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MSperceptions: Candid HCP/Patient Clinical Conversations about MS

Announcer:
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Dr. Jacqueline Nicholas:
Hi, my name is Dr. Jacqueline Nicholas and I'm the System Chief of Neuroimmunology and MS at the Ohio Health Multiple Sclerosis Center. Today I'm excited to be joined by Dr. Barry Singer and Rosario, who is a person living with MS, and I will discuss the long-term considerations for MS treatment and the use of TYSABRI, which is also known as natalizumab.

Dr. Barry Singer:
Hi Dr. Nicholas. Glad to be joining you again. As you mentioned, my name is Dr. Barry Singer and I'm the Director of the MS Center for Innovations and Care at Missouri Baptist Medical Center. Rosario, it's great to speak with you again. Can you please introduce yourself to our audience?

Rosario:
Hi Dr. Nicholas and Dr. Singer. My name is Rosario. I'm an artist and photographer from Puerto Rico and I've been living with MS for over 10 years now. I was diagnosed in 2011 and I've been taking TYSABRI since 2013, and I'm looking forward to sharing my experience with you.

Dr. Barry Singer:
Thanks, Rosario. Looking forward to hearing your perspective on being treated with TYSABRI long term. As our listeners know, most people are diagnosed with MS when they're between 20 and 40 years old and the disease is a lifelong illness. So when I interact with my patients, I'm always thinking about trying to reduce disability progression, not only in the short term, but more importantly in the long term. As a neurologist, one of my goals is to minimize disability in my MS patients as they age over decades. When thinking about treatment options for my MS patients in addition to the clinical trial data, I like to look at the real-world efficacy and safety data from patients who have been on treatment for five years, 10 years, or even longer.

Dr. Jacqueline Nicholas:
I agree, and it's important to remember that the use of an MS therapy not only impacts our patients now, but it can affect them in the future as well. Along with efficacy, we may need to consider long-term safety. The effects of DMT use can vary over time and may include an increased risk of certain adverse events, including infections and malignancy.

Dr. Barry Singer:
Yeah, I agree. And another key to success for MS treatment is long-term adherence. Treatment administration, including the route of administration, the frequency of dosing are things I discuss with my patients during shared decision-making so that they feel confident that they can adhere to their MS treatment as I prescribed it.

Dr. Jacqueline Nicholas:
That's great. I completely agree. And while I hope my patients remain stable for a long time on the treatment we choose, the reality is that patients may eventually need to switch treatments for a number of reasons. These can include disease progression, tolerability, or changes in their treatment needs or lifestyle. One example would be that as patients age, we know that they may experience

immunosenescence and this can be associated with an increased risk for infections or comorbidities.

Also, patients may decide to become pregnant in the future. In my experience, it's important to discuss the long-term effects of DMTs and the potential need to switch when first starting and throughout the course of treatment. I think it's helpful, so that our patients know to inform us of any changes in their lifestyle or treatment needs.

Dr. Barry Singer:
Yeah, I think it's really important to talk about the need for change in treatments, and I like to add it's important to take in account the immunologic impact from the prior treatment. For example, some DMTs cause prolonged lymphocytopenia, which can impair initiation of another DMT that may require normal lymphocyte counts before initiation. Whenever discontinuing treatment, it's important to consider the lasting effects on the immune system which can last from weeks to months to years after treatment is stopped. Rosario, do you recall if and how your neurologist spoke with you about the need for long-term treatment and the potential need to switch treatment over time?

Rosario:
As you both mentioned, my neurologist also made it clear that MS is a lifelong condition that requires long-term treatment. When I first started TYSABRI in 2013, my neurologist said that I would be on it for two years based on the studies and data available at that time. During those first couple of years, I remember talking with other TYSABRI patients at the infusion center, and to my surprise, many of them had been on TYSABRI for more than two years. By the time my two years on TYSABRI had passed, my neurologist informed me that based on the most recent data, I could continue taking it as long as we were comfortable with the benefits and risks of continued treatment. And here we are, nine years later, and I'm still responding positively with TYSABRI as my MS treatment.

