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Review

NOVEL APPROACHES IN DRUG TREATMENT OF MIGRAINES

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SUMMARY – Migraine treatment can be aimed at the acute treatment of pain attacks and accompanying symptoms and at preventing the recurrence of headaches. The choice of drug depends on clinical effectiveness based on scientific evidence. If general analgesics are not appropriate for the acute treatment of migraines, the first choice are specific drug agonists of serotonin receptors class 1B and 1D triptans. Since triptans are contraindicated in patients with vascular diseases due to their vasoconstrictor effects, lasmiditan, a class 1 F agonist that does not have such an effect, was developed. A revolution in the treatment of migraine was achieved through the use of antagonist molecules against calcitonin gene-related peptide (CGRP) and its receptor. There are two types of such molecules: large molecules of monoclonal antibodies (Mabs) that are exclusively used as prophylaxis for migraines, and small molecules called gepants that can be used in acute treatment as well as for prophylaxis in migraines. Due to the pharmacological profile of Mabs, they are suitable for treatment in the parenteral form at longer application intervals (4 weeks / 1 month, or 3 months). They have an excellent clinical effect on reducing the frequency of frequent episodic and chronic migraines, which ca be achieved in a few weeks with good tolerability, in contrast to non-specific prophylactics that have lower effectiveness and tolerability. According to the latest European guidelines, CGRP Mabs may be given as the first choice in migraine prophylaxis.

Key words: *migraine; drugs; acute treatment; prophylaxis*

Introduction

Because of the prevalence and disability caused by migraine, adequate migraine treatment is of utmost importance. Depending on the frequency and severity of attacks as well as subsequent disability, patients can be treated with acute and prophylactic therapy. Modern acute migraine therapy development started in the 1960s with the discovery that an intravenous injection of serotonin (5-HT) alleviates migraine pain, although this was associated with serious side effects. Almost 30 years had to pass until 1991, when the first triptan named sumatriptan was discovered. First used in its subcutaneous form, this selective 5-HT_{1B} agonist showed excellent results with tolerable side effects. Shortly thereafter, other triptans followed in subcutaneous, oral or intranasal forms. Their efficacy stems from selectively activating the 5-$HT_{1B,1D}$ receptor, mostly prevalent in the cranial arteries, without activating other 5-HT receptors in systemic circulation. To this day, it is unclear whether they only constrict cranial vessels that are distended or if they also act by inhibiting trigeminal afferent neurons and thereby blocking the transmission of pain signaling[1].

Another key molecule in the pathophysiology of migraine is calcitonin-gene-related peptide (CGRP). A migraine attack is initiated at the periphery of the nervous system in the trigeminovascular complex,

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where CGRP, along with vasodilation, causes neurogenic inflammation, an event that causes pain stimuli in the brain. As the migraine progresses, peripheral sensitization of the trigeminal ganglion promotes sensitization of secondary brain structures, with consequent worsening of headaches and increased hyperexcitability.

To achieve its function, CGRP binds to a transmembrane receptor consisting of three subunits: receptor activity-modifying protein 1 (RAMP1), calcitonin-like receptor (CLR) and receptor component protein (RCP). Several antagonists against the CGRP molecule or its receptor were developed specifically for the treatment of migraine.

