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Review Article

Lasmiditan: the first neurally acting anti-migraine drug

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ABSTRACT

Lasmiditan is the first neurally acting drug for the treatment of acute migraine. It is a highly selective, orally acting 5-HT_{1F} agonist that was approved in November 2019, for the acute treatment of migraine in adults, with or without aura, by USFDA. Lesmiditan may help in terminating the acute attack of migraine by inhibiting the central and peripheral neuronal activity and the release of CGRP.

Keywords: Lasmiditan, 5-HT_{1F} agonist, Migraine

INTRODUCTION

Migraine is a primarily a headache disorder characterized by pulsating headache, moderate to severe in intensity, usually restricted to one side, often associated with nausea, vomiting, sensitivity to light and sound which often aggravates by routine physical activity. It is more common in women due to hormonal influences.[1] It ranks sixth in the years lost due to disability (YLD) worldwide.[2] Therefore, prompt treatment and prophylaxis of the chronic patients becomes imperative.

There are various classes of drugs used for the treatment and prophylaxis of migraine, depending upon the severity, such as non-steroidal anti-inflammatory drugs like paracetamol, aspirin, metamizole, ibuprofen and indomethacin and their combinations, selective 5-$HT_{1D/1B}$ agonists (triptans), ergot alkaloids, antiemetics, beta blockers, tricyclic antidepressants, calcium channel blockers and antiepileptics. Cardiovascular diseases like uncontrolled hypertension, myocardial infarction and arrhythmias, stroke and hemiplegic migraine require the restricted and cautious use of triptans.[3] This led to the search for newer effective drugs for the treatment of migraine without vasoactive properties.

Calcitonin gene related peptides (CGRP) receptor antagonists or "gepants" have been found to be effective for the prevention and treatment of acute migraine. Ubrogepant and rimegepant are the orally active drugs belonging to this class which have been approved by the United States food and drug administration (USFDA) in December 2019 and February 2020 respectively.[4,5]

A new drug, lasmiditan, a member of the novel class "ditans", a serotonin (5-HT)$_{1F}$ receptor agonist, has been approved for the treatment of adult patients suffering from acute migraine with or without aura in October 2019. Lasmiditan is devoid of vasoconstricting action and is the first neurally acting antimigraine agent (NAAM).[3,6]

5-HT_{1F} RECEPTOR AND MIGRAINE

The trigemino-vascular system has a pivotal role in the migraine headache. It comprises of the trigeminal nucleus caudalis, trigeminal ganglia and the C1-C2 segments of the spinal cord. The activation of this system results in a cascade of events leading to the symptomatology of migraine.[7]

The 5-HT_{1F} receptors are widely expressed in the CNS. They are found centrally and peripherally in trigeminal

nucleus caudalis and trigeminal ganglion respectively, in the cerebral cortex, hypothalamus and the locus coeruleus i.e. the sites involved in the migraine pathophysiology.[8]

As the 5-HT_{1F} receptors are located in the trigeminal system, which is involved in the pathophysiology of migraine, it was hypothesized that 5-HT_{1F} receptor selective agonists may help in terminating the acute attack of migraine by inhibiting the central and peripheral neuronal activity and the release of CGRP.[3]

Lasmiditan is the newest, highly selective, orally acting 5-HT_{1F} receptor agonist found to be effective in the treatment of acute migraine (Figure 1).

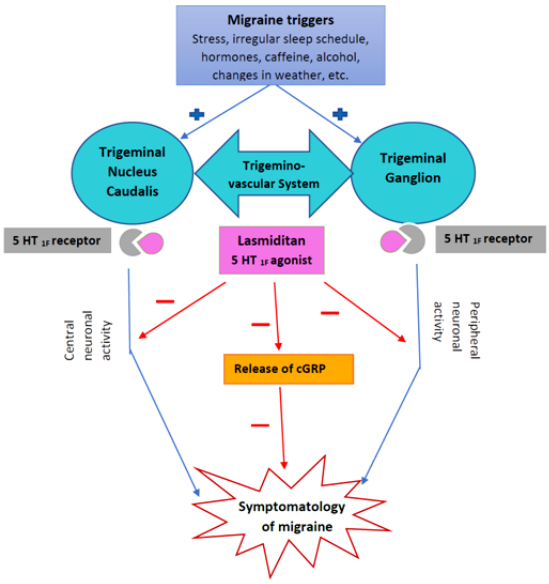

Figure 1: Mechanism of action of lasmiditan.

