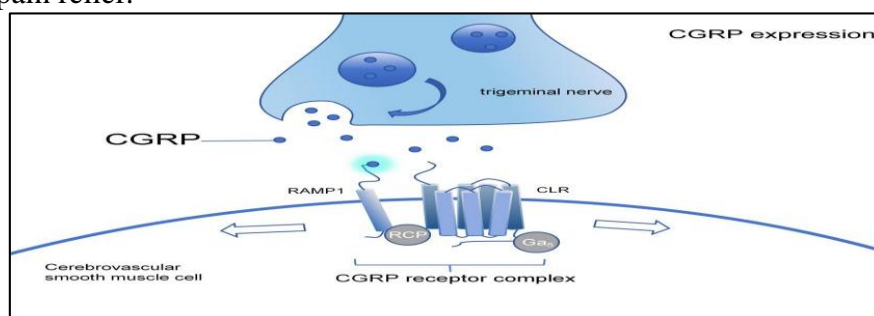


Figure 1: Trigeminal Neurovascular Pathway Activation Nociceptive neurons are stimulated and release calcitonin gene related peptide(CGRP).

2.2. The Theory of Vascular Dysfunction

It claims that migraine is a primary vascular disease. In this theory, migraine symptoms can be attributed to the contraction of the intracranial blood vessels, which leads to transient cerebral ischemia and triggers aura nerve symptoms. On the other hand, the dilation of extracranial blood vessels may draw the nerve endings on the blood vessel wall and trigger nociception, and the irregular blood flow may stimulate the surrounding nerve tissue, further causing headaches.

According to this theory, drugs have been developed, such as adrenergic receptor antagonists and calcium antagonists, which have been developed to effectively dilate intracranial blood vessels and relieve headaches. However, the effective use of a range of non-vascular drugs, such as topiramate and valproate, and the inability of this mechanism to fully explain other properties of migraine, such as unilateral, aura and accompanying symptoms, make the vascular theory controversial.

2.3. Theory of Neurogenic Inflammation

It is believed that the pain associated with migraine may be caused by sterile, neurogenic dural inflammation, as manifested by peripheral tissues of plasma proteins through small vessels. Although plasma protein extravasation blockers have failed to treat migraine in clinical trials, this extravasation process can be prevented by substances such as ergot alkaloids, indomethacin, acetylsalicylic acid and serotonin 5 HT 1 B / 1D agonist, sumatriptan, which can effectively inhibit the inflammatory response and relieve headache symptoms [2].

2.4. Diffusion Suppression Theory

According to the existing studies, the etiology of migraine can be attributed to the diffusion inhibition of the cerebral cortex. In the onset of migraine, certain areas of the cerebral cortex are in a significant state of inhibition, known as Cortical Spreading Depression (CSD). CSD leads to the activation of meningeal nociceptors, and locally produced substances such as adenosine triphosphate (ATP), glutamate, K⁺, H⁺, CGRP, and nitrous oxide are thought to diffuse to and trigger meningeal nociceptors. Furthermore, peripheral trigeminal vascular neurons become abnormally sensitive to dural stimulation after stimulation with endogenous mediators, which lowers their response threshold and increases their response amplitude [3].

3. Drug Therapy of Migraine

3.1. Current Conventional

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of widely used drugs, including ibuprofen, naproxen, sodium, diclofenac potassium, ketorolac, etc., which have the effect of inhibiting cyclooxygenase (COX), and then inhibit the synthesis of prostaglandin (PG). They inhibit neurogenic inflammation and reverse migraine central sensitization, reducing pain and anti-inflammatory, relieving migraine symptoms while reducing damage to normal tissues. These drugs are used not only clinically for migraine, but also widely used to treat a variety of pain and inflammation-related diseases. However, the use of NSAIDs is also accompanied by some side effects, such as gastrointestinal discomfort, bleeding, and allergic reactions. Therefore, attention should be paid to observe the clinical adverse effects when using these drugs.

Dihydroergotamine drugs not only affects the serotonin system through 5-HT 1 b and 5-HT 1 D receptors, but may also act on other neurotransmitter systems, such as dopamine and norepinephrine. It may relieve migraine headache by activating the dopamine D2 receptor. Moreover,

dihydroergotamine may also relieve migraine by inhibiting norepinephrine synthesis and release.

