Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Faces of RMS Progression: Examining Treatment Considerations Through Real-World Patient Cases

Announcer:

You're listening to ReachMD. This medical industry feature, titled "The Faces of RMS Progression: Examining a Treatment Option Through Real-World Cases," is sponsored by Novartis Pharmaceuticals Corporation, which participated in the review of this content. This program is intended for US health care professionals.

The Important Safety Information for MAYZENT, or siponimod, will be available at all times underneath the player of this audio presentation. A link to the full Prescribing Information, including Medication Guide, is available below this presentation.

The speakers have been compensated by Novartis Pharmaceuticals Corporation to conduct this presentation.

Dr. Barry:

Hello everyone and welcome. My name is Dr. Brian Barry, and I am an attending neurologist at MedStar Georgetown University Hospital in Washington, DC. I'm here alongside my co-host, Dr. Amos Katz.

Dr. Katz:

Hi, everyone. My name is Dr. Amos Katz and I'm the Medical Director at the Linda E. Cardinale Multiple Sclerosis Center in Freehold, New Jersey.

Dr. Barry:

In this podcast, we will discuss two real-world patient cases with different manifestations of progression in their relapsing multiple sclerosis, or RMS, how we identify early signs of progression, why it is imperative to act on early signs of progression and why Mayzent, also known as siponimod, was an appropriate choice for these RMS patients with first signs of progression. Finally, we will discuss how we get our patients started on Mayzent.

Announcer:

Before we get started with our real-world patient cases, I think now is a good time to let our listeners know that Mayzent is indicated for the treatment of relapsing forms of multiple sclerosis, MS, to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.

Mayzent is contraindicated in patients with a CYP2C9*3/*3 genotype in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure, or presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome unless the patient has a functioning pacemaker.

Please note additional Important Safety Information provided throughout this podcast. Full Prescribing Information, including Medication Guide, is available below this presentation.

Dr. Barry:

Now, let me introduce you to a patient of mine, Susan, though that is not her real name. Susan is a 40-year-old female who was diagnosed 10 years ago with MS by a previous neurologist. She first started on an injectable therapy and had done well for about 5 years. However, she later had a few breakthrough relapses, and had to switch to a different disease-modifying therapy, or DMT. She

had a recent relapse about 6 months ago that resulted in decline in her walking ability and has since recovered from it. But she continued to have issues with bladder function, which is when she was referred to me.

Dr. Katz:

Sounds like Susan was failing her DMT and experiencing disability progression. What went through your mind when you considered her case at this juncture?

Dr. Barry:

I wanted to make sure that her accumulation of disability was related to RMS progression, in which case we will need to assess switching therapy to help delay disability progression. I asked Susan to think about how she was meeting her health goals 2 years ago compared to now. I would then go system by system from top to bottom to ask about any potential changes in vision, speech, sensation, bowel movement, etc. In Susan's case, it was the bladder issue that became prominent over time for her. I also considered her MRIs. But sometimes I find that MRIs can be considered stable even when patients are experiencing cognitive decline or worsening physical symptoms.

Dr. Katz, what do you think about this case?

Dr. Katz:

One of the most challenging parts of managing RMS patients is identifying the non-motor part of progression like cognition. It takes time to complete the neurological assessment, and it is not as straightforward as an MRI.

If the patient has a caregiver, I ask for his or her observations of the patient's daily life. I ask specific questions related to the patient's daily functions. I also track cognitive performance on standardized tests, like the Symbol Digit Modality Test, or SDMT, over time to provide some objective data points.

Dr. Barry:

Great point.

Circling back to Susan's case, I made an evidence-based decision to switch Susan to Mayzent. Mayzent is the first and only oral DMT studied and proven to delay disability progression in a more progressed RMS population. Mayzent has been studied in a broad range of SPMS patients with moderate to advanced disability, and was proven to delay disability progression in the *EXPAND* clinical trial, demonstrating a 21% relative risk reduction in time to 3-month confirmed disability progression, or CDP, compared to placebo. The post hoc analysis of the active SPMS subgroup in *EXPAND* also showed a 31% relative risk reduction in time to 3-month CDP compared to placebo. Based on post hoc analysis alone, no conclusions of statistical or clinical significance can be drawn. Susan has been stable on Mayzent for 15 months, and with physical therapy, she has regained confidence in walking.

Announcer:

Before we introduce our second patient case, let's review some additional Mayzent Important Safety Information.

Infections: Mayzent may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred.

Before starting Mayzent, review a recent complete blood count (CBC) i.e., within 6 months or after discontinuation of prior therapy. Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy. Consider discontinuing treatment if patient develops a serious infection.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine-1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with Mayzent. If CM is suspected, Mayzent should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) were reported in Mayzent clinical trials. However, they have been observed in patients treated with another S1P receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, Mayzent should be discontinued.

