WILL THE FIRST MARKETED CGRP ANTAGONIST BE AN IMPORTANT ADDITION TO THE MIGRAINE TREATMENT ARMAMENTARIUM: YES

A. Rapoport
USA
alanrapoport@gmail.com

Migraine is a common, chronic, intermittent, painful, disabling disease causing many neurological and autonomic symptoms. Migraineurs often have severe, unilateral throbbing headaches, lasting over 12 hours, associated with nausea, vomiting, sonophobia, phonophobia and sometimes various auras. Auras usually precede the pain and are usually visual but can be sensory or speech arrest. Some patients have vertigo during the attack or interictally. Migraine affects about 12% of western populations, three times more in women than men. It causes much disability measured in pain and suffering as well as money. It is estimated that migraine costs 30 billion dollars per year, more in indirect employment lost labor costs than in direct costs of physicians, drugs and hospital care.

There are various acute care migraine treatments available, and the triptans, (serotonin$_{1B,1D}$ agonists) are widely considered the most effective treatments. The release of sumatriptan in many countries in 1991 changed the face of acute migraine treatment. Since then 6 additional triptans have been released in various countries. But triptans do not work on every patient and they often do not work optimally due to patient delays in taking their medications, poor choice of mode of administration, lack of GI absorption and a variety of adverse events, also known as triptan sensations. These can include chest and neck pain and pressure, hot feelings, dizziness, somnolence, nausea and paresthesias. These often cause patients to delay or not take their treatment. In addition there are several contraindications to using triptans such as certain migraine subtypes (e.g. hemiplegic migraine and basilar migraine) and various medical conditions including coronary artery disease, cardiac arrhythmias, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension and sensitivity to the drug. There are various drug-drug interactions that preclude the use of a specific triptan with a drug a patient is currently taking. For all these reasons, it would be helpful to have another category of acute care migraine medication that works as well or better than a triptan, has fewer triptan adverse events, could be given to patients unable to take a triptan and might be considered a safer medication than a triptan.

After over 20 years of research on calcitonin gene-related peptide (CGRP), originally thought to be the cause of migraine related pain due to vasodilation, it was discovered that blocking CGRP is helpful in acute migraine therapy, without producing triptan adverse events or causing vasoconstriction in preclinical studies in animals. To date there has been several articles on an IV preparation of olcegepant and an oral preparation of telgacepant, all showing efficacy in migraine without vasoconstriction. The phase IIB and two phase III studies on telcagepant show it to work as well triptans with fewer adverse events.

It is unclear which of these drugs will eventually be approved by the authorities but as of this writing, public disclosures suggest that Merck's telcagepant could be approved within 2 years if there are no further set backs. This drug was found to have some liver toxicity in preliminary studies to see if it would work as a preventive drug given twice per day. Hopefully further safety studies on acute care use will show it to be safe. A follow on compound was also shown to produce liver toxicity. Since this news was released publicly, there has been only silence on olcegepant.

There is no doubt that large numbers of patients could benefit from the addition of the first CGRP antagonist to our migraine treatment armamentarium. Patients with any contraindication to triptans can try this new drug. Patients who do not respond to triptans can try this drug. More importantly, the 40% or more of patients who do not have optimal efficacy or who have too made AEs from triptans can be switched to this drug. If it is shown that this new CGRP antagonist is safer than a triptan, general physicians world over will feel more comfortable giving this drug to their patients. What would you rather take for your migraine, or give to your patients Dr. Levin?