Triptans have properties of ergotamine (serotonin 5-HT 1B/1D receptor agonist activity), used in moderate to severe migraine, migraine-specific drugs, and about 20% of patients have a contraindication to cardiovascular disease, so caution is needed when used.

In addition to triptans, there are many other drugs available for migraine treatment. For example, adrenergic drugs, antiepileptic drugs, anticonvulsants, antidepressants, etc. Some of these drugs may have contraindications, interactions, and limitations due to moderate efficacy or high incidence of adverse events (AEs), limiting their use.

3.2. Anti-CGRP Class

CGRP receptor antagonists or monoclonal antibodies against their typical receptors have been widely used in clinical practice and treatment guidelines for [4]. These treatments have demonstrated efficacy in phase 3 trials, with easy administration, rapid onset, and mild to moderate adverse events. Moreover, real-world studies also demonstrated improvement of monoclonal antibodies and worsening of migraine frequency after withdrawal, with most patients resuming treatment as soon as possible after treatment interruption due to regulatory restrictions and high adherence to this treatment. The European Headache Federation currently recommends CGRP monoclonal antibodies as first-line drugs.

Two CGRP receptor antagonists recently introduced to the market, ategapant and rimegepant, have experimentally shown effective and well tolerated for migraine prophylaxis with a half-life of about 11 h, similarly beneficial for prophylactic treatment. Since their half-life is different from monoclonal antibodies, they have the advantages of fewer adverse events and higher safety. Atogepant Has received FDA approval for the treatment of episodic migraine and is being used directly as a prophylactic agent. In phase B and phase a studies, at 10% daily doses of 60mg each, the most common side effects were constipation and nausea.

Conclusion: Since the late 19th century, with the use of ergotamine, some other drugs have joined in the prevention of migraine, such as tricyclic antidepressants, β -blockers, calcium channel blockers, and anticonvulsants. They were developed for other indications and were incidentally found to be effective when treating migraine, but the mechanism of action is not fully defined. For patients with migraine, these prophylactic drugs, while relieving pain, are often accompanied by tolerance problems and are relatively less effective. This makes the treatment of migraine patients unusually difficult and unpredictable. Some patients, after using these drugs, find that the drugs have become less effective or even completely ineffective, causing them to face frequent headache attacks and persistent pain. In addition, the side effects of these drugs are also unbearable to patients. For example, some medications cause symptoms such as fatigue, nausea, dry mouth, and these side effects affect a patient's quality of life and ability to work. Moreover, even if a repositioning of the drug is well tolerated, a significant proportion of patients may not respond adequately (or not at all) [5].

Anti-CGRP drugs are well safe and well tolerated, adverse reactions are usually mild, and can be alleviated by dose adjustment or temporary withdrawal, and their efficacy has been demonstrated in clinical trials. Anti-CGRP drugs not only provide a new means for treating migraine headaches, but also provide new ideas for the treatment of other neurological diseases. With the market and wide application of anti-CGRP drugs, migraine patients will receive more effective treatments.

4. The Mechanism and Sensitization of CGRP

The physiological roles of CGRP are very extensive, the most striking of which is its potent vasodilatory effect. This effect is achieved after binding of CGRP to receptors on vascular smooth

muscle and can cause vascular dilation and increased blood flow. In the human body, α -CGRP and β -CGRP exist in two distinct forms that differ structurally and functionally. α -CGRP exists mainly in primary sensory neurons in the dorsal root ganglia, trigeminal ganglia and vagal ganglia and can transmit nociceptive information from these neurons. It is also distributed in the brain and cerebellar cortex, inhibitory nociceptive nuclei in the hypothalamus, the trigeminal – neck complex, and the trigeminal vasculature, regions that are closely related to physiological processes such as nociception transmission, sensorimotor coordination, and nociception. Higher nociceptive centers, such as the cingulate cortex, brainstem, insula, caudate nucleus, and thalamus, are also rich in CGRP, which play an important role in the perception and regulation of pain. However, β -CGRP is mainly found in intestinal neurons to regulate intestinal motility and secretory activity. Moreover, CGRP also has regulatory effects on neurons and glial cells, which can affect the neuronal excitability and the metabolic activity of glial cells.

In sum, CGRP is widely expressed in peripheral and central neurons and has robust expansion properties. It also shows modulatory effects on both secondary and tertiary neurons, which appear to underlie its modulatory role in central pain mechanisms.

