Migraine prevention by targeting glutamate receptors?

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When migraine strikes, because of severe pain, often accompanied by nausea and sensitivity to light and sound, sufferers are effectively disabled for up to 72 hours. Since they are forced to stop what they are doing until the pain and other symptoms subside, migraine causes a significant loss in productivity at work and the personal lives of those affected. Migraineurs - especially the 25% of migraineurs who experience more than three migraine attacks per month - are looking to drug developers to provide new drugs to prevent migraine attacks before they start. In the U.S. alone, approximately 30 million people suffer from migraines and the cost to employers has been estimated at $13 billion annually in lost productivity. Currently, several types of drugs, like generic beta blockers, calcium channel blockers, tricyclic antidepressants and anti-epileptic drugs, some of which are used off-label, are given to prevent migraines. However, many patients have only a partial response to these products, many of which have troubling side effects. Nevertheless, many migraine patients use existing drugs, illustrating how badly new drugs are needed.

Given the role of glutamate in the pathophysiology of migraine, the future of migraine prophylaxis, may lie in modulating one of the receptors in the glutamate system, mGluR5.

At the forthcoming annual meeting of the American Academy of Neurology in Seattle (April 25 - May 2), Addex Pharmaceuticals (SIX: ADXN) will present Phase IIa data on ADX10059, a negative mGluR5 allosteric modulator, which shows efficacy in treating acute migraine

attacks and provides evidence that inhibition of this glutamate receptor subtype could play a role in stopping migraine attacks before they start.

Preclinical experiments and small scale studies in migraineurs with drugs like ketamine, which acts on glutamate signaling through NMDA receptors (functionally related to mGluR5) and the NMDA antagonist memantine, suggest that mGluR5 could play a role in the "migraine circuit," a positive feedback loop that generates the symptoms of a migraine attack. The initial step to test this hypothesis was Addex' proof of concept study in acute treatment of migraine attacks.

In the Phase IIa clinical trial of 129 migraine patients, significantly more patients taking ADX10059 than those taking placebo (16.7% vs 4.7%, respectively $p = 0.039$) were pain-free two hours after dosing. ADX10059 administration yielded better pain improvement than placebo at all time points up to two hours after treatment of a migraine attack. In addition, there were trends to superiority for ADX10059 over placebo for migraine pain improvement (mild or no pain) at all time points up to two hours post-dosing.

"Medication is available to prevent migraine but these treatments are often secondary uses of the drug and come with potentially limiting side-effects," noted Dr. Peter Goadsby of the UCSF Headache Center. "New therapies specifically developed for migraine prevention are urgently needed especially for the substantial proportion of migraine sufferers who have frequent attacks and have significant disability in their daily lives. Targeting mGluR5 signaling with ADX10059 is an interesting approach that is showing significant promise in early clinical evaluation."

"The clinical trial data for ADX10059, presented here at AAN, proved the concept that by terminating acute attacks in some patients, mGluR5 inhibition plays a role in migraine pathophysiology. Now we are looking forward to the data from our ongoing Phase IIb migraine prevention

study in the first half of 2010," said Charlotte Keywood, chief medical officer.

In December 2008, Addex initiated a Phase IIb trial to study ADX10059 as a prophylactic agent in migraine. The 12-week trial will compare ADX10059 (25mg, 50mg or 100mg) versus placebo in migraine patients who suffer three or more attacks per month. Data from the migraine prevention trial are expected in the first half of 2010.

Source: Halsin Partners