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EDITORIAL

New Therapeutic Options for Migraine

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1. INTRODUCTION

There are more than 200 types of headache disorders, but migraine remains one of the most important causes of morbidity in the general population. The International Classification of Headache Disorders (ICHD-3) defines migraine a common neurological disease which has at least two characteristics such as unilateral location, pulsating quality, pain intensity from moderate to severe, and/or worsening with physical activity. Nausea and/or vomiting or photo and phonofobia are symptoms that are often associated with pain [1]. The social, economic and psychosomatic impacts of the condition represent the most important variable of burden disease rather than the prevalence itself, which is estimated to be around 14-15%, with a global population ill health quantified in years lived with disability (YLDs) of 4.9% [1, 2]. Therefore, goals of migraine management are the control of acute symptoms and the reduction of intensity of crises and the number of monthly episodes. International guidelines recommend prevention regimes with drugs such as beta-blockers (*e.g.* metoprolol, propranolol), low dosages of antidepressants (*e.g.* amytriptiline), or second-generation antiepileptic drugs such as topiramate [3]. However, the use of these drugs can be complicated by several side effects especially if they are administered chronically (*e.g.*, fatigue, dizziness, hypotension, bradycardia, insomnia, sleep changes and erectile disfunction with beta-blockers; blurred vision, drowsiness, weight gain, constipation, and dry mouth with amytriptiline; loss of appetite, coordination, paresthesias, and weight loss with topiramate), and the risk of symptom relapse after drug interruption is high [4].

The recent introduction of drugs targeting the Calcitonin Gene Related Peptide (CGRP), which is a 37-aminoacids composed neuropeptide of the calcitonin peptide family has improved the available options for migraine prevention [5]. CGRP enhances the glutamate and acetylcholine transmission and the nociceptive effect of noxious stimuli, being most abundant in the trigeminal system, a crucial pathway of the migraine pathophysiology. The CGRP overexpression is associated with mechanisms such as mast cell degranulation, vasodilation, neurogenic inflammation and consequent trigeminovascular system dysfunction [6].

Two types of drugs blocking CGRP have been approved by the Food and Drug Administration, monoclonal antibodies (mAbs) against CGRP or its receptor (fremanezumab, erenumab, eptinezumab and galcanezumab) and small-peptide antagonists (gepants) *versus* CGRP-r (atogepant and rimegepant). Randomized controlled trials (RCTs) have demonstrated an overall efficacy of mAbs *versus* placebo in reducing monthly migraine days (MMD) in both chronic and episodic migraine. A MMD $\geq$ 50% responder rate was observed in up to 57, 34, 38, and 49% of patients treated with erenumab, frenezumab, galcanezumab, and eptinezumab, respectively. The treatment was well tolerated without significant side effects; these were most often erythema in the site of injection, nasopharyingitis and influenza. Results from the real-world studies have confirmed the anti-CGRP(-R) mAbs efficacy even in patients who were not enrolled in RCTs for failure of multiple treatment regimens with prophylactic drugs, confirming the benefits in terms of migraine prevention [7]. However, the high cost of these drugs limits their use in clinical practice [8], which is reserved to cases of difficult-to-treat migraine where other available treatments are not tolerated and/or have not been effective for at least 8 weeks of therapy [3].

Two CGRP-r antagonists (ubrogepant, rimegepant) have been approved for the acute management of migraine. These drugs have demonstrated a good safety and tolerability profile (nausea as the most common side effect), and an optimal response rate without any risk of Medication Overuse Headache (MOH), for repeated treatments, especially rimegepant. Ubrogepant was associated with a significant pain relief in up to 80.4% of participants in a prospective observational real-world study using the Migraine Buddy application, and rimegepant was associated with a $\geq$ 30% reduction of baseline MMD in 78.6% of participants in another large study [9].

Lasmiditan is a high affinity agonist of the 5-hydroxytryptamine 1F (5-HT1F) receptor, for treatment of the acute migraine attack. Full information about its complete mechanism of action is unknown, but the migraine relief presumably derives from the inhibition of pain pathways, including the nerve trigeminal pathway and from a reduction of neuropeptide release. *Ex-vivo* studies show that lasmiditan is not associated with human coronary arteries vasoconstriction probably for a high affinity for 5-HT1F rather 5-HT1B (respectively mediating vasodilatation and vasoconstriction) receptors [10].

The A Study of Two Doses of lasmiditan (100 mg and 200 mg) Compared to Placebo in the Acute Treatment of Migraine: A Randomized, Double-blind, Placebo-controlled Parallel Group Study (SAMURAI) and the A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute Treatment of Migraine: A Randomized, Double-blind, Placebo-controlled Parallel Group

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Study (SPARTAN) studies have demonstrated that lasmiditan was effective and well tolerated in reducing migraine attacks at different two and three dosages, respectively, also in patients with a high cardiovascular risk (SAMURAI). A two-hour pain relief was reached in up to 64% of patients having an acute migraine attack [11, 12].

Also a celecoxib oral solution was effective in reducing migraine attacks, however serious safety concerns such as ulceration, spontaneous bleedings and thrombotic events (*e.g*., myocardial infarction) limit significantly its use in clinical practice, especially in older adults [13]. Growing evidence shows that neuromodulatory devices (Remote Electrical Neuromodulation, REN) can modulate pain by activating endogenous analgesia with transcutaneous upper arm electrical stimulation and relieve migraine episodes, with no significant safety concerns (paresthesia has been described as the most common symptom after the treatment) [14].

CONCLUSION

In conclusion, the récent introduction of new therapeutic options for migraine has improved the avalable drugs in migraine prévention and attack treatment. Future research should compare the efficacy and safety profile of these drugs with the regimes that are currently available as first-line treatment. The development of new drugs with the best cost-effectiveness ratio could change in the future the first choice options for reducing migraine attacks.

Another important problem is the risk of Medication Overuse Headache (MOH); this could be limited by the routine use of REN, which is however currently unavailable in most headache centers. Rimegepant should be considered in patients at risk of MOH, such as those with refractory chronic migraine and that can worsen with multiple therapies.

LIST OF ABBREVIATIONS

CGRP = Calcitonin Gene Related Peptide

ICHD-3 = International Classification of Headache Disorders

5-HT1F = 5-Hydroxytryptamine 1F

mAbs = Monoclonal Antibodies

MMD = Monthly Migraine Days

MOH = Medication Overuse Headache

RCTs = Randomized Controlled Trials

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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