Furthermore, accumulating evidence suggests that CGRP can also sensitize and maintain pain through activation of the vascular nociceptive system of the trigeminal nerve. Trigeminal afferent fibers C fiber pain neurons in TG neurons release CGRP, can stimulate satellite cells, and then act on TG neurons, increasing the production of CGRP and release of [6]. This mechanism of self-stimulation allows the maintenance of pain sensation. At the same time, CGRP secreted by TG neurons can also increase the production of cytokines (such as tumor necrosis factor- α (TNF- α)) in TG neurons and satellite glia, and increase the production and release of neurons themselves), to maintain a sensitive state and enhance pain, which is shown in Figure 2. Immunofluorescence studies showed that primary afferent terminals expressing CGRP make contact with astrocytes in layers I and II of the TNC, providing further evidence for the sensitization of CGRP. We show that CGRP injection into the TMJ of astrocytes and microglia activated by TNC helps to maintain central sensitization, with important implications for understanding the mechanisms of sensitization.

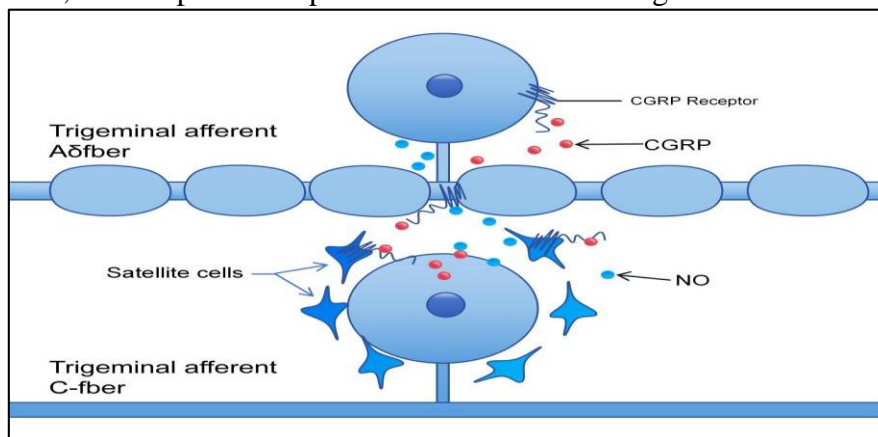


Figure 2: Trigeminal afferent fiber-C fiber nociceptive neurons can secrete CGRP in the trigeminal ganglia, and CGRP can diffuse into satellite cells, triggering the release of NO. NO diffuses back to TG neurons, as well as adjacent non-CGRP receptor neurons, thereby enhancing their activity.

Furthermore, CGRP can act directly on adjacent cell bodies of non-CGRP A δ sensory neurons expressing CGRP receptors, leading to their sensitization.

Moreover, in TG, simultaneous injection of CGRP or nitroglycerin in migraine patients can induce migraine attacks and increase jugular blood CGRP levels, and CGRP and NO can amplify each other's activity in reciprocal ways throughout the trigeminal neurovasculature, acting on the

peripheral neurovasculature. The activation of CGRP receptors on vascular smooth muscle cells can lead to cyclic adenosine phosphate (cAMP) and endothelial nitric oxide synthase (eNOS) increasing NO, NO plays the role of messenger molecules, when the endothelium to muscle relaxation instructions to promote blood flow, will produce some NO molecules, perivascular smooth muscle cells receive signal relaxation, make the blood vessel expansion, which may be sensitive to adjacent trigeminal nerve endings, to maintain peripheral sensitization state. In TG, neurons secrete CGRP by activating the signaling cascade by interacting with CGRP receptors on satellite glia and adjacent non-cgrpergic TG neurons, thereby releasing additional CGRP, activating the signaling cascade, and increasing the production of proinflammatory mediators. Furthermore, CGRP can act directly on adjacent cell bodies of non-CGRP A δ sensory neurons expressing CGRP receptors, leading to their sensitization [7].

From the perspective of pathophysiological mechanism, pain can be alleviated by inhibiting the synthesis and release of CGRP on the one hand, and analgesia can be achieved by enhancing the signal transduction of CGRP receptors on the other hand, as shown in Figure 3. In addition, corresponding treatments can be taken for different links of CGRP in the pain conduction pathway.