Acute migraine therapy

The current approach in acute migraine therapy is a stratified treatment method in which patients report the type and severity of their headache and decide on optimal medication. For mild headaches, non-steroidal anti-inflammatory medications are often effective, while triptans are still the main treatment option in moderate to severe attacks. For migraines with rapid onset, nausea and vomiting, intranasal and subcutaneous sumatriptan and intranasal zolmitriptan should be used. In event of the recurrence of migraine in the first 24 hours, another dose of triptan should be applied. Triptans act as 5-$HT_{1B/D}$ and 5-HT_{1F} receptor agonists, causing vasoconstriction and blocking the release of CGRP. It is important to note that because of their mechanism of action, triptans must be avoided in patients with uncontrolled hypertension, coronary artery disease, peripheral vascular disease and uncontrolled hypertension, as well as hemiplegic migraine and migraine with brainstem aura[2]. Today, options for acute migraine therapy are still very limited, especially in patients with severe migraine attacks and comorbidities. When using triptans, only about 1/3 of patients are pain-free two hours after taking them, and headache reoccurs in 30-40% of treated patients in 24 hours[3]. Additionally, up to 50% of patients experience a suboptimal therapeutic effect on current medications[4]. Another possible treatment target is another serotoninergic receptor 5-HT_{1F}, which does not have an effect on cerebral microcirculation and is not present in coronary vessels. Lasmiditan is a new, highly-selective receptor agonist which blocks the trigeminal pain pathway and can be used in patients with coronary disease and other comorbidities[5]. As seen in prophylactic therapy, CGRP is an effective new therapeutic target. Small molecules (gepants) act as CGRP receptor antagonists and block their action. They block vasodilatation and neurogenic inflammation and are believed to be safe in patients with most comorbidities. Because of their short half-life, they take effect rapidly and can be used in acute migraine attack treatment[6]. Ubrogepant was the first gepant approved by the Food and Drug Administration (FDA) in the USA for use for this indication, subsequently followed by rimegepant.

When faced with status migrainosus (a migraine lasting for more than 72 hours), opioids can exceptionally be used to break the pain cycle. Their frequent usage is contraindicated, as they can lead to medication-overuse headaches and progression to chronic migraine[7].

Prophylactic therapy

Because of limited acute treatment options and the significant disability and economic burden, it is reasonable to start with prophylactic treatment as soon as possible. Current guidelines recommend employing this treatment if there are 2 or more migraine attacks per month, if attacks last 48 hours or more, if there is a significant disability in patients due to acute treatment not being effective or if there is overuse of acute medications[8]. When choosing appropriate medication, physicians should take into consideration the patient's comorbidities, wishes, financial resources, and path of administration. Treatment starts with a low dose and that is gradually increased and must be continued for 3 to 6 months to evaluate effects. The goal is to reduce the frequency and severity of headaches by 50%[9].

Nonspecific prophylactic therapy

The first line of treatment are beta-blockers (propranolol and metoprolol). Their side effects are mild and consist of hypotension and bradycardia. First-line treatment also includes anticonvulsants, mainly valproate and topiramate. Their mechanism of action in the pathophysiology of migraine is not yet fully understood. Valproate causes blockade of voltage-gated sodium channels, but is also a strong cytochrome P450 inductor and can cause liver damage, stomach pain, diarrhea, weight loss, hair thinning and osteoporosis. Topiramate acts by increasing GABA activity and inhibiting glutamate activity. Its side

effects are paresthesias, decreased appetite, difficulty with memory and weight loss. Both drugs are also contraindicated in pregnancy[9]. Medications belonging to the second line of treatment for migraine prophylaxis are the antidepressants amitriptyline, venlafaxine and duloxetine as well as and selective beta-blockers such as atenolol and bisoprolol. Naproxen can be used for several days for short prophylaxis of menstrual migraine. Less effective medications, such as gabapentin, candesartan, lisinopril and cyproheptadine belong to the third line of migraine prophylaxis. Lamotrigine can be used as a prophylactic drug for migraine with aura[10].

OnabotulinumtoxinA is administered intramuscularly via superficial injections into selected places on the pericranial and neck musculature and has proven to be effective as a prophylactic medication in chronic migraine. It also has good tolerability and safety. Especially beneficial results have been reported in two PREEMPT studies, which recommend a minimal dose of 155 IU. However, onabotulinumtoxinA is not indicated in patients with acute migraine[11].

Additionally, there are several non-pharmacologic treatments for the prophylaxis of migraine. In some patients, behavioral therapy, relaxation and biofeedback can have positive effects on migraine. It is recommended that these methods be accompanied by prophylactic medications.