Cases of herpes viral infection, including cases of meningitis or meningoencephalitis caused by VZV reactivation, have been reported. Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting Mayzent. If VZV antibodies are not present, or detected, then VZV immunization is recommended, and Mayzent should be initiated 4 weeks after vaccination. Use of live vaccines should be avoided while taking Mayzent and for 4 weeks after stopping treatment. Caution

should be used when combining treatment (i.e., anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

Please see additional Important Safety Information throughout this podcast and full Prescribing Information, including the Medication Guide, at MayzentHCP.com.

Dr. Barry:

Dr. Katz, what is your real-world Mayzent patient case you would like to share with us?

Dr. Katz:

Yes, I have a 56-year-old female. We will call her Mary. She was first diagnosed 20 years ago when she was admitted to the hospital for speech impairment and gait imbalance. With a history that long, you may already anticipate disease progression to pick up speed. Mary had multiple relapses in the earlier years of her MS, and she was previously treated with a DMT. By the time Mary came to me for consultation, she had a history of increasing blurring of vision, weakness in the extremities, increasing confusion, and cognitive difficulty. She expressed that she felt, if her general neurologist was not hearing her progression concerns.

Dr. Barry:

It sounded like the general neurologist might have missed some of Mary's earlier signs of progression by the time she reached your office.

Dr. Katz:

What concerned me was that we might have already lost a significant amount of time as she experienced the symptoms of progression. I knew right away we had to switch DMT to treat her progression.

Dr. Barry:

Why do you think it is important to identify early signs of progression and intervene once you have identified those signs?

Dr. Katz:

It's important because progression, by definition, is diagnosed retrospectively. Every month that goes by without catching the signs of progression may have an impact on the patient's lives, and potentially progress their disease course. Additionally, we know that the beginning of RMS is primarily driven by inflammation which later gives way to neurodegeneration when the disease enters the progressive phase.

Mayzent is the first and only oral DMT studied and proven to delay disability progression in a more progressed RMS population, including active SPMS in the *EXPAND* trial. Additionally, Mayzent had a different mechanism of action. Mayzent is an S1P modulator. That is a small molecule that can penetrate both the brain and spinal cord, and has a dual mechanism of action that targets two key receptors that are thought to play a role in RMS inflammation and neurodegeneration. The mechanism by which siponimod exerts therapeutic effects on MS is unknown, but may involve reduction of lymphocytes in the CNS.

Dr. Barry, are there any other considerations you would include in selecting Mayzent for a patient?

Dr. Barry:

Before I get to the additional clinical data, I want to note that Mayzent had two key secondary endpoints.

A prespecified hierarchical analysis consisted of the primary endpoint and the two key endpoints of time to 3-month confirmed deterioration of timed 25-foot walk and reduction of T2 lesion volume expansion at 12 and 24 months, as 3-month confirmed deterioration of timed 25-foot walk did not reach significance, the reduction seen and T2 lesion volume expansion at 12 and 24 months compared to placebo was considered nominal. Due to the statistical design of the study, we cannot make statistical interpretation of the remaining data beyond these endpoints.

With that caveat in mind, I want to highlight that Mayzent had exploratory cognitive endpoint results with three cognitive tests. The Symbol Digit Modalities Test, Paced Auditory Serial Addition Test, and Brief Visuospatial Memory Test–Revised, or BVMT-R for short. There was an overall reduction of 21.3% in the SDMT score of greater than or equal to 4 points for Mayzent, which is regarded as a clinically meaningful change.

Overall, there was a 2.48-point difference versus placebo. The results from the PASAT and BVMT-R tests showed no clinically meaningful difference between Mayzent and placebo. As noted, no conclusions of statistical or clinical significance can be drawn.

Dr. Katz:

Thank you for sharing that, Dr. Barry. I would also like to highlight that Mayzent has interim analysis data up to 5 years from the *EXPAND* open label extension study, which was designed to evaluate the long-term safety and tolerability of Mayzent. The extension study allowed patients who completed the core 3-year part of the study to continue with Mayzent or switch from placebo to Mayzent. Select efficacy assessments up to 5 years were consistent with the core study. Time to 6-month CDP in the continuous Mayzent group showed a 22% relative risk reduction compared to those who switched from placebo to Mayzent later. Additionally, there was a 52% relative reduction in annualized relapse rate, and a 23% overall reduction in the risk of decrease in SDMT scores compared to the placebo switch group. What these data tell me is that patients who start on Mayzent earlier, experienced a greater reduction in the risk of disability progression versus patients who started Mayzent later. These exploratory analyses represent chance findings, no conclusions of statistical or clinical significance can be drawn. Consider interim analyses open label extension study is not blinded, not controlled, and includes inherent self-selection bias for remaining in the trial.

Dr. Barry:

Dr. Katz, what safety information do you highlight with your patients when speaking about the safety of Mayzent?

