Lasmiditan: A New Promising Drug in Migraine

Migraine is a major cause of disability worldwide. Despite the high prevalence and significant morbidity, the pathogenesis of migraine is still not fully understood and understanding about migraine is still evolving. As the paradigm of migraine pathogenesis has changed over time, different therapeutic agents have been developed over the years. Until recently, cerebral and meningeal arterial vasodilation was considered the main pathophysiological event behind the various symptoms of migraine.[1] Various vasoconstrictors including ergotamine were discovered that aborted migraine headaches. However, these non-selective vasoconstrictors had an affinity for several receptors causing various cumbersome side effects.

The vasoconstrictor effects in human cerebral arteries are primarily mediated by 5-HT (serotonin) receptors. Therefore, more selective 5-HT receptor agonists were developed as anti-migraine drugs with the intention of having fewer side effects. 5-HT1B/1D receptor agonists, triptans, are nowadays the first-line therapy for moderate-to-severe migraine attacks. However, the vasoconstriction properties of triptans make them unsuitable for patients with a history of cardiac and cerebrovascular diseases. Cases of myocardial infarction and stroke have been reported in the literature in relation to triptan therapy. Therefore, triptans are not recommended in patients having risk factors for cardiac and cerebrovascular disease.[2]

In recent years, it has been shown that cranial vasodilation is mainly a secondary phenomenon because of activation of the trigeminovascular system.[3] Therefore, it was hypothesized that vasoconstriction is not essential to treat migraine headaches. So, drugs targeting neurons (trigeminal pathway) were suggested and 5-HT1F receptors were considered as a potential target for it. The 5-HT1F receptors are located on the trigeminal ganglion, trigeminal neurons, brainstem, cerebral cortex, and the cerebellum, but not on vessels. Hence, a search for a drug targeting 5-HT1F receptors was made and it led to the development of lasmiditan.[4] This class of drug is called neurally acting anti-migraine agents (NAAMAs) or ditans. Lasmiditan is the only drug in this class that has been evaluated in phase III clinical trials, and the Food and Drug Administration (FDA) has approved its use in October 2019 for the acute treatment of migraines with or without aura in adult patients.

Lasmiditan is administrated orally in 50–200 mg doses. In this issue of the journal, a meta-analysis have been published for the optimal dose of lasmiditan for the treatment of acute migraine attack.[5] The authors noted that lasmiditan 200 mg is more suitable for the treatment of acute migraine in adult patients with cardiovascular risk factors for attaining headache pain-free at 2 h and sustained pain freedom at 24 h compared to lasmiditan 100 mg. Compared with lasmiditan 100 mg, headache pain freedom at 2 h is about 77% higher with lasmiditan 200 mg. The difference was significant even in sustained pain freedom at 24 h in lasmiditan 200 mg group. However, there was no significant difference in relief of headache at 2 h and in disability level at 2 h between both groups. Lasmiditan appears to be a promising drug for migraine attacks, and some authors believe that it can be a first-line therapy for migraine attacks in patients with cardiovascular or cerebrovascular risk. It can be also used as a second-line treatment if patients do not show a response to triptans or NSAIDs.[6] However, several issues need to be explored before such claims. The efficacy of lasmiditan has not been evaluated in any comparative studies with triptans and NSAIDs. Lasmiditan should be tested in comparative studies with NSAIDs and triptans.

Lasmiditan is a centrally penetrant drug and several central nervous system (CNS) associated adverse events were noted in clinical trials. The incidence of adverse events increased with increasing dose of lasmiditan. The common side effects of lasmiditanare were dizziness, fatigue, paresthesia, and sedation (more than 5% each). Other less common side effects include vertigo, incoordination, visual impairment, anxiety, tremor, sleep disturbance, cognitive changes, confusion, euphoric mood, and hallucinations. Most of the adverse effects reported with lasmiditan treatment are mild and well tolerated and there were no treatment-related serious side effects. However, discontinuation of lasmiditan in the long-term safety study was noted in in 11.2% and 14.4% of lasmiditan 100 mg and 200 mg groups. Dizziness was the most common side effects resulting in discontinuation of lasmiditan in the long-term safety study.[7,8]

Driving impairment is a notable risk with lasmiditan and patients must be advised not to drive or perform hazardous activities for at least 8 h after taking lasmiditan. FDA suggests that if patients who cannot follow this advice should be warned not to take lasmiditan.[9] It can be a big limitation in using this drug. Moreover, there is a need to be aware of other potential side effects that can be associated with lasmiditan. Euphoric mood and hallucinations associated with lasmiditan use may increase abuse potential. Clinical trials have demonstrated a higher abuse potential with lasmiditan than placebo. Although it was noted at a low frequency (about 1% of patients), a warning should be issued to every patient. Serotonin syndrome is another concern. Clinical features consistent with serotonin syndrome were reported in clinical trials.[9] The incidence of serotonin syndrome may increase during co-administration with serotonergic agents. SS typically occurs within minutes to hours of initiating a serotonergic agent and it can be fatal. As overuse of any acute migraine medications leads to medication overuse headaches, a possibility of MOH exists with lasmiditan. Physicians and patients should be aware of all these potential side effects.

Overall, the prospect of lasmiditan looks excellent. But we need to be cautious till more data are available, especially in relation to long-term term use of the drug.

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