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New Drug Update

Lasmiditan: new drug for acute migraine

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ABSTRACT

Migraine is ranked by the World Health Organization as the world's second leading cause of disability. The current state of knowledge suggests that migraine is a neuronal process involving activation and sensitization of the trigeminal nociceptors and the trigeminocervical complex, as well as cortical spreading depression and abnormal brainstem activity. The present non vascular etiological basis has opened a new horizon in the treatment of acute migraine targeting the trigeminal pathways. Lasmiditan, a highly selective 5-HT1F receptor agonist, acts on the trigeminal system without causing vasoconstriction because of its low affinity for 5-HT1B receptors. The compound belongs to a new class of drugs "ditans" and its mechanism of action is neuronal without evidence of vasoactive effects as seen with triptans. It lowers plasma protein extravasation decreasing the neurogenic inflammation of the dura and suppress neuronal firing within the trigeminal nucleus caudalis. Also, 5HT1F agonists have shown to decrease c-fos activity within trigeminal nucleus thereby reducing the level of synaptic activation. The onset of action of lasmiditan is fast, shows rapid absorption, oral bioavailability of 40% and linear pharmacokinetics. Most common adverse reactions seen are dizziness, paresthesia, somnolence, nausea, fatigue and lethargy with dizziness being the most recurrently reported adverse event. Clinical trials for lasmiditan to date have been positive, and maiden results suggest that lasmiditan may be a new safe and effective option for acute migraine treatment, especially for patients refractory to or unable to tolerate triptans, and/or for patients with pre-existing cardiovascular disease. With Eli Lilly and Co. having already applied for US FDA approval in Nov 2018, lasmiditan may soon be a new addition to the mounting armoury of drugs against migraine.

Keywords: Lasmiditan, Migraine, 5 HT1F receptors

INTRODUCTION

Migraine is ranked by the World Health Organization as the world's second leading cause of disability.[1] Being an episodic disorder, the centrepiece of which is a severe headache generally associated with nausea and/or light and sound sensitivity, it is one of the most common complaints encountered by neurologists in day to day practice. The current state of knowledge suggests that migraine is a neuronal process involving activation and sensitization of the trigeminal nociceptors and the trigeminocervical complex, as well as cortical spreading depression and abnormal brainstem activity.[2,3] The once popular vascular theory of migraine, which suggested that migraine headache was caused by meningeal vessel dilatation, is no longer considered viable and is now thought to be an

epiphenomenon resulting from instability in the central neurovascular control mechanism.[4,5] Triptans, selective 5-HT1B/D agonists induce cerebral vessel vasoconstriction, are currently a first-line treatment for acute migraine. Their activity works not only on cerebral vessels but also on cardiac endothelial cells, causing cardiac vasoconstriction.[4] As per a study carried out by Visser et al, it was observed that 76% of patients taking oral sumatriptan experienced heavy arms and 50% experienced chest pressure.[6,7] Besides, case reports of myocardial infarction and stroke after instigation of sumatriptan have also been documented.[8-10] Triptans are contraindicated in patients with cardiovascular disease, cerebrovascular disease, uncontrolled hypertension, and hemiplegic migraine.[6] Another class of drugs, NSAIDS, used for acute migraine treatment, have been allied with increased risk of myocardial infarction.[11] Because cardiovascular conditions, events, and procedures are common in migraine and because ≈30% to 40% of patients with migraine do not respond to triptans, there is an impending need for new acute migraine treatments.[12]

Now with the present non vascular etiological basis of migraine, efforts are being made to develop new acute migraine treatments targeting the trigeminal pathways while avoiding the vasoactive 5-HT1B and 5-HT1D receptors. The 5-HT1F receptor is a potential target in this regard with promising preliminary results as a putative migraine treatment target. Lasmiditan, a highly selective 5-HT1F receptor agonist, acts on the trigeminal system without causing vasoconstriction because of its low affinity for 5-HT1B receptors.[13] Lasmiditan is being developed as an acute therapy for migraine to cater significant unmet needs in patients with cardiovascular risk factors, those with stable cardiovascular disease, or patients who respond poorly to their current treatment.