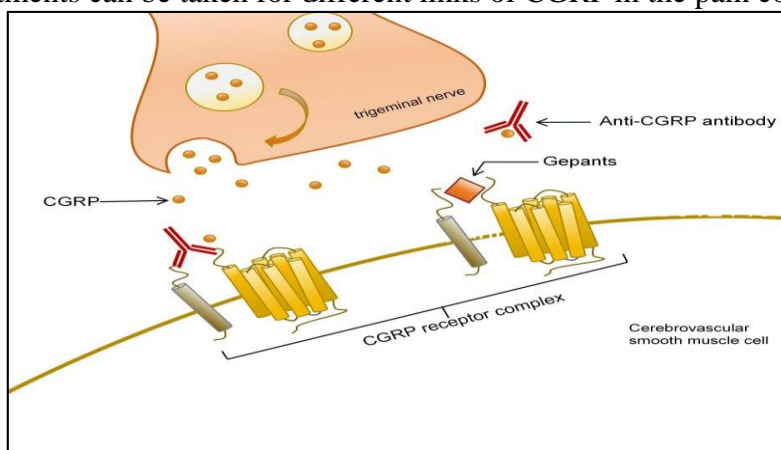


Figure 3: Small molecule CGRP receptor antagonists (gepants) has a high affinity for the canonical CGRP receptor, that prevents CGRP binding and hinders subsequent signaling in the treatment of migraine. The mechanism of action of the CGRP receptor monoclonal antibodies is mainly by binding to CGRP to prevent its binding to receptors on pain receptors, thereby reducing pain and inflammatory responses.

The current study shows that CGRP levels in saliva and plasma are significantly higher than in healthy individuals, and it has been observed that CGRP infusion causes migraine attacks in approximately 60% of study patients, revealing the role of CGRP in the pathogenesis of migraine [8].

However, it has also been shown that about 40% of migraine patients have an inadequate response to drugs targeting the CGRP pathway, which may be related to the proportion of migraine patients who cannot induce migraine attacks (approximately 35%-40%). The lack of response to the CGRP pathway may have different reasons: on the one hand, perhaps because the CGRP pathway may not be completely blocked; on the other hand, CGRP ligands or receptors may be fully blocked, but other polypeptides can activate CGRP receptors, or CGRP ligands may act on different receptors; finally, after the CGRP pathway may be fully blocked, migraine induced through other signaling pathways [6].

Novel migraine prophylaxis, such as anti-calcitonin gene-related peptide (CGRP) or CGRP receptor monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab), and small molecule CGRP receptor antagonists (gepants: atzogepant and rimegepant), have been developed

and approved by the US Food and Drug Administration.

The first-generation small-molecule CGRP receptor antagonist gepants showed promising efficacy, but further studies were stopped for various reasons, including hepatotoxicity issues. Second-generation gepants that do not cause hepatotoxicity have now been developed. Rimegepant is an oral administration and as second-generation gepant, it has been approved in several countries including the US and EU [9].

Rimegepant and ubrogepant are calcitonin gene-related peptide antagonists and thus have completely different pharmacological targets from triptans, whose site of action is considered outside the blood–brain barrier, and the most common adverse reaction is the injection site reaction [10]. Unlike triptans, rimegepant and ubrogepant are not contraindicated in patients with cardiovascular disease. Post hoc analysis of Lasetam-treated patients with cardiovascular risk factors, as defined by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, demonstrated no increase in cardiovascular events [11].

Trials using these drugs showed a greater reduction in the percentage of mean migraine days per month and the number of migraine days per month in onset and chronic migraine patients compared to placebo. Several randomized trials, including several CGRP antagonists, have shown promising results in migraine prevention, and a detailed account of several current drug classes is given below.

5. Small-molecule CGRP Antagonists and Anti-CGRP Monoclonal Antibodies

A comprehensive description of these drugs will be provided in the following article.

5.1. Small-molecule CGRP Antagonists—Gepants

CGRP receptor antagonists are a drug that targets the pathophysiological mechanisms of migraine, also known as "gepants". It has a high affinity for the canonical CGRP receptor that prevents CGRP binding and impedes subsequent signaling (is shown in Table 1). Numerous clinical trials have established that both intravenous and oral gepants are effective in relieving acute migraine symptoms. However, the efficacy of gepants in the prevention of migraine is currently still controversial. Moreover, the prophylactic use of CGRP receptor antagonists requires further study and evaluation. Although their efficacy in the prevention of migraine requires further research and confirmation, their effect in acute treatment has been widely recognized by [12].