Dr. Jacqueline Nicholas:
That's really great to hear Rosario, and I'm glad to hear that your experience with TYSABRI over the past nine years has been positive. Some patients and healthcare professionals caring for individuals with MS may still be under a misimpression that TYSABRI treatment should be stopped after two years, mainly due to safety concerns surrounding the rare risk of PML. There have been multiple long-term, real-world studies on TYSABRI with follow-up as long as 10 years showing its sustained efficacy with a well-understood safety profile, including risk stratification strategies to help minimize the risk of PML.

Dr. Barry Singer:
Yeah, that's right, Dr. Nicholas. In fact, in the US over 40% of patients currently on TYSABRI have been on it for more than five years. In my practice, we have many patients who have been on TYSABRI for 10 years or longer. Most of my TYSABRI-treated patients are happy with their treatment selection based on their experience. Rosario, I'm curious, after all this time on TYSABRI, what have you found important to discuss with your neurologist?

Rosario:
Even after nine years, I see my neurologist often to discuss how I'm feeling on TYSABRI, and also whether I'm experiencing any changes in my life. My life has been full of stressful events. In the past few years, I've experienced major hurricanes as well as the pandemic. When Hurricane Maria hit, we were left with no electricity and had difficulty getting certain supplies and communications like cell phones were not working for the first two weeks. I was worried about how I was going to continue my treatment, but fortunately I was able to talk to my neurologist quickly and was told that the infusion center and the TYSABRI medical team were prepared and equipped to deliver the medication and treat patients without delay. That was a huge relief. Life events like these, in addition to how I'm feeling, are things I bring up with my neurologist and infusion team to ensure I'm receiving the treatment that works for me.

Dr. Barry Singer:
Wow. Thanks Rosario, for sharing that story. That's pretty harrowing. You make a really good point. Keeping the dialogue open between patients and providers, whether they're neurologists, nurse practitioners, physician assistants. It's important when treating a lifelong condition like MS. You know, we talked earlier about some of the concerns that patients have about long-term use of MS treatment. Have you had any concerns about staying on TYSABRI for so many years as you have? And if so, did you speak with your neurologist about these concerns?

Rosario:
Yes. The potential risk of PML has always been a concern and something we have discussed. When I first started on TYSABRI, I was negative for the John Cunningham virus, or JCV, which led to straightforward conversations regarding the risk of PML. I understood that as long as I was JC virus negative, my risk of PML was very low. But in 2017, when I tested JC virus positive, I was worried I'd have to stop TYSABRI. At that point, my neurologist educated me more on the risk of PML in JC virus-positive patients and reassured me that based on my particular test results and his assessment of other risk factors, he was comfortable keeping me on TYSABRI. It's been five years since I became JC virus positive and with regular monitoring, I've continued to benefit from TYSABRI.

Dr. Jacqueline Nicholas:
That's a really important point, Rosario. Sometimes my TYSABRI-treated patients ask what would happen if they become JC virus positive. They worry if that would mean they need to stop TYSABRI. With my JC virus-negative patients, I remind them regularly about the potential to seroconvert to positive on the JC virus antibody test so that they fully understand what that result means for them. If someone is JC virus positive, that just means that their body has seen the JC virus at some point, but not that they automatically have or will actually get PML.

Dr. Barry Singer:
So Dr. Nicholas, in your practice, if someone becomes JC virus positive, who makes the decision to stop or continue treatment? Is it the patient, you, or both?

Dr. Jacqueline Nicholas:
That's a great question, and I think the shared decision-making approach is really important here. So whether we stay on treatment is really between the patient on the treatment and myself. I tell my patients we would continue to monitor the risk of PML with the stratified JC virus test, which is the only FDA-approved test validated specifically for TYSABRI to aid in risk stratification for PML, along with other factors that are important, such as prior immunosuppressant use and the length of time on TYSABRI treatment.

After reviewing the patient's potential risk, we can then have a discussion about whether both they and I are comfortable with them continuing on TYSABRI. Treatment choice and continuation is something both the medical team and the patient need to be comfortable with. If there is ever a time someone is no longer comfortable continuing treatment, we have a conversation about what that means moving forward, and that may include a treatment switch.