With phase 2B study showing promising results, phase 3 pivotal trial, with a prespecified modified intent-to-treat (mITT) analysis population, was conducted under Special Protocol Assessment with the US Food and Drug Administration (FDA).[14,15] Results of the trial show that Lasmiditan dosed at 200 and 100 mg was efficacious and well tolerated in the treatment of acute migraine among patients with a high level of cardiovascular risk factors.[16]

MECHANISM OF ACTION

Lasmiditan, earlier known as COL-144 and LY573144, is a highly selective 5-HT1F agonist. Structurally different than triptans, this compound constitutes a new class of drugs, "ditans". In contrast to triptans which possess an indole structure, ditans replace this indole group with a pyridine-piperidine scaffold. Triptans non-specifically bind to the 5-HT1B and 5-HT1D receptors and with varying affinity bind the 5-HT1F receptors, causing direct vascular vasoconstriction.[17] In contrast, ditans are selective for the 5-HT1F receptor and its mechanism of action is neuronal without evidence of vasoactive effects as brought out in pre-clinical and clinical models.[18,19]

Lasmiditan is a highly selective 5-HT1F agonist, having a greater than 450-fold increased affinity for 5-HT1F over 5-HT1A, 5-HT1B and 5-HT1D receptors. Also, the 5-HT1F receptor is not found on vascular structures and lasmiditan has not been shown to have vasoconstrictive effects.[17]

In the context of present accepted pathophysiology of migraine pain, activation of trigeminal neurons stimulates the release of signalling proteins including calcitonin gene related peptide (CGRP), plasma protein extravasation, and mast cell degranulation.[5,20-22] Various studies have shown that 5-HT1F receptor agonists lower plasma protein extravasation decreasing the neurogenic inflammation of the dura[17] and suppress neuronal firing within the trigeminal nucleus caudalis.[23] Also, 5HT1F agonists have shown to decrease c-fos activity within trigeminal nucleus thereby reducing the level of synaptic activation.

PHARMACOKINETICS

There is a paucity of data on the pharmacokinetics of lasmiditan. During Phase I clinical trials, the peak drug concentrations (Cmax), time at peak concentration (Tmax), area under the curve from administration to time 30 hours (AUC[0-t]) were measured in fed and fasted states. The Cmax (ng/mL) and Tmax (hours) with 200mg of lasmiditan were 394.7ng/mL and 2.5 hours in the fed state and 322.8ng/mL and 1.5 hours in the fasted state. The AUC(0-t) was higher in the fed (2,244ng.h/mL) than the fasted state (1,892ng.h/mL) respectively.[24] In a larger multicenter, double-blind, placebo controlled parallel-group, dose-ranging study rapidly disintegrating tablets of lasmiditan were used for acute migraine treatment.[25] This formulation shows rapid absorption, oral bioavailability of 40% and linear pharmacokinetics.[26]

The onset of action was fast. Lasmiditan reduced headache severity starting as early as 30 minutes in the 400mg group versus placebo (Cochran- Mantel-Haenszel [CMH] mean score test, $p = 0.0137$). After 1 hour all but the lowest dose of lasmiditan (50mg) were superior to placebo, and from 1.5 to 4 hours, all lasmiditan groups were superior. The therapeutic gain (2 h) for oral lasmiditan 100 mg was 38% (95% confidence interval [CI] 28-51%).

CLINICAL TRIALS

Lasmiditan has been studied in three Phase III clinical trials. The two-double blind, placebo-controlled, randomized controlled trials are complete and have submitted results. The one ongoing study, an open-label, long-term safety study, has reported interim results.

SAMURAI (ID NCT02439320, COL MIG-301)

The first Phase III clinical trial is SAMURAI, a prospective randomized, double blind, placebo-controlled, parallel group study which aimed to evaluate the efficacy of two doses of lasmiditan compared to placebo for acute

migraine. Primary end points noted were headache freedom at 2 hours post-dose and secondary end points were relief of headache, use of any rescue medication, recurrence of headache, relief from most bothersome symptom (nausea, phonophobia, photophobia), and safety. The study enrolled patients till July 2016 (total 1856). The percentage of patients with headache freedom at 2 hours was statistically significant (P<0.05) when compared to placebo (43%) for both 100 (59%) and 200 mg doses of lasmiditan (59%). Likewise (Table 1), the 2-hour headache-free rates were statistically significant (P<0.05) for the 100 mg (28.2%) and 200 mg (32.2%) doses when compared to placebo (15.3%). Nearly 41% of patients had relief of the most bothersome symptom in both 100 and 200 mg groups compared to 30% with placebo (P<0.05). As seen with the Phase II trials, the most common side effect was dizziness, reported in 12.5% and 16.3% of those in the 100 and 200mg group, respectively.[27]

Table 1: Results summary of COL MIG-202, SAMURAI and SPARTAN.

