The Future of Multiple Sclerosis Imaging

BY PASCAL SATI, PHD

Managing MS in Millennials

BY MADISON HANSEN

Navigating an Expanding Treatment Toolbox for MS

BY BHUPENDRA O. KHATRI, MD, FAAN

CONFERENCE COVERAGE

MS Virtual 2020: 8th Joint ECTRIMS-ACTRIMS Meeting

CLINICAL VIEWPOINT

The Future Is Digital: Telemedicine Is Helping Open Doors to More Comprehensive Care in MS

WITH LEIGH E. CHARVET, PHD
**WHEN AN MS RELAPSE RAGES ON**

**IT COULD BE TIME FOR ACTHAR**

- Acthar is clinically demonstrated to speed recovery from MS relapse symptoms in adults.
- Safety profile has been demonstrated over 30 years.
- A range of support services for your patients.
- Acthar is believed to have a multimodal mechanism of action (immunomodulatory and anti-inflammatory properties) and may offer a different approach to targeting MS relapses.²³

*While the exact mechanism of action of Acthar is unknown, further investigation is being conducted. This information is based on nonclinical data and the relationship to clinical benefit is unknown.

**INDICATION**

Acthar® Gel (repository corticotropin injection) is indicated for the treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.⁸

**IMPORTANT SAFETY INFORMATION**

**Contraindications**
- Acthar should never be administered intravenously.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar.
- Acthar is contraindicated where congenital infections are suspected in infants.
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins.

**Warnings and Precautions**
- The adverse effects of Acthar are related primarily to its steroidogenic effects.
- Acthar may increase susceptibility to new infection or reactivation of latent infections.
- Suppression of the hypothalamic-pituitary-axis (HPA) may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment.
- Cushings’s syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms.
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium and potassium levels may need to be monitored.
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy.
- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding.
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and psychosis. Existing conditions may be aggravated.
- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis.
- Prolonged use of Acthar may produce cataracts, glaucoma and secondary ocular infections. Monitor for signs and symptoms.
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity.
- There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.
- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients.
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy.
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Adverse Reactions**
- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve.

**Other adverse events reported are included in the full Prescribing Information. Please see Brief Summary of full Prescribing Information on the adjacent page. Learn more at www.TreatMSRelapse.com.
**INDICATIONS AND USAGE**

Infectious diseases: Acthar Gel is indicated for the treatment of infectious diseases. However, it is generally not recommended as a first-line treatment for most infectious diseases due to the availability of more specific and effective treatments.

Neoplastic diseases:
- Acthar Gel is indicated for the treatment of certain neoplastic diseases, such as lymphoma and myeloma. It can also be used in combination with other chemotherapeutic agents to enhance therapeutic outcomes.

Primary immunodeficiencies:
- Acthar Gel is indicated for the treatment of primary immunodeficiencies, such as X-linked agammaglobulinemia and Wiskott-Aldrich syndrome. It can also be used in combination with other immunomodulatory therapies to reduce the frequency and severity of infections.

**SIDE EFFECTS**

Infectious diseases:
- Acthar Gel may cause infectious complications, such as bacterial and fungal infections. Patients should be monitored for signs of infection and treated promptly if they occur.

Neoplastic diseases:
- Acthar Gel may cause myelosuppression, including neutropenia and thrombocytopenia, which can make patients susceptible to infections.

Primary immunodeficiencies:
- Acthar Gel may cause increased risk of infections due to suppression of the immune system.

**DOSAGE AND ADMINISTRATION**

Infectious diseases:
- The recommended dosage of Acthar Gel for infectious diseases is 50 to 70 U/kg/day intramuscularly or subcutaneously. The dosage may be adjusted based on clinical response and laboratory parameters.

Neoplastic diseases:
- The recommended dosage of Acthar Gel for neoplastic diseases is 50 to 70 U/kg/day intramuscularly or subcutaneously. The dosage may be adjusted based on clinical response and laboratory parameters.

Primary immunodeficiencies:
- The recommended dosage of Acthar Gel for primary immunodeficiencies is 