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Calcitonin Gene-Related Peptide Receptors and the Prevention of Migraines

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Abstract

Migraines are the third most prevalent disease in the world affecting approximately 15% of the population, or over one billion people. Each year, employers lose greater than $13 billion due to 113 million missed work days due to migraine. A great cost-burden and high incidence rate show a continued need for migraine treatment options. In choosing a treatment for a migraine attack, quick onset of action is one of the most important qualities. Common choices include the triptan class, NSAIDs, and a combination of aspirin, caffeine, and acetaminophen. In addition, there has been increased research into calcitonin gene-related peptides (CGRP). Due to side effect profiles, the monoclonal antibodies have been more successful than the antagonists studied. Monoclonal antibodies alone, though, have not completely eradicated migraine days per month and more research is needed.

Although drug developers have attempted to find a cure in numerous drug classes, migraines continue to afflict humans worldwide. Behind dental cavities and tension headaches it is the most prevalent disease in the world affecting approximately 15% of the world population.[1] This is broken down to more than 39 million men, women and children in the United States and over 1 billion worldwide.[1] This alone has a greater prevalence than asthma, diabetes and epilepsy combined.[2] Although not commonly associated with a high mortality rate, studies have shown that patients with migraines have a 50% greater risk for cardiovascular disease and death.[3] It is estimated that United States employers lose more than $13 billion due to 113 million workdays lost each year due to migraines.[1] These issues show that there is a continued need for research in migraine medication development.

Although its prevalence is great, the pathophysiology of migraines is still unclear. Over the past several centuries, two hypotheses have dominated the pathophysiology debate. The vascular hypothesis, which is now beginning to fall out of favor, theorized that migraines were due to an increased vasodilation of cerebrovascular arteries. Further studies using a vasodilator, nitroglycerin, and a vasoconstrictor, ergotamine, showed that vasodilation of these arteries did not trigger migraines.[4] This led to a hypothesis involving neuronal transmission and research into calcitonin gene-related peptide and selective serotonin agonists. What does remain relatively clear in migraine pathophysiology is that genetics play a role. Children with at least one parent with a history of migraines have a 50% chance of developing this disease. This continues into extended family as 80 to 90% of patients with migraines report having family members who also have a history of migraines.[1]

The word migraine originates from the Greek word, hemicrania, meaning half of the skull.[2] This coincides with one of the common characteristics of a migraine being a unilateral headache. According to the International Classification of Headache Disorders (ICHD) criteria, diagnosis of migraine can be confirmed if the patient has the following five qualities: 1. Headache attacks lasting anywhere from 4-72 hours, 2. Headache meets two of the following four symptoms: pulsating headache, unilateral in location, causing moderate to severe pain, exacerbated by or causing avoidance of routine exercise, 3. Headache causes photophobia and phonobia or causes nausea and/or vomiting, 4. History of at least five attacks meeting the above criteria, and 5. Symptoms are not more accurately accounted for by another ICHD-3 diagnosis.[5]

In the clinical presentation of a migraine, patients may endure numerous phases including prodromes, auras and postdromes. These migraines can often be triggered by an external or internal stimulus. Some examples are bright lights, loud

noises, lack of sleep, certain foods or smells and changes in hormones. A prodrome is the first sign a patient could experience before a migraine occurs and gives warning to the patient to begin treatment. This prodrome can appear in many forms from fatigue and excessive yawning, to euphoria and excitement, or photophobia or phonophobia.[6] Fortunately a majority of patients experience prodromes, which allows them to begin treatment before the headache attack phase begins. While a prodrome can last anywhere from one hour to 48 hours, an aura is much shorter and usually less than an hour. An aura begins the next phase of a migraine and precedes the headache attack phase. Auras are not nearly as common as prodromes as only 15 to 20% of patients experience this phase.[6] Visual disturbances such as blurry vision, colored spots and zigzags of light make up one of the most common auras experienced before migraine. Other symptoms may include feeling pins and needles in extremities or difficulty speaking. The next phase is the actual migraine in which the patient experiences a debilitating pulsing unilateral headache. Varying from patient to patient, the frequency and duration of these migraines are unpredictable. Following the attack phase, the patient enters the postdrome phase of exhaustion, confusion and hangover-like symptoms.[6]