Oral dose	50mg	100mg	200mg	400mg	Placebo
COL MIG-202					
Number of subjects	79	81	69	68	81
2 hours headache pain freedom (%)	13.9	13.6	18.8[a]	27.9[a]	7.4
Headache pain relief (%)	43.0[a]	64.1[b]	50.7[b]	64.7[b]	25.9
SAMURAI					
2 hours headache pain freedom (%)	---	28.2[b]	32.2[b]	---	15.3
MBS freedom (%)	---	40.9[b]	40.7[b]	---	29.5
SPARTAN					
2 hours headache pain freedom (%)	28.6[b]	31.4[b]	38.8[b]	---	21.3
MBS freedom (%)	40.8[b]	44.2[b]	48.7	---	33.5

Data from studies.[25-28]
[a]p<0.05 (compared to placebo). [b]p<0.05 (compared to placebo).
MBS-most bothersome symptoms

SPARTAN (ID NCT02605174, COL MIG-302)

With an analogous study design and similar primary and secondary outcomes as SAMURAI, SPARTAN evaluated three doses of lasmiditan (50, 100, and 200mg) compared to placebo in the treatment of acute migraine. However, in comparison to SAMURAI's participants who were healthy, SPARTAN did not exclude patients with coronary artery disease, cardiac arrhythmias or uncontrolled hypertension thereby enhancing the relevance of study. By 2017, the study reached its primary and secondary end points in all three doses being evaluated (Table 1).

The percentage of patients with headache freedom 2 hrs post dose of 50mg (28.6%), 100mg (31.4%), and 200mg (38.8%) of lasmiditan was statistically significant (P<0.005) when compared to placebo (21.3%). Relief from the most bothersome symptom after 2 hours post-treatment were statistically significant when compared to placebo (33.5%) with 50mg (40.8%, P=0.003), 100mg (44.2%, P<0.001), and 200mg (48.7%, P<0.001) doses of lasmiditan.[28]

Nevertheless, a major limitation of SPARTAN for demonstrating safety in people with cardiovascular risk factors is that these patients only used a single dose of lasmiditan; the study does not validate cardiovascular safety with repeated doses.

GLADIATOR (ID NCT02565186, COL MIG-305)

GLADIATOR, a prospective, open-label study evaluating the safety and tolerability of lasmiditan enrolled participants who completed the SAMURAI or SPARTAN trials. The study started in October 2015with an expected completion date of September 2019. As in November 2018, GLADIATOR has enrolled 2580 subjects. Subjects were randomized to receive either 100mg or 200mg of oral lasmiditan. The primary end points are the proportion of patients who experienced adverse events and the proportion of migraine attacks associated with adverse events. Also, the study aims to evaluate the proportion of attacks treated after 2 hours of drug administration. In 2016, preliminary GLADIATOR results were presented at the fifth European Headache and Migraine Trust International Congress. With almost 1100 participants enrolled by that time, it was noted that approximately 20% of patients taking both 100 and 200mg of lasmiditan experienced side effects. As seen with prior studies, dizziness was the most commonly reported side effect. No cardiovascular events or side effects have been observed or reported.[29]

ADVERSE EFFECTS AND SPECIAL POPULATION

Most common adverse reactions seen were dizziness, paresthesia, somnolence, nausea, fatigue and lethargy. In

COL MIG-202 study, dizziness was the most recurrently reported adverse event[26] and is consistent with the preliminary findings of the Phase III trials.[27-29] It is prospective that the side effect of dizziness will be dose-limiting in some patients and may lead to cessation of lasmiditan in other patients. No chest pain or chest symptoms were reported in the Phase II clinical trials.[25]

While in the Phase II clinical trials and the Phase III SAMURAI study, participants were healthy without cardiovascular risk factors, the Phase III SPARTAN clinical trial enrolled patients with pre-existing cardiovascular disease. Results of the Phase III studies have not yet been published, but initial data report no chest pain or cardiovascular side effects.[27-29] The long-term tolerability is yet to be seen but preliminary results suggest lasmiditan embraces potential for patients with pre-existing cardiovascular disease or who do not tolerate triptans due to side effects.

CONCLUSION

As on date, Triptans are the current first line treatment for acute migraines not responsive to other over-the-counter medications. However, as seen in day to day practice, there is a large group of patients who either do not respond or tolerate or have contraindications to triptans. This has led to an inevitable requirement for discovering safe and effective acute migraine treatments. Clinical trials for lasmiditan to date have been positive, and maiden results suggest that lasmiditan may be a new safe and effective option for acute migraine treatment, especially for patients refractory to or unable to tolerate triptans, and/or for patients with pre-existing cardiovascular disease. While preclinical work suggests that lasmiditan does not cause vasoconstriction, clinical evidence to date is insufficient to conclude the safety of lasmiditan with long-term use in patients with cardiovascular risk factors, and especially not in patients with a history of coronary artery disease or stroke. With Eli Lilly and Co. having already applied for US FDA approval in Nov 2018, lasmiditan may soon be a new addition to the mounting armoury of drugs against migraine.

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