Table 1: The mechanisms of action, indications, and common adverse effects of anti-CGRP drugs.

| Medication | mechanism of action | Indication | common adverse effect |
|-------------------------------|---|------------|---|
| Rimegepant | Prevent CGRP binding and impede subsequent signaling | Acute | Nausea and urinary tract infection. |
| Ubrogepant | | | Nausea and dizziness |
| Galcanezumab, Fremanezumab | Binding to CGRP, preventing its binding to the receptor on the pain receptor surface and Inhibition the synthesis and release of CGRP | Prevention | Infusion reaction |
| Eptinezumab | | Prevention | U upper respiratory infection; urinary tract infection. |
| Erenunmab | | | Infusion reaction and constipation |

Importantly, gepants do not directly cause vasoconstriction, so they may be safer than migraine patients with a statistically higher prevalence of cardiovascular disease, providing a new, effective treatment option for migraine patients. Such drugs are generally well tolerated and are unlikely to develop resistance associated with existing drugs.

Originally developed for migraine treatment had six gepants, where rimegepant and Ubrogepant received FDA approval for next-generation oral gepants for acute migraine treatment after phase 3 studies.

The initial trial of rimegepant, which has a short half-life of about 11 hours, benefits its

preventive indications, is taken every other day to prevent onset migraine in adults and can be used simultaneously during migraine attacks. In a clinical trial, rimegepant 75 mg, three phase 3 treatment trials evaluated the efficacy of adult migraine, showing that Rimegepant is effective in acute treatment in adults and current users of migraine, similar in the effectiveness of migraine attacks, but less associated with triptan-related side effects, such as paresthesia and chest discomfort. The efficacy of its co-primary endpoint did not differ by the number of inadequate triptans responses [13]. The drug was well tolerated, with nausea and urinary tract infections which are the most common side effects. So it has the advantages of fewer adverse events and improved safety.

Ubrogepant, in a phase 2b double-blind, randomized, placebo-controlled trial showed good dose-effect correlation with negligible side effects. In a phase 3, multicenter, randomized, open-label extension trial, long-term intermittent use of ubrogepant 50 and 100 mg at 1 or 2 doses of migraine was safe, well tolerated for migraine treatment with low incidence of adverse events (TEAEs) and serious adverse events (SAEs) [14].

As a first-line choice for antimigraine drugs, gepants has certain advantages for patients with an elevated risk of cardiovascular events or known cardiovascular disease. By not causing cerebral vasoconstriction, it becomes a backup strategy when triptans do not work. Despite the gepants with FDA approval, more studies and clinical trials are needed to comprehensively assess its long-term efficacy and safety. Furthermore, adequate consultation and discussion should be conducted with physicians before use to understand potential side effects and interactions.

5.2. CGRP mAb (Monoclonal Antibody)

In recent medical practice, monoclonal antibodies against CGRP peptides (e. g., galcanezumab, galcanezumab, fremanezumab, and eptinezumab) or their target receptors (e. g. erenumab) have been widely adopted and included in treatment guidelines. These therapies have proven sustained efficacy in phase 3 trials and are easy to use, rapid onset, with mild to moderate adverse effects. Such drugs have superior pharmacological properties, which include a long half-life, the absence of vasoconstriction, or other significant hemodynamic alterations. Furthermore, due to their high molecular weight, they fail to cross the BBB, thus reducing the risk of developing CNS-related side effects. These drugs can be administered by subcutaneous (SC) or intravenous (IV) and vary from three months to monthly, depending on the properties of the different compounds, which enhances long-term patient compliance.

Galcanezumab Is a humanized-IgG 4 mAb, but with a different mechanism of action. It inhibits the activity of the CGRP by binding to the ligand itself. The half-life of galcanezumab was 27 days, mean Tmax5 days, with a monthly subcutaneous dose of 120 mg (initial loading dose of 240 mg).

Results of a randomized controlled clinical trial of the efficacy and safety of galcanezumab for onset migraine were randomized to 120 mg or 240 mg or placebo. The results showed that the 120 mg and 240 mg galcanezumab groups decreased by 4.3 and 4.2 days, respectively, and 2.3 days in the placebo group, both doses were better than placebo, and the most common adverse event in the treatment was pain at the injection site [15].