Anti-CGRP monoclonal antibodies

Recently, there has been an emergence of new and effective medications for migraine prophylaxis. It started with the development of monoclonal antibodies that target CGRP receptors or ligands (CGRP Mabs) and consequently block the development of pain. In 2018, erenumab became the first FDA-approved CGRP receptor antagonist, administered at a dose of 70 mg subcutaneously once a month. In some patients, it can be administered at a dose of 140 mg sc. Other monoclonal antibodies work as CGRP ligand antagonists. Fremanezumab is administered subcutaneously at a dose of 225 mg monthly or 675 mg quarterly, while galcanezumab also uses subcutaneous administration and a 240 mg initial loading dose, followed by a monthly dose of 120 mg. Lastly, on January 24, 2022, the European Medical Agency approved eptinezumab as an intravenous infusion in a dose of 100 mg or 300 mg once every three months. Many CGRP Mabs studies with a large number of patients (4632 in episodic and 3191 in chronic migraine) have shown the same or even better efficacy with a far superior safety profile[12]. A recently published study from Vandervorst analyzed efficacy and safety studies of currently available prophylactic agents, including monoclonal antibodies against CGRP[13]. Meta-analysis has shown that CGRP mAbs had the highest reduction of migraine monthly days, both in episodic and chronic migraine (1.9 and 2.2 days, respectively). The second most effective drug for episodic migraine was valproate (reduction of 1.7 migraine monthly days), and onabotulinumtoxinA for chronic migraine (2.0 migraine monthly days). Furthermore, studies found very high dropout rates for valproate, topiramate and amitriptyline, while CGRP mAb and propranolol had significantly lower dropout rates[14]. Another meta-analysis from China found similar efficacy and safety for erenumab, fremanezumab and galcanezumab in subgroup analysis[14]. Studies have shown that monoclonal antibodies are generally safe in patients with various comorbidities. The main side effects are injection site reactions, constipation and nasopharyngitis[15]. Direct head-to-head studies between novel CGRP mAbs and older prophylactic drugs are rare, one of them being the HER-MES study. This was a 24-week, randomized, double-blind, controlled trial conducted in 82 sites in Germany that compared the efficacy and safety of topiramate and erenumab. Results showed that 55.4% of patients on erenumab had a more than 50% reduction in monthly migraine days, compared with 31.2% of patients on topiramate. What is also very significant, 38.9% of patients on topiramate discontinued therapy due to adverse events, in comparison with only 10.6% of patients on erenumab[16].

Taking into account all the advantages of using CGRP mAbs and its increased prescribing in migraine prophylaxis, the European Headache Federation (EHF) 2019 published guidelines on the use of monoclonal antibodies[17]. They stated that CGRP mAbs should be offered to patients with episodic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance. It is recommended to discontinue oral preventive drugs when starting therapy with CGRP mAbs in patients with episodic migraine, while CGRP mAbs should be added to already present oral therapy in patients with chronic migraine. Additionally, EHF suggests continuing CGRP mAbs therapy for 6-12

months, at which point it should be reevaluated. It is also recommended to employ a therapeutic pause after 12 months of application. Anti-CGRP monoclonal antibodies should be avoided in pregnant or nursing women, in individuals with cardio and cerebrovascular diseases and in thosewith severe mental disorders or substance abuse[17]. The latest update of the EHF guidelines on the prophylactic use of anti-CGRP mAbs, published in 2022, suggests that monoclonal antibodies targeting the CGRP pathway be included as a first-line treatment option for migraine prophylaxis[18].

Gepants

Small molecules that target CGRP receptors called gepants are novel therapeutic options, both in acute treatment and prophylaxis of migraine. Their advantage is not causing cardiovascular and hemodynamic symptoms, and, in contrast to triptans, they can be applied in patients with different comorbidities. Second-generation gepants are available for clinical use in migraine: ubrogepant for acute treatment, atogepant for migraine prophylaxis and rimegepant for both. There is also vazegepant, a potential first intranasal gepant for the acute treatment of migraine (not yet approved). All of these medications have a favorable safety profile and good clinical efficacy[19]. Two important studies were published last year: a phase II/III study examining rimegepant administered every 48 hours in a dose of 75 mg, and same phase study examining atogepant in three doses (10, 30 and 60 mg), administered once daily for 12 weeks. Both studies found a reduction in the number of migraine days and headache days when compared with placebo, in acute and chronic migraine. The medications were also safe, with nasopharyngitis and nausea as the most prevalent side effects for rimegepant and constipation and nausea for atogepant[20,21]. Due to these results, rimegepant was approved by the EMA in February 2022 for acute and preventive treatment.

