Transcript Details
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Decision Points in the Treatment of Progressing RMS and active SPMS

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Decision Points in the Treatment of Patients with More Progressed RMS and Active SPMS,” is sponsored by Novartis Pharmaceuticals Corporation, and the presenters have been compensated for their time.

Dr Singer:
Hello, everyone. I'm Dr Barry Singer, director of the MS Center for Innovations and Care at Missouri Baptist Medical Center in St. Louis, Missouri. Today we'll be joined by Dr Ann Bass, MS Clinic Medical Director at the Neurology Center of San Antonio in San Antonio, Texas.

Dr Bass:
Thank you so much, Dr Singer. Glad to be here with you today.

Dr Singer:
Awesome. Thank you, Dr Bass.

On today's program, we'll be discussing decision points in managing patients with relapsing MS that are developing worsening disability. This includes patients who are progressively worsening, but still have relapses or new MRI activity called active secondary progressive MS or active SPMS. We'll learn about MAYZENT, siponimod, the first and only oral disease-modifying therapy studied and proven to delay disability progression in patients with active SPMS. Dr Bass and I will also be sharing our real-world experiences of starting patients on MAYZENT. Let's get right into it.

As many of us know, MS is a chronic inflammatory and neurodegenerative disease with a highly variable clinical course. Most patients who have relapsing remitting MS will eventually transition to a secondary progressive course, what we call secondary progressive MS, or SPMS. In SPMS, disability slowly increases over time.

For example, patients may experience slowly worsening leg weakness or balance problems. When this transition occurs in SPMS, there's a shift from predominantly inflammatory disease activity towards more neurodegenerative processes.

Dr Bass:
So, Barry, how would you determine if your patient has relapsing MS that is progressing, or active SPMS?

Dr Singer:
First of all, it's important to determine that that patient had relapsing remitting disease earlier in their MS course. Next, it's important to look for early signs of progressive disability worsening such as gait or cognitive impairment. If that patient is transitioned to the progressive phase of the disease and is still having relapses or new MRI activity, then active SPMS is the appropriate diagnosis.

Dr Bass:
Barry, that reminds me of one of my patients. He was a young man with about a 10-year history of MS, which was diagnosed when he was about 18 years old. He had both high disease burden and activity in the earlier years after his diagnosis, and had been on a disease-modifying therapy and responded well. However, in a recent follow-up with him, his MRI actually show a new T2 lesion. And more importantly, I noted a few key signs of progression on his examination. For example, he mentioned having to use a cane for walking longer distances, whereas before he didn't have any assistive devices at all. I also noted that his prior EDSS score was about 4.0, and now we had bumped up to 6.0. And in terms of cognitive function, he and his family reported him having more difficulty concentrating and multitasking at home and at work. So, it's interesting because these signs were not necessarily a concern to be an

actual overt clinical relapse, but certainly this patient was progressing.

Dr Singer:
Dr Bass, thanks so much for sharing your insights on your patient.

That brings us to our first key decision point. Dr Bass, how do you determine when your patient has started down a progressive pathway when you see them in your office?

Dr Bass:
You are right. Timely identification of progression is key, especially when progression can manifest itself in a very subtle way, such as worsening physical or cognitive function. Specifically, in my practice, I perform an MS disability assessment about every 12 months and even every 6 months for patients with more active disease. My assessment includes the Symbol Digit Modalities Test, known as SDMT, Timed 25-Foot Walk, and EDSS.

And then beyond these objective measures, it is also important to take a thorough and extensive history focusing on changes over time. So, for example, I will ask my patient, 'How are you different this year compared to last year?' I call it my litmus test of life, knowing how they're functioning on a day-to-day basis. And sometimes the patient will tell me things like, 'Well, I used to do two flights of stairs and now I can only do one.' I'm just so amazed that when these conversations with my patient come up about their daily life, it can really uncover those subtle signs and symptoms of progression.

Dr Singer:
With that, I'd like to pose this next decision point. Where do we go from here? Do we continue monitoring for changes, Dr Bass, or do we take action?

Dr Bass:
So, for a patient with progressing forms of relapsing MS or active SPMS, as we all know, we cannot reverse progression, and our central nervous system does have a finite capacity to compensate.

Dr Singer:
I totally agree with that. But for patients with relapsing MS who are showing first signs of progression, it's vital to stay ahead of the disease. And I think it's a perfect place for us to talk about MAYZENT, which is the first and only oral disease-modifying therapy studied and proven to delay disability progression in patients with active SPMS.

MAYZENT is a once daily oral pill. It's a sphingosine-1-phosphate, or S1P, receptor modulator that targets S1P1 and S1P5, two key receptors thought to play a role in relapsing MS, inflammation and neurodegeneration. However, the exact mechanism by which MAYZENT exerts its therapeutic effects on MS is unknown. Before we talk about the data behind this medication, we should hear about the indication and Important Safety Information for MAYZENT.

