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Short Article

Rimegepant -a breakthrough drug for migraine treatment - literature review

Rimegapant - przełomowy lek w leczeniu migreny - przegląd literatury

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Abstract:

Migraine is a chronic condition that manifests itself periodically. It is characterized by recurrent, severe, often hemiplegic, throbbing headaches accompanied by autonomic symptoms in the form of nausea, vomiting, hypersensitivity to noise and light. For many years, triptans have been the gold standard in the treatment of migraine, acting by constricting blood

vessels and inhibiting the release of neuropeptides. However, their efficacy is not satisfactory for all patients, especially those with cardiovascular disease. In response to the need for effective and safe therapies, gepants, a new class of drugs that block the calcitonin gene-related peptide (CGRP) receptor, have emerged. Rimegepant, one of the newest representatives of gepant, has been approved for the treatment of migraine both in the acute attack phase and prophylactically. Clinical trials have shown its effectiveness in reducing the number of days with migraine and alleviating associated symptoms. Rimegepant also has a favorable safety profile, making it a promising therapeutic option for migraine patients.

This article aims to discuss in detail rimegepant as a new treatment option for migraine, including its mechanism of action, efficacy, safety profile, clinical trial and outlines the benefits of introducing this drug into standard clinical practice.

Keywords: CGRP;gepant; headache; rimegepant; migraine;CGRP receptor antagonist

Introduction:

1.Migraine, which is one of the most common neurological diseases in the world, affects about 15% of the global population, including both adults and children.[1] It is more common in women than men, and its first symptoms usually appear between the ages of 20 and 40. It is characterized by recurrent, intense headaches, often unilateral, accompanied by symptoms such as nausea, vomiting, and hypersensitivity to light (photophobia) and sound (phonophobia).[17]Migraine significantly affects patients' quality of life, making it difficult to function both professionally and personally on a daily basis.

Despite the numerous available treatment methods, managing migraines remains challenging for both patients and doctors due to the variety of symptoms and the varying efficacy of medications among different patients. The exact etiology of this condition is still not fully understood, though it is known that both genetic and environmental factors play a role.

Biologically, migraines are associated with brain dysfunctions, including abnormal neuronal activity and neurogenic inflammation.

Methods of treating migraine:

Migraine treatment is complex and includes both pharmacological and non-pharmacological strategies.Ad hoc migraine treatment, which aims to quickly and permanently stop the attack, prevent recurrences and return the patient to pre-attack functioning, most often involves the use of non-steroidal anti-inflammatory drugs (NSAIDs). One example is acetylsalicylic acid (ASA), which, by blocking cyclooxygenase (COX), reduces prostaglandin synthesis, leading to a reduction in inflammation and pain.

For many years, the gold standard in the treatment of migraine was triptans, which work by inhibiting the release of neuropeptides from nerve fiber endings and constricting blood vessels . Despite their efficacy, triptans are not suitable for all patients, especially those with cardiovascular disease, due to their vasoconstrictive effects, including on the coronary vessels.[2,3,4,23]

Preventive treatment of migraines aims to reduce the frequency and severity of migraine attacks. [7,8]Various groups of drugs are used for this purpose, including antiepileptic drugs, beta-blockers, and antidepressants.[23] Some of these medications may have contraindications, limited to moderate efficacy, moderate to high adverse event rates (which limit their use), or cause interactions.[5,6] Consequently, there is a need for the development of new therapies that are effective and safe for a broader group of patients, both in the treatment and prevention of migraines. [9]

Methodology:

The authors, relying on databases such as PubMed and Google Scholar, created this article summarizing a review of currently available publications on the new gepant migraine treatment drug, rimegepant.

CGRP antagonist receptor:

In response to the previously mentioned needs, a new class of drugs called gepant has been introduced that act as antagonists of the calcitonin gene-related peptide (CGRP) receptor. One of the newest and most promising drugs in this group is rimegepant. Rimegepant, known by the trade name Nurtec ODT, has been approved for use in the treatment of migraine in both the acute attack phase and prophylactically.[24]

Rimegepant:

Rimegepant works by blocking CGRP receptors, which play a crucial role in migraine pathophysiology. CGRP is a neuropeptide that dilates blood vessels and is released during migraine attacks, contributing to pain and inflammation. By inhibiting CGRP, rimegepant effectively disrupts the pain signaling pathway associated with migraine attacks. This results in reduced inflammation, limited blood vessel dilation, and decreased pain signal transmission

in the brain. Consequently, patients experience relief from migraine symptoms, including headache, nausea, and sensitivity to light and sound. [10,13,14]

Rimegepant is available in tablet form for oral use, with simple and convenient dosing for patients. For acute migraine treatment, one 75 mg tablet is recommended at the onset of symptoms. It is available as an oral tablet or an orally disintegrating tablet (ODT), which is convenient especially for patients who have difficulty swallowing during a migraine attack. For migraine prevention, the recommended dose is one 75 mg tablet every other day. Dose adjustment is not necessary for elderly patients or those with mild to moderate renal or hepatic impairment. [24]

Rimegepant shows a low risk of interactions with other drugs, which is important because migraine patients often use different drugs simultaneously. Minimizing drug interactions is crucial to ensure the safety of therapy.[24]It is also worth mentioning that unlike previous gepant drugs, rimegepant does not show significant hepatic toxicity, which improves its safety profile and makes it safe to use even in the long term.

