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Pharmacogenomics in the Treatment of Multiple Sclerosis: A Guide to Siponimod

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Abstract

Pharmacogenomics is the study of personalized medicine based on a person's DNA. With a greater understanding of DNA in our modern society, pharmacogenomics is quickly changing the way we treat diseases. A new pharmacogenomic medication being used in the treatment of Multiple Sclerosis (MS) is siponimod (Mayzent). Mayzent has been approved as the first oral medication to treat secondary progressive MS with active disease. This is an important medication that may help to close the gap in therapy for patients who suffer from secondary progressive MS.

Multiple Sclerosis (MS) is a chronic multifactorial inflammatory disease that causes the immune system to destroy the protective covering of the nerves called the myelin sheaths.[1] The National MS Society estimates that roughly one million people suffer from MS in the United States and that roughly 2.3 million people suffer globally.[2] MS is an extremely aggressive disease that leaves many patients with an impaired quality of life. MS disrupts the normal functioning of the brain, optic nerves, and spinal cord through inflammation and tissue loss[3] that can result in lesions throughout the brain. The inflammation and demyelination causes lesions in the brain.[1] Depending on where the lesions are located will affect the types of symptoms individulas will display. These symptoms can be anything from slurred speech to losing the ability to walk.[4] Some patients only have minor symptoms, while other patient's symptoms could be debilitating. No matter the symptoms, the most important part of any treatment is preventing relapses, which causes new lesions to form, and can cause the progression of the disease to occur.

Patient's first encounter with MS is usually classified as Clinically Isolated Syndrome (CIS). This lasts for at least 24 hours with signs of the formations of one or more lesions. There are four types of MS. Relapsing-remitting MS (RRMS) which is the most common form of MS where remission is possible. Secondary progressive MS (SPMS) is defined as having little to no signs of remission. The symptoms steadily progress with time. Most people suffering from RRMS will one day progress to SPMS. Primary progressive MS (PPMS), has less inflammation than what is seen in RRMS. PPMS progresses from the beginning without relapse or remission. Progresive relapsing MS (PRMS) is a rare form of MS that progresses from the beginning and has acute relapse without remission.[5]

Over the last 50 years, the knowledge and understanding of genetic influences on an individual have advanced astronomically, leading to the development of medication With actionable pharmacogenomic information. Pharmacogenomics is the study of the effects an individual's DNA has on a medication. In theory, these medications would reduce many of the issues that current medications face, for instance improving effectiveness, preventing dangerous reactions, saving time, and money- because these medications would be designed to have the "perfect" dose for every patient. Unfortunately, this field is still very new and has its limitations. Even with these limitations, pharmacogenomics is a crucial part of modern medicine.

As of March 27, 2019, the Food and Drug Administration (FDA) approved the pharmacogenomic medication Mayzent for

the treatment of RRMS and SPMS. The FDA approval of this medication was extremely significant because few treatments for SPMS currently exist. Up to 80% of patients with RRMS will develop SPMS[3]. SPMS will continue to cause damage to the brain and spinal cord and will gradually progress over time without remission. Some patients may even suffer from the active form of SPMS meaning they have evidence of new relapses. Mayzent was needed to help fill this gap in therapy. Mayzent is a next-generation, selective S1P receptor modulator indicated for the treatment of relapsing forms of MS, to include CIS, RRMS, and active SPMS, in adults. Mayzent selectively binds to S1P1 and S1P5 receptors in the CNS. The S1P1 receptor, prevents the lymphocytes from egressing the lymph nodes and entering the CNS of patients with MS. This process leads to the anti-inflammatory effects of Mayzent[3]. Mayzent also enters the CNS and directly binds to the S1P5 and S1P1 sub-receptors on specific cells in the CNS known as oligodendrocytes and astrocytes to promote remyelination and prevent inflammation[3].

Before beginning treatment, genetic testing is required in order to determine the correct dosage for the patient. Patients will be tested for CYP2C9 variants and varicella-zoster virus (VZV) antibodies. If the patient is antibody-negative they should receive the vaccination before treatment with Mayzent. If a patient is currently taking or has taken an antineoplastic, immunosuppressive, or immune-modulating therapy, it is possible that they will have an increased immunosuppressive effect while taking Mayzent. It is also recommended that patients have an ophthalmic examination with a focus on the fundus and macula. Other prior testing that is recommended is an EKG, CBC, and transaminase and bilirubin levels within the last six months. Mayzent is contraindicated in pregnancy.[6]

Mayzent is an oral medication that can be taken with or without food. Patients with the CYP2C9 Genotype *1/*1, *1/*2, or *2/*2 will begin the initial dosage of 0.25mg once for the first two days. 0.5mg on the third day, 0.75mg on the fourth day and 1.25mg on the fifth day. After the fifth day, patients are to take 2mg daily for the duration of the treatment[7]. Patients with the CYP2C9 Genotype *1/*3 or *2/*3 will begin the treatment with an initial dose of 0.25mg for the first two days. On the third day, the dosage will be increased to 0.5mg and then be increased again on the fourth day to 0.75mg[7]. From the fifth day and on, the dosage will be 1mg[7]. If the treatment has been missed or interrupted after the initial titration for four consecutive days the treatment should be started over with the dosage beginning from day one[7]. The dosage does not need to be readjusted for patients with renal impairment or hepatic impairment.[7]

Upon the first dose patients should be monitored for the first six hours in case symptoms of bradycardia occur. The blood pressure and heart rate should be monitored every hour to monitor for symptoms. A second EKG should be administered to ensure that an AV blockage has not formed.[2]

The most common side effects of Mayzent are high blood pressure and headaches. Other possible side effects include the following: macular edema, vision changes, slowed heart rate, lung problems, liver damage, and birth defects.[6]

The FDA's approval of Mayzent was based on the Phase III EXPAND trial in 2016[8], which was the largest controlled clinical study of SPMS patients, showing that Mayzent significantly reduced the risk of the disease progression[8]. The EXPAND study is a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of Mayzent versus placebo in people with SPMS with varying levels of disability, Expanded Disability Status Scale (EDSS) scores of 3-6·5. The study consisted of 1651 patients from 31 countries. Mayzent was able to show improved confirmed disability progression by 21% (p=0.013).[3]

There is currently no generic version of Mayzent. The initial titration is available in a starter pack (Mayzent Starter Pack Oral) consisting of 0.25mg tablets. After the starter pack, 0.25 mg tablets cost $72.74 each. Each 2mg tablet costs $290.96.[7]

Upon review, Mayzent is an important new medcation in the treatment of SPMS. As mentioned previously, the gap in therapy poses a threat to the quality of life of patients suffering from MS. Mayzent gives patients more options and chances to find an effective treatment. As shown in the EXPAND study, Mayzent has shown great potential in helping to manage SPMS.

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