A major advantage of these drugs is their short half-life and oral administration, which allow more flexibility in their titration, especially in patients with a fluctuating nature of migraine attack frequency. Another advantage is faster elimination in case of toxicity and serious adverse events. It is important to note that they, due to their mechanism of action, are not likely to cause medication overuse headaches when used often for the acute treatment of migraine attacks.

New perspectives

There are several medications currently in development that target pituitary adenylate cyclase-activating polypeptide (PACAP) or its pituitary adenylate cyclase-activating polypeptide type 1 (PAC1) receptor.

Another potentially applocable drug acts as an orexin 1 and orexin 2 receptor antagonist and has an effect on migraine onset in the hypothalamus. Some formulations target glutamate pathways, and several molecules have been developed for ion channels.

Of these abovementioned drugs, the majority are in phase I and II trials, and there is a long way to go before they reach the market. Nonetheless, the perspective is looking promising regarding migraine prophylaxis[22].

Conclusion

Triptans remain the standard specific acute therapy for migraine. Novel acute therapy options, including ditans and gepants, do not have better clinical responses than triptans in patients with migraine; they may be useful for those patients who do not respond to triptans or have contraindications for their use due to different mechanisms of action. When faced with repeated severe and disabling attacks, prophylactic treatment is a mainstay for the improvement of patient quality of life. Prophylactic options have been limited until recently, and patients had problems with compliance and the side effects of therapy. Various new anti-CGRP medications represent a new hope after years of mostly ineffective migraine treatment. Although they have excellent efficacy and short-term safety, some unknowns need to be addressed. One of the major issues is the safety of long-term use of anti-CGRP medications in the prophylaxis of migraine. Although clinically controlled studies did not show an increased risk, their wide clinical application has been implemented for less than 3 years, while questions about long-term risks of use remain to be answered[23]. There is also a question about the effect of anti-CGRP medication in pregnancy, especially in light of the fact that CGRP contributes to vascular adaptations during pregnancy[24]. These issues may perhaps be solved by the use of novel anti-CGRP medications (gepants) which are administered orally, have a shorter half-life and are more flexible in titration. Some of them show similar efficiency to triptans in acute migraine attacks. Although further follow-up and real-

world clinical studies are still needed, novel therapies present a better opportunity for adequate management of patients with migraine.

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Sažetak

NOVI PRISTUPI U LIJEČENJU MIGRENE LIJEKOVIMA

D. Jančuljak i *Z. Popović*

Terapija migrene može biti usmjerena k akutnom liječenju napadaja boli i popratnih simptoma i na sprječavanje ponavljanja napadaja glavobolje. Izbor lijeka ovisi o kliničkoj učinkovitosti na temelju znanstvenih dokaza. Ako opći analgetici nisu primjenjivi za akutno liječenje migrene prvi izbor su specifični lijekovi agonisti serotoninskih receptora razreda 1B i 1 D - triptani. Budući da su triptani zbog vazokonstriktorskih učinaka kontraindicirani u bolesnika s vaskularnim bolestima razvijen je Lasmiditan, agonist razreda 1 F, koji nema takav učinak. Preokret u liječenju migrene je učinila uporaba molekula antagonista na kalcitonin gen povezani peptid (CGRP) i njegov receptor. Postoje dvije vrste molekula:velike molekule monoklonskih antititijela (Mab) koji se isključivo koriste u profilaksi migrene i male molekule ,gepanti, koji se mogu koristiti u akutnom liječenju,kao i u profilaksi migrene. Zbog farmakološkog profila Mab su pogodni za liječenje u parenteralnom obliku u većim razmacima aplikacije (4 tjedna / mjesec dana ili 3 mjeseca). Imaju odličan klinički učinak na redukciju frekvencije učestale epizodne i kronične migrene, koji se postiže za nekoliko tjedana, uz dobru podnošljivost, za razliku od nespecifičnih profilaktika koji imaju slabiju učinkovitost i podnošljivost. Prema najnovijim europskim smjernicama CGRP Mab mogu se davati kao prvi izbor u profilaksi migrene.

Ključne riječi: *migrena, lijekovi, akutno liječenje, profilaksa*