The adverse effects of therapy:

The efficacy and safety of rimegepant for treating migraine attacks were evaluated in randomized, multicenter, double-blind phase three trials (Croop et al., 2019; Lipton et al., 2018, 2019a, 2019b). These studies included adult patients diagnosed with migraine at least a year prior, according to the third edition of the International Classification of Headache Disorders, with disease onset before age 50 and experiencing 2-8 moderate to severe attacks per month.

According to the International Headache Society (IHS) guidelines, the primary endpoint for assessing the effectiveness of migraine medications is pain relief after 2 hours. Rimegepant 75 mg was evaluated in three phase III trials (Croop et al., 2019; Lipton et al., 2018, 2019a). The percentage of patients achieving pain relief at 2 hours ranged from 19.2% to 21%, and those with relief from associated symptoms ranged from 35% to 37.6%. In each trial, rimegepant was significantly more effective than placebo, confirming its efficacy in treating migraine attacks. Clinical trials also demonstrated that rimegepant has a favorable safety profile. [15,16]

Another study that evaluated the efficacy and safety of rimegepant in patients with episodic migraine was a multicenter, double-blind phase III clinical trial . The study enrolled adult patients with at least a one-year history of migraine and two to eight migraine attacks of moderate or severe severity per month . Patients were randomly assigned to a group receiving rimegepant (75 mg) for the treatment of a single migraine attack or a placebo group. The primary efficacy endpoints were the absence of pain (which was defined as the absence of pain in a person who experienced moderate to severe pain immediately prior to dosing) and the absence of the patient's most bothersome migraine-related symptom (i.e., phonophobia, photophobia or nausea) 2 hours after dosing. 19.6% of patients taking rimegepant, compared to 12.0% in the placebo group, experienced no pain. The percentage of patients who did not

experience the most bothersome symptom 2 hours after dosing was 37.6% in the rimegepant group compared to 25.2% in the placebo group.[25]

Rimegepant has been studied not only in the treatment of migraine attacks but also in their prevention in patients with episodic migraine. One such study was a phase III study - Croop et al., 2021.The study included adult patients with migraine diagnosed at least one year earlier according to the International Classification of Headache Disorders criteria, with disease onset before age 50. All participants had experienced at least four migraine attacks per month for the previous three months.The study included 741 patients, 370 of whom were randomized to the group treated with rimegepant (75 mg every other day) and 371 to the group receiving placebo. The majority of participants were female (83%) and Caucasian (82%).The primary endpoint was the change in the number of days with migraine per month over 12 weeks of therapy.The average monthly number of days with migraine was reduced by 4.3 days in the rimegepant-treated group, compared to 3.5 days in the placebo group.In addition, 49% of patients in the rimegepant group achieved at least a 50% reduction in the number of days with migraine, compared to 41% in the placebo group. [11,12,18]

Side effects:

Rimegepant (Nurtec ODT) is generally well tolerated, but like any drug, it can cause side effects. The most commonly reported side effects associated with its use are nausea, dry mouth, dizziness and fatigue[19,20,24]. Rare adverse reactions include shortness of breath and allergic reactions such as rash, pruritus, swelling of the face, tongue, throat or difficulty breathing[21,22,24].

Conclusion:

The favorable safety profile, unique mechanism of action, and ability to substitute rimegepant for both acute and chronic treatment confirms the fact of rimegepant's breakthrough in the treatment of migraine, and offers hope of significantly improving the quality of life of migraine sufferers worldwide. Importantly, unlike triptans, which can increase the risk of cardiovascular problems in some patients, rimegepant has no such risk. This makes it a safer option for patients with heart disease or increased cardiovascular risk. Results of clinical trials indicate that rimegepant is highly effective in treating acute migraine attacks, providing headache relief after two hours in about 20% of patients. In addition, the number of days with migraine was reduced by at least 50% in about 50% of subjects. Overall, rimegepant is a promising option for migraine sufferers, especially for those whose previous treatment was limited due to cardiovascular problems or the ineffectiveness of other therapies.

Disclosures

Author's contribution:

Conceptualization: KKul, JG; Methodology: AM,ND,EK; Software: AS,AF; Check: KKuś,MG; Formal analysis: AF,MG; Investigation:PK,AM ; Resources: JG; Data

curation:AS Writing - rough preparation: PK,KKuś,JG , Writing - review and editing: KKul, AF, ND, Visualization:EK, AM , Supervision: KKul Project administration: MG

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