SELECTIVE 5-HT_{1F} AGONIST: LASMIDITAN

Lasmiditan has been recently approved for the acute treatment of migraine in adults with or without aura in 2019. It is not indicated for the prophylaxis of migraine.[9] It is available as 50 mg and 100 mg tablets and the recommended daily dose is 50 mg, 100 mg or 200 mg orally, with not more than one dose to be taken in 24 hours.[10] However, doses between 100-400 mg have shown antimigraine activity.[11]

EFFICACY AND SAFETY DATA

The approval of lasmiditan was based on the results of two-phase III trials, SPARTAN and SAMURAI. It was observed that patients treated with 100 mg and 200 mg lasmiditan showed significantly higher rates of pain freedom and total migraine freedom, starting at 60 minutes compared with placebo.[12] Also, the rate of freedom from most bothersome symptoms was significantly higher in the above two groups in comparison to placebo.[12] Lasmiditan in 200 mg dose produces freedom from migraine related functional disability in 60 minutes as against 90 minutes required by lasmiditan in dose 50 and 100 mg to produce the same.[12] Moreover, fewer patients who took first dose of lasmiditan, compared to placebo, required a second dose of it.[13]

In another phase 3 migraine trial, lasmiditan in doses 200 mg and 100 mg was found to be significantly effective in relieving headache of 32.2% and 28.2% of migraine patients respectively with ≥1 cardiovascular risk factors after 2 hours of dosing as compared to relief seen in 15.3% patients by placebo. Further, statistically significantly more patients treated with lasmiditan 200 mg ($p<0.001$) and 100 mg ($p<0.001$) had relief from their most bothersome symptoms after the first dose as compared to placebo. A statistically significant ($p<0.05$) relief was also seen in the phonophobia, photophobia and global disability ratings with lasmiditan as compared to placebo.[14]

In a phase 3 trial, Lasmiditan, in doses 50 mg, 100 mg and 200 mg, was found to significantly produce freedom from pain and freedom from most bothersome symptom 2 hours after first dose, in patients with migraine, including those with ≥cardiovascular risk factors.[15]

Lasmiditan was observed to be safe and well tolerated in all the doses i.e. 50 mg, 100 mg and 200 mg. Dizziness, fatigue, vertigo, paresthesia, somnolence and nausea were the dose dependent, treatment emergent adverse events (TEAEs) observed with lasmiditan across clinical trials.[3,13,15] The patients should be advised not to drive or operate any machinery until at least 8 hours after taking a dose.[10]

There was a low incidence of cardiovascular TEAEs which included palpitations, bradycardia and tachycardia.[13,15] Lasmiditan was found to be safe in persons having cardiovascular risk factors.[13,15,16] Further, it does not produce QT prolongation even at 400 mg dose.[17] The adverse events observed were mild or moderate in intensity and did not warrant its discontinuation.[13] However, caution has to be exercised while taking it.

It should not be used in combination with alcohol or other CNS depressants as it may cause sedation. Its concomitant administration with trazodone, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors and tricyclic antidepressants may increase the risk of serotonin syndrome. It should be used with caution in patients taking drugs which lower the heart rate. It should be avoided in patients taking substrates of P-glycoprotein and breast cancer resistant protein (BCRP).[10]

CONCLUSION

Lasmiditan is a new highly selective 5-HT_{1F} agonist approved for the treatment of acute migraine. It is a drug

without vasoactive properties and has the benefit of a good safety profile with mild side effects. Therefore, it seems to be a promising drug for migraine, upon looking at new theories of pathogenesis of migraine.

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