Announcer:

INDICATION

MAYZENT® (siponimod) 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.

IMPORTANT SAFETY INFORMATION

Contraindications

- 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/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

Dr Singer:
Please note additional Important Safety Information provided throughout this podcast. Full Prescribing Information, including Medication Guide, is available at mayzenthcp.com.

Dr Bass:
So, Dr Singer, what is unique about MAYZENT that makes it appropriate for patients with more progressed relapsing MS, including

those with active SPMS?

Dr Singer:
Great question. So, I think one of the key factors is the patient population studied in a MAYZENT clinical trial, *EXPAND*. The study enrolled in 1,651 patients with confirmed diagnoses of SPMS and is the largest phase three study of patients with SPMS to date. The mean age of patients in the MAYZENT arm of *EXPAND* was 48 years old and range from 21 to 61 years of age. Seventy-eight percent of patients were previously treated with a disease-modifying therapy and have been living with an MS diagnosis for 13 years on average. The trial included a subset of patients with inflammatory activity. Twenty-one percent of patients had gadolinium-enhanced lesions at baseline, but 36% had at least one relapse within two years prior to study entry. Patients in the trial represented a broad range of disability with EDSS scores ranging from 3 to 6.5 with an average of 5.4, and 56% of patients needed assistance to ambulate.

Dr Bass:
So, Barry, it sounds like *EXPAND* is a unique trial in terms of patient population because it studied more progressed relapsing MS patients. In fact, as one of the principal investigators in the *EXPAND* trial, I know there are clinical sites we took a lot of care in identifying this particular population. We ensured that patients fulfill criteria for progression with documented changes in EDSS in the two years before the study. And many of our patients were clearly in the higher range of EDSS with a mean score of 5.4. So, in my practice, we see many patients with progressed relapsing MS with a broad range of disability, inflammatory activity, and recent signs of progression.

Dr Singer:
I agree as well. And that brings us to our next decision point: determining which data are most relevant when we consider a treatment for our patients.

Dr Bass:
To me, proven efficacy in delaying disability progression is certainly one of the most important factors to consider when choosing a disease-modifying therapy for patients with more progressed relapsing MS and active SPMS.

Dr Singer:
Well, Ann, in the *EXPAND* clinical trial, MAYZENT was studied across a broad range of endpoints, and many of them reflect measures of disease progression or worsening, in addition to measure a relapse and/or inflammatory activity. The MAYZENT group, which included 1,099 patients experienced a relative risk reduction of 21% in three-month confirmed disability progression compared to the placebo group, which included 546 patients. Although MAYZENT had a significant effect on confirmed disability progression in patients with active SPMS, its effect on patients with non-active SPMS was not statistically significant. Active SPMS was defined as the presence of relapses in the two years prior to screening and/or at least one T1 gadolinium-enhancing lesion at baseline. In a post hoc analysis of the active SPMS subgroup with the *EXPAND* trial, the MAYZENT group, which included 519 patients with active SPMS, experienced a relative risk reduction of 31% at three-month confirmed disability progression compared to the placebo group, which included 263 patients with active SPMS. Note that this analysis has not been adjusted for multiple comparisons and no conclusions of statistical or clinical significance can be drawn.

Key secondary endpoints in the *EXPAND* clinical trial included evaluation of Timed 25-Foot Walk and the change in total T2 lesion volume compared to baseline.

In the Timed 25-Foot Walk Test, MAYZENT did not significantly delay the time to 20% deterioration compared to placebo. However, treatment with MAYZENT decreased the change in volume of T2 lesions from baseline compared to placebo. In *EXPAND*, a pre-specified hierarchical analysis consisted of the primary endpoint and the two key secondary endpoints. The key secondary endpoints of Timed 25-Foot Walk was not significant; therefore, the key secondary endpoint of T2 lesion volume was considered nominal. The remaining endpoints were not corrected for multiple comparisons.

Dr Bass:
So, Barry, what can you tell me about the safety profile of MAYZENT?

Dr Singer:
So, Ann, in the *EXPAND* trial, the most common adverse reactions with MAYZENT that occurred in at least 10% of patients were headaches at 15%, hypertension, 13%, and transaminase increases, 11%. It's important to note that the *EXPAND* open-label extension study is ongoing.

Dr Bass:
Thank you so much, Dr Singer, for your review of the MAYZENT data.

Dr Singer:
Excellent, Dr Bass. Let's also take a moment to review some additional Important Safety Information for MAYZENT.

Announcer:

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) (ie, 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 one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, 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 (ie, anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

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 is 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 patient 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 sino-atrial 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 anti-arrhythmic 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.