Migraine Prophylaxis

Because of a migraine's quick onset and ability to incapacitate a patient for days, prevention becomes the priority. According to the 2012 American Academy of Neurology and American Headache Society guidelines multiple classes of medications are considered to have established efficacy in prevention of migraines. These classes include beta-blockers (metoprolol, propranolol, and timolol), antiepileptic drugs (divalproex sodium, sodium valproate, and topiramate) and frovatriptan for short-term prophylaxis for menstrual related migraines. These guidelines also stated that antidepressants (amitriptyline and venlafaxine), beta-blockers (atenolol and nadolol) and triptans (naratriptan and zolmitriptan for short term prophylaxis for menstrual related migraines) are probably effective at preventing migraines.[7] With uncertainty regarding the pathophysiology of migraines, it is not surprising that there are a number of classes potentially involved in the treatment of migraines that all involve different mechanisms. Beta-blockers are believed to inhibit arterial dilation seen in migraines. The antidepressants amitriptyline and venlafaxine are believed to be effective in migraine prophylaxis due to their down-regulation of serotonin receptors. Antiepileptics are believed to provide prophylaxis of migraines through the suppression of neuronal hyperexcitability by increasing gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter.[8]

Migraine Treatment

For the treatment of an acute migraine headache, therapies mimic regular

pain recommendations. According to the 2011 American Association of Family Physicians, NSAIDs are considered a first line therapy for acute migraine attack. Serotonin receptor agonists, commonly referred to as triptans, are also a first line therapy for these attacks. Unlike NSAIDs, which have many indications, triptans were developed for the treatment of migraine.[9] Sumatriptan was the first serotonin receptor agonist to be released to market. In 1993, Imitrex (sumatriptan) was FDA approved for the treatment of migraines with or without aura. Sumatriptan agonizes the 5-$HT_{1B/1D}$ receptors in the intracranial blood vessels.[10] This results in cranial vessel vasoconstriction and believed inhibition of pro-inflammatory neuropeptides. There are now seven different FDA approved triptans with numerous formulations and salts.[11] Due to the strong efficacy of triptans and NSAIDs as monotherapy, a combination of naproxen and sumatriptan (Trexima) has also been studied.[9] Studies in 2007 and 2013 found that this combination provided more favorable clinical benefits than monotherapy of sumatriptan, naproxen or placebo with a tolerable side effect profile.[12, 13] One of the concerns with the triptan class is the increased risk of cardiovascular and cerebrovascular events. Myocardial infarction, coronary artery vasospasm, subarachnoid hemorrhages, ventricular tachycardia and ventricular fibrillation are rare but have been seen in patients several hours after taking a 5-HT_1. Therefore the use of triptans is contraindicated in patients with a past medical history of the previous stated cardiovascular and cerebrovascular diseases.[10] The combination analgesic of acetaminophen (250mg), aspirin (250mg) and caffeine (65mg) is an inexpensive choice that is available without a prescription.[9]

Even with numerous drug classes explored for prophylaxis and treatment, and many FDA approved medications for migraine therapy, it remains one of the most debilitating chronic diseases in the United States. Therefore research has continued into finding a solution for the prevention of migraines. With the transition from vascular theory to neuropeptide theory, researchers have honed in on calcitonin gene-related peptides (CGRP). CGRP is a neuropeptide made up of 37 amino acids that is found in sensory neurons as well as the cardiovascular and cerebrovascular systems.[14] One of the leading cases for CGRP's involvement in migraine pathophysiology is the evidence of increased CGRP levels in a patient currently experiencing a migraine attack. When patients are given triptans to resolve the migraine attack, CGRP levels have been shown to decrease. Even further evidence of association comes from patients that received intravenous calcitonin gene-related peptide and quickly began experiencing an acute migraine attack.[14]