Dr. Katz:

I like to highlight that in the core *EXPAND* study, the most common adverse events with greater than or equal to 10% incidence were headache, hypertension, and transaminase level increase. Treatment discontinuation rates due to adverse events were similar across treatment arms; 8.5% of patients taking Mayzent discontinued treatment due to adverse events compared to 5.1% of patients with placebo. The safety profile of Mayzent remained consistent with the core study up to 5 years.

Announcer:

I also want to note to our audience some additional Important Safety Information for Mayzent.

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus including the macula is recommended, and at any time if there's a change in vision. The use of Mayzent in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patients should be considered.

Bradyarrhythmia and atrioventricular conduction delays: Prior to initiation of Mayzent, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of Mayzent treatment to help reduce cardiac effects.

Mayzent was not studied in patients who had:

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders including complete left bundle branch block, sinus arrest, or sinoatrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second-degree AV block or higher-grade AV-block (either history or observed at screening) unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class IA or Class III antiarrhythmic drugs

Reinitiation of treatment (initial dose titration, monitoring effects on heart rate and AV conduction [ie, ECG]) should apply if ≥4 consecutive daily doses are missed.

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Dr. Katz:

After deciding on Mayzent for Susan based on these data, how did she get started on Mayzent?

Dr. Barry:

From my experience, the Alongside Mayzent an onboarding process is helpful. Once the start form is submitted, Alongside Mayzent assists patients with necessary baseline assessments in just one or two visits, either in their home, at my office, or at a nearby medical

facility. Once the assessments are complete, patients are initiated in treatment with a free starter pack that includes medication for eligible patients participating in the Bridge Program. I like to think of this as smooth onboarding to getting medication in a patient's hands.

Dr. Katz, what has your experience been?

Dr. Katz:

In my experience, patients are eager to start this medication. I receive assistance from my nurses in setting up Alongside Mayzent for my patients, and it alleviates the burden for my patients.

So to conclude, early RMS progression is notoriously challenging to identify, because it could manifest in many different ways. And we don't have definitive diagnostics to determine where progression starts. It's up to us clinicians to talk through histories and diligently ask specific questions with patients and caregivers, if they are available, to uncover signs of progression during each patient visit and track objective changes on cognitive function and imaging results. I put my patient, Mary, on Mayzent because it is the first and only oral DMT that is proven to delay disability progression in a more progressed RMS patient population, including active secondary progressive multiple sclerosis, or SPMS.

Dr. Barry:

My key callout here is to act as soon as those signs are recognized. Also, on a final note, Mayzent can be initiated in a two-step onboarding process, and Alongside Mayzent is a dedicated support program that can be integrated into practice to help patients get started on Mayzent.

Announcer:

And now, let's take a final look at the additional Mayzent Important Safety Information.

Respiratory Effects: Mayzent may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy if clinically warranted.

Liver Injury: Elevation of transaminases may occur in patients taking Mayzent. Before starting treatment, obtain liver transaminase and bilirubin levels. Closely monitor patients with severe hepatic impairment. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked, and Mayzent should be discontinued if significant liver injury is confirmed.

Cutaneous Malignancies: The risk of cutaneous malignancies, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma is increased in patients treated with S1P modulators. Use of Mayzent has been associated with an increased risk of BCC and SCC. Cases of other cutaneous malignancies, including melanoma, have also been reported in patients treated with Mayzent and in patients treated with another S1P modulator.

Skin examinations are recommended at the start of treatment, and periodically thereafter for all patients. Monitor for suspicious skin lesions and promptly evaluate any that are observed. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with high protection factor. Concomitant phototherapy with UVB radiation or PUVA-photochemotherapy is not recommended.

Increased Blood Pressure: Increase in systolic and diastolic pressure was observed about 1 month after initiation of treatment, and persisted with continued treatment. During therapy, blood pressure should be monitored and managed appropriately.

Fetal Risk: Based on animal studies, Mayzent may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping Mayzent therapy. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Mayzent during pregnancy. Healthcare providers are encouraged to enroll pregnant patients, or pregnant women may register themselves in the MotherToBaby Pregnancy Study in Multiple Sclerosis by calling 1-877-311-8972, sending an email to mothertobaby@health.ucsd.edu, or visiting www.mothertobaby.org/join-study.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving an S1P receptor modulator. Such events have not been reported for patients treated with Mayzent in clinical trials. If patients develop any unexpected neurological or psychiatric symptoms, a prompt evaluation should be considered. If PRES is suspected, Mayzent should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Treatment or After Stopping Mayzent: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects.

Initiating treatment with Mayzent after treatment with alemtuzumab is not recommended.

After stopping Mayzent therapy, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. However, residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore, caution should be applied 3-4 weeks after the last dose of Mayzent.

Severe Increase in Disability After Stopping Mayzent: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of an S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping Mayzent treatment. Thus, patients should be monitored upon discontinuation.

Most Common Adverse Reactions: Most common adverse reactions >10% are headache, hypertension, and transaminase increases.

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Dr. Barry:

As these final thoughts bring us to the end of today's program, I would like to thank you all for joining us.

Announcer:

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