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

Now, let's turn to our last decision point. How do we start patients on MAYZENT, Dr Bass?

Dr Bass:
MAYZENT can be started in two steps, assessment and initiation. And there's also a dedicated patient support program called

Alongside MAYZENT to support patients starting MAYZENT. In step-one assessment, my patients undergo blood work including a complete blood count or CBC, a varicella zoster virus, or VZV antibody titer test, a liver function test, and a Novartis-sponsored CYP2C9 genotype test.

It's worth mentioning that this genotype test is similar to most routine lab work. It helps to ensure that MAYZENT is precisely dosed to fit your patient's distinct metabolism. With genotype testing, we know that we're prescribing the most appropriate dose for each patient. In addition, patients undergo medical exams such as an ophthalmic and cardiac evaluation. It's also important to note that first dose observation is required only for patients with certain pre-existing cardiac condition. And since the launch MAYZENT, a first-dose observation was required for approximately 15% of patients as of March 2021.

Dr Singer:
Hey, Dr Bass, you mentioned VZV antibody titer test. In my own practice, if the result is negative I perform the full vaccination against VZV. I do this four weeks before starting MAYZENT therapy. Also, many of my patients take other medications, so it's important to consider potential drug-to-drug interactions prior to starting MAYZENT. Definitely check the Prescribing Information for details.

Dr Bass:
Well said, Barry. And that leads us to step two, which is initiating therapy. For this, we have a tailored titration schedule based on genotype test results to ensure that patients safely reach their appropriate maintenance dose.

Dr Singer:
So, where does the Alongside MAYZENT program fit into all of this?

Dr Bass:
So, for my patients, Alongside MAYZENT has enabled these blood tests and medical exams to be conducted in the comfort of their own homes, at my office, or at a nearby medical facility. My patients have been able to take care of their assessments in just one or two visits. Also, Alongside MAYZENT helped coordinate any assessments or medical exams unavailable at my practice. In my experience, the results of these assessments come very quickly, which allow appropriate patients to start MAYZENT therapy immediately once assessments are completed. The Alongside MAYZENT program also provides dedicated in-office access and reimbursement support.

Eligible patients enrolled in Alongside MAYZENT also receive a welcome kit. My patients have voiced their experiences with a MAYZENT welcome kit, which provides a clear method to share information with caretakers. Any time patients can better understand and involve their support network in their care is very helpful. Patients will also receive the help of a dedicated coordinator who can walk them through initiating treatment step by step. Our patients have found the program to be very helpful. We even noticed a reduction in the number of patient calls asking for clarification.

Dr Singer:
So, Dr Bass, what advice can you offer our listeners to help ensure their patients are initiating MAYZENT therapy quickly and seamlessly?

Dr Bass:
Well, I can offer three tips. The first is to check for program assistance for any assessments that are not available at your practice. Next, engage early and often with Alongside MAYZENT and pharmacies for insurance support. And lastly, prepare your patient to anticipate program outreach such as phone calls.

Dr Singer:
Thank you for that advice, Dr Bass. With that said, let's take a final look at additional MAYZENT Important Safety Information.

Announcer:

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 UV-B 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 a S1P receptor modulator. Such events have not been reported for patients treated with MAYZENT in clinicaltrials. 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.

Dr Singer:
Please see additional Important Safety Information throughout this podcast for full Prescribing Information, including the Medication Guide, at **mayzent**hcp.com.

Dr Bass, it's been a pleasure speaking with you today. I'd love for you to recap what we've learned.

Dr Bass:
Thank you so much, Dr Singer. I would be happy to sum up today's talk by saying that there are key junctures where we as healthcare professionals need to make management decisions regarding our more-progressed patients with relapsing MS, including those with active SPMS, at the first signs of progression.

First, when we follow up with our patients with relapsing MS or active SPMS, we should actively monitor for subtle signs of progression. And when we do see signs of progression, we should help patients stay ahead of it, instead of waiting for the disease to potentially worsen. When deciding on a disease-modifying therapy, we should choose a therapy based on evidence relevant to this specific patient population. I will note here that MAYZENT is the first and only oral disease-modifying therapy studied and proven to delay disability progression in a more progressed relapsing MS patient population, including those with active SPMS.

Lastly, with the evidence from the *EXPAND* trial, MAYZENT may be an appropriate option for patients with progressing RMS, including those with active SPMS. And with the Alongside MAYZENT program, we know patients will have support along the way.

Dr Singer:
Superb, Dr Bass. That was a great summary on the key points and the management of our patients with relapsing MS who are showing

signs of progression, including those with active SPMS.

This concludes our program for today. Thank you again so much for listening.

Announcer:
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