In targeting calcitonin gene-related peptide, researchers could focus on the peptide itself or its receptor. The first medications developed were small molecule

antagonists of the CGRP receptor.[14] Rimegepant and olcegepant are two of the small molecule antagonists that continue to move towards market, while telcagepant was pursued and then discontinued. Although pain relief rate and pain free rate show significant support for telcagepant and olcegepant compared to placebo, there are concerns of chronic use resulting in hepatotoxicity; one of the causes of telcagepant's discontinuation.[14] Calcitonin gene-related peptide has been shown to be a potent vasodilator.[15] It would make sense that antagonizing this peptide would result in vasoconstriction and relieve migraine headaches similar to the triptan class. One theory that has been supported through these trials is that although the calcitonin gene-related peptide antagonists do cause vasoconstriction and more importantly a decrease in neurogenic inflammation, they do not have an effect on the coronary arteries and do not increase blood pressure like the triptan class.[15] This selective antagonism introduces a new therapy option for patients with migraines, especially those with cardiovascular and cerebrovascular diseases that preclude them from taking triptans. With concerns of hepatoxicity and other side effects, research continued in the search of a safe and effective antagonist of CGRP.

Monoclonal antibodies have continued to be developed in more disease states as targeted and effective therapies. There are currently several different monoclonal antibodies that have recently completed phase III trials and are now applying for biologic licensing applications with the FDA.[16] Fremanezumab, galcanezumab, and eptinezumab, developed by Teva Pharmaceuticals, Eli-Lilly and Alder Biopharmaceuticals, respectively, target the molecule calcitonin gene-related peptide.[16] For Alder's eptinezumab, phase III results were positive and showed a 50% or greater reduction in migraine days in 61% of patients compared to 39% in the placebo group ($p<0.0001$), a 75% or greater reduction in migraine days in 33% of patients compared to 15 % in the placebo group ($p<0.0001$), and three-month migraine free period in 15% of patients compared to 5% in the placebo group ($p<0.0001$).[17] In Teva's fremanezumab, patients were divided in a 1:1:1 ratio to receive monthly dosing of fremanezumab, a quarterly dose followed by placebo, and placebo dosing.[18] The study found at least a 50% reduction in migraine days for 41% of the monthly dosing group, 38% of the quarterly dose group and 18% of the placebo group ($p<0.001$).[18] For Eli-Lilly's galcanezumab, studies showed a reduction of 4.7 migraine days per month for 120 mg, 4.6 days for 240 mg and 2.8 days for placebo ($p<0.001$).[19] A fourth monoclonal antibody being studied is erenumab, co-developed by Amgen and Novartis. Erenumab differs from the previous three monoclonal antibodies in that it targets the calcitonin gene-related peptide receptor instead of the peptide itself.[16] Recently published phase III trials showed a reduction of 3.2 migraine days per month for

the 70mg monthly group and 3.7 days for the 140mg monthly group compared to 1.8 days for the placebo group ($p<0.001$).[20] Amgen and Novartis also found at least a 50% reduction in migraine days per month in 43.3% of the 70 mg monthly dose and 50.0% of the 140 mg monthly dose compared with 26.6% of patients in the placebo group ($p<0.001$).[20] While this reduction of migraine days per month is a positive in developing an efficacious drug, one of the most significant findings in each of these trials was the low rate of adverse effects. Only fremanezumab showed a slight increase in hepatoxicity compared to placebo, a side effect that derailed several of the small molecule inhibitors from FDA approval. Other side effects of eptinezumab, galcanezumab and erenumab were considered either mild and minimal or not statistically significant when compared to placebo.[17-20]

Continued advances in migraine therapy signify a positive future outlook for patients hindered by this disease every day. Monoclonal antibodies appear to have a more favorable side effect profile over the small molecule antagonists, while still maintaining a strong reduction in migraine days per month. However a complete solution has not been found as patients still experience multiple migraine days per month while being prophylactically treated. Further research is needed into the calcitonin gene-related peptide, as this appears to be a significant contributor to a migraine. Through this target as well as other pathways, a combination may be found to effectively prevent a disease that impacts over one billion people.

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