Dr. Barry Singer:
I've had similar conversations with my patients. As we've mentioned in our previous podcast episode, we have data out to eight years. It shows that the risk of PML remains less than 1% regardless of JC virus status. In TYSABRI-treated patients who are JC virus negative, the risk of developing PML is one in 10,000 or 0.01%, while in JC virus-positive patients, the risk does not exceed 0.7% out to eight years. So Rosario, what are some of the reasons that you've continued to take TYSABRI?

Rosario:
I've continued on TYSABRI because my MS has been stable, and I feel the benefits of TYSABRI outweigh any potential risks. Like I said, based on early conversations, I wasn't sure if I could stay on TYSABRI after two years of treatment. As more long-term, real-world data became available, my neurologist shared that information with me, which contributed to our decision to stay on TYSABRI.

Dr. Jacqueline Nicholas:
Rosario, I'm really glad to hear that your neurologist utilizes the long-term, real-world data to aid in informed discussions with you regarding your MS treatment. When I discuss TYSABRI with my patients, I let them know that it has a well-established safety profile based on over 15 years of clinical trial and real-world data. It has been used to treat over 250,000 patients with MS globally, with more than 1 million patient-years of experience.

Dr. Barry Singer:
Yeah, that experience is really important. Knowing the safety of real-world experience of TYSABRI is key for my patients as well. So, before I prescribe TYSABRI, I usually review some safety findings from the two-year AFFIRM pivotal trial, which includes potential adverse events such as infections and acute hypersensitivity reactions. And my patients are also interested in efficacy, so often I'll discuss some of the results from that same trial. In the AFFIRM trial, 83% of patients taking TYSABRI had no sustained disability progression for 12 weeks compared to 71% on placebo. The study also showed there was a 67% relative reduction in the annualized relapse rate, ARR, with TYSABRI versus placebo, and 97% of TYSABRI-treated patients showed full suppression of gadolinium-enhancing lesions versus 72% on placebo. So Dr. Nicholas, could you tell us more about the long-term data you mentioned?

Dr. Jacqueline Nicholas:
Sure, I'd be happy to. So, to assess the use of TYSABRI in a real-world setting, the TYSABRI Observational Program, also known as TOP, is an ongoing study of relapsing-remitting MS patients located in 17 countries outside of the United States. Data from 6148 patients taking TYSABRI provide insights into the safety and efficacy of TYSABRI use for up to 10 years. In the study, safety was assessed by the incidence and types of serious adverse events. To measure efficacy, disease activity was measured by annualized relapse rate and changes in disability.

Dr. Barry Singer:
Dr. Nicholas, before you dive into the results from TOP, were there any limitations to the study?

Dr. Jacqueline Nicholas:

Yes, there were. Those are important to discuss. Because this is a real-world study without randomization or a placebo control group, the results may be impacted by unconsidered variables or incomplete adjustment. Also, analysis of attrition bias is limited by the low number of patients in the less than eight-year treatment group. And lastly, because this study took place in 17 countries outside of the United States, results should be interpreted with caution as treatment practices vary by country.

Dr. Barry Singer:
Yeah. Thanks for those notes, let's dive on into the results. So, what were the most meaningful results for you?

Dr. Jacqueline Nicholas:
Yeah, so I think the most meaningful result was that over this 10-year study, there was no new safety concern identified, with greater than 85% of patients experiencing no serious adverse events. You know, as we discussed, some of the concerns with immunotherapy over time include increased risk of opportunistic infections or malignancies; however, in this study, the rates of infection and malignancy remained low and did not increase with longer use of TYSABRI.

When we look at efficacy, patients taking TYSABRI had an 88% reduction in ARR at Year one, which was sustained over 10 years. In addition, the median Expanded Disability Status Scale or EDSS scores remained between three to four, which indicated that patients remain stable and ambulatory or able to walk over 10 years.