Fremanezumab: A human IgG 2 mAb, randomized, double-blind, placebo-controlled, parallel-group trial, showed that the mean number of monthly migraine days decreased from 8.9 to 4.9 in the fremanezumab monthly dose group, from 9.2 to 5.3 in the fremanezumab single high-dose group, and from 9.1 to 6.5 in the placebo group. The most common adverse event was injection-site erythema. In patients with episodic migraine who had not failed previous multiple classes of drugs, subcutaneous fremanezumab statistically significantly reduced the mean number of monthly migraine days by 1.3 to 1.5 days compared with placebo. But further studies are needed to evaluate efficacy as well as in patients with multiple prophylactic drug classes of failure and to determine long-term safety and efficacy [16].

Eptinezumab is a human-derived IgG 1 mAb whose targeted biomolecule is CGRP (calcitonin gene-related peptide). In the treatment of migraine, the mechanism of action of eptinezumab is

mainly by binding to CGRP to prevent its binding to receptors for pain and inflammatory responses. Moreover, eptinezumab can also inhibit the vasodilation and increased blood flow induced by CGRP to further reduce migraine symptoms.

In addition to the aforementioned inhibition effects of CGRP, eptinezumab can improve migraine symptoms through other mechanisms. For example, it can reduce the excitability of nerve cells, thereby reducing neurotransmitter release and further relieving migraine symptoms. Moreover, eptinezumab can suppress inflammatory and immune responses, thereby reducing the inflammatory and immune responses during migraine attacks.

In a phase 3, randomized, double-blind, placebo-controlled study, patients received a maximum of two 30-min intravenous doses of eptinezumab 100 mg, 300 mg or placebo at a 12-week interval. The results demonstrated that intravenous eptinezumab of 100 mg or 300 mg on day 0 with repeated administration at week 12 provided sustained migraine prophylactic benefit throughout the 24 weeks and demonstrated an acceptable safety profile in patients with chronic migraine headache. Regarding the incidence, nature, and severity of adverse events occurring during treatment, no new safety concerns were identified in the second dose [17].

Erenumab is an IgG2 CGRP blocker, acting by specifically targeting and blocking the CGRP receptors. In a randomized, double-blind, placebo-controlled phase 3 study, 577 adults with onset migraine were randomized to 70 mg erenumab or placebo. The results showed that the monthly change in -2.9 d and -1.8 d in the placebo group as a prophylactic treatment for episodic migraine, a 70 mg monthly dose of erenumab significantly reduced the frequency of migraine and the use of specific medications for acute migraine. The safety and adverse event characteristics of erenumab were similar to those of placebo. The most common adverse events were upper respiratory tract infection, injection site pain, and nasopharyngitis [18]. Erenumab Received FDA approval in May 2018 for the prevention of migraine in adults.

6. Conclusion Knowledge Gaps and future Research

Migraine is a common brain dysfunction, closely related to calcitonin gene-related peptide (CGRP). In recent years, significant progress has been made in drug development for CGRP, including CGRP receptor antagonists and monoclonal antibodies. These drugs have shown good efficacy in preventing and treating migraine, with fewer side effects. Monoclonal antibodies (CGRP mAb) against CGRP peptide or its receptors are widely used in clinical practice, with the advantages of a long half-life, no vasoconstrictor effect, and mild to moderate adverse events. Among them, CGRP receptor antagonist, a drug that can block CGRP receptor, can effectively inhibit the pain and accompanying symptoms of migraine attack, while monoclonal antibody is a specific antibody against CGRP peptide or its receptor, which plays a role in the prevention and treatment of migraine by inhibiting the release and activity of CGRP.

In addition, these new drugs not only has significant treatment effect, and has a short development cycle and high development success rate, which makes them become the future of migraine treatment research direction, with the continuous development of medical technology, people have a deeper understanding of the etiology and pathogenesis of migraine, the new drug development provides more ideas and direction. For example, through technologies such as gene sequencing and proteomics, more genes and proteins related to migraine can be discovered, providing theoretical support for the development of more accurate drugs. The application of new technologies such as artificial intelligence also provides new opportunities for migraine treatment. By establishing migraine prediction model and drug design model, we can more accurately predict the disease onset and develop more effective drugs.

In conclusion, the drug development and the medical technology of CGRP have brought unprecedented opportunities and challenges for migraine treatment. It is believed that in the future treatment, there will be more new drugs and technologies, to bring better treatment effect and quality of life for the majority of migraine patients.

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