Dr. Barry Singer:
Oh, that's really great information for our listeners to know for discussion with their patients when considering starting or continuing TYSABRI. With 15 plus years of clinical experience, my patients are reassured by the long-term, real-world data. And along with this study like this, many of my patients find it really impactful to hear how other patients have done on TYSABRI, and I tell them I've had many patients respond very well to TYSABRI long-term, similar to you Rosario. And before we go, do you have any recommendations, Rosario, for MS providers who are discussing the long-term efficacy and safety of TYSABRI with their patients?

Rosario:
As I mentioned, I never thought I could be on TYSABRI this long based on the information that was available at the time I started treatment. I really think it's important to keep your patients up to date on the real-world, long-term data that's available for TYSABRI. That way patients know it can be a safe and effective long-term treatment option for them.

Dr. Barry Singer:
Thanks, Rosario, for providing your insights as someone living with this disease. As healthcare providers, we have the honor of treating our own patients with the goal of preventing future disability. It's key that we focus on reducing disability, not only in the near term but in the long term for our patients. The goal is for people living with MS like Rosario to live their best life as best as they can.

Dr. Jacqueline Nicholas:
I completely agree, and I'd just like to conclude by reminding our listeners that TYSABRI is a highly effective therapy that could be considered for appropriate adult patients with relapsing MS. We know from TOP results that effectiveness is maintained out to 10 years with no change in the safety profile. Thanks to all of you for taking the time to listen to us today and thanks Dr. Singer and Rosario.

Dr. Barry Singer:
Appreciate it.

Announcer:
TYSABRI HCP Indication and Important Safety Information

INDICATION:
TYSABRI® (natalizumab) is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. TYSABRI increases the risk of PML. When initiating and continuing treatment with TYSABRI, physicians should consider whether the expected benefit of TYSABRI is sufficient to offset this risk.

IMPORTANT SAFETY INFORMATION:

WARNING: Progressive Multifocal Leukoencephalopathy (PML)

TYSABRI® (natalizumab) increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include the presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.

Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

Because of the risk of PML, TYSABRI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program.

- Infection by the JC Virus (JCV) is required for the development of PML
- There are no known interventions that can reliably prevent PML or that can adequately treat PML if it occurs
- Postmarketing data suggest that the risk of developing PML may be associated with relative levels of serum anti-JCV antibody compared to a calibrator as measured by ELISA (often described as an anti-JCV antibody index value)
- MRI findings may be apparent before clinical signs or symptoms suggestive of PML. Monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Consider monitoring patients at high risk for PML more frequently. Lower PML-related mortality and morbidity have been reported following TYSABRI discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis
- PML has been reported after discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for at least 6 months after discontinuation of TYSABRI
- Adverse events that may occur during plasma exchange (PLEX) include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although PLEX has not been prospectively studied in TYSABRI-treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation. There is no evidence that PLEX has any benefit in the treatment of opportunistic infections such as PML. JCV infection of granule cell neurons in the cerebellum, i.e., JCV granule cell neuronopathy (GCN), with symptoms similar to PML, has been reported in patients treated with TYSABRI. JCV GCN can occur with or without concomitant PML and can cause cerebellar dysfunction. Diagnosis and management of JCV GCN should follow guidance provided for PML
- Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI-treated patients who developed PML and subsequently discontinued TYSABRI. In almost all cases, IRIS occurred after PLEX was used to eliminate circulating TYSABRI. It presents as a clinical decline in the patient's condition after TYSABRI removal (and, in some cases, after apparent clinical improvement) that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing treatment with TYSABRI for reasons unrelated to PML. In TYSABRI-treated patients with PML, IRIS has been reported within days to several weeks after PLEX. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken

Contraindications:

- TYSABRI is contraindicated in patients who have or have had PML
- TYSABRI is contraindicated in patients who have had a hypersensitivity reaction to TYSABRI

TYSABRI TOUCH Prescribing Program:

- Because of the risk of PML, TYSABRI is available only through a restricted distribution program under a REMS called the TOUCH® Prescribing Program
- Patients must be enrolled in the TOUCH Prescribing Program, read the Medication Guide, understand the risks associated with TYSABRI, and complete and sign the Patient-Prescriber Enrollment Form

Herpes Infections – Encephalitis, Meningitis and Acute Retinal Necrosis:

- TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses
- Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI
- The duration of treatment with TYSABRI prior to onset ranged from a few months to several years
- Monitor patients receiving TYSABRI for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYSABRI should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered
- Patients being administered TYSABRI are at a higher risk of acute retinal necrosis (ARN), a fulminant viral infection of the retina caused by the family of herpes viruses. Patients with eye symptoms such as decreased visual acuity, redness or eye pain should

be referred for retinal screening as serious cases of ARN can lead to blindness of one or both eyes
- Following clinical diagnosis of ARN, consider discontinuation of TYSABRI

Hepatotoxicity:

- Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with TYSABRI in the postmarketing setting
- Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses
- TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence)

Hypersensitivity/Antibody Formation:

- Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%
- Reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain
- If a hypersensitivity reaction occurs, discontinue administration of TYSABRI and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI
- Hypersensitivity reactions were more frequent in patients with antibodies to TYSABRI compared with patients who did not develop antibodies to TYSABRI in both MS and CD studies
- Patients who receive TYSABRI for a short exposure (1 to 2 infusions) followed by an extended period without treatment are at higher risk of developing anti-natalizumab antibodies and/or hypersensitivity reactions on re-exposure, compared to patients who received regularly scheduled treatment

Immunosuppression/Infections:

- The immune system effects of TYSABRI may increase the risk for infections
- In Study MS1, certain types of infections—including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections—occurred more often in TYSABRI-treated patients than in placebo-treated patients. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI in Study MS1
- In Studies MS1 and MS2, an increase in infections was seen in patients concurrently receiving short courses of corticosteroids. However, the increase in infections in TYSABRI-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids
- In a long-term safety study of patients, opportunistic infections (pulmonary mycobacterium avium intracellulare, aspergilloma, cryptococcal fungemia and meningitis, and Candida pneumonia) have been observed in <1% of TYSABRI-treated patients
- Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections over the risk observed with use of TYSABRI alone
- In Studies MS1 and MS2, the rate of any type of infection was approximately 1.5 per patient-year in both TYSABRI-treated patients and placebo-treated patients
- In Study MS1, the incidence of serious infections was approximately 3% in TYSABRI-treated patients and in placebo-treated patients. Most patients did not interrupt treatment with TYSABRI during infections

Laboratory Test Abnormalities:

- In clinical trials, TYSABRI was observed to induce increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persisted during TYSABRI exposure, but were reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI induces mild decreases in hemoglobin levels (mean decrease of 0.6 g/dL) that are frequently transient

Thrombocytopenia:

- Cases of thrombocytopenia, including immune thrombocytopenic purpura (ITP), have been reported with the use of TYSABRI in the postmarketing setting. Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae. Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. If thrombocytopenia is suspected,

TYSABRI should be discontinued
- Cases of neonatal thrombocytopenia, at times associated with anemia, have been reported in newborns with *in utero* exposure to TYSABRI. A CBC should be obtained in neonates with *in utero* exposure to TYSABRI

Adverse Reactions:

- The most common adverse reactions reported at an incidence of ≥10% with TYSABRI and ≥2% difference with placebo were headache (38% vs 33%), fatigue (27% vs 21%), infusion reactions (24% vs 18%), urinary tract infections (21% vs 17%), arthralgia (19% vs 14%), depression (19% vs 16%), pain in extremity (16% vs 14%), rash (12% vs 9%), gastroenteritis (11% vs 9%), and vaginitis (10% vs 6%)
- The most frequently reported serious adverse reactions in Study MS1 were infections (3.2% vs 2.6% placebo), including urinary tract infection (0.8% vs 0.3%) and pneumonia (0.6% vs 0%), acute hypersensitivity reactions (1.1% vs 0.3%), including anaphylaxis/anaphylactoid reaction [0.8% vs 0%]), depression (1.0% vs 1.0%, including suicidal ideation or attempt [0.6% vs 0.3%]), and cholelithiasis (1.0% vs 0.3%)
- Based on animal data, TYSABRI may cause fetal harm. TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Please see full Prescribing Information, including **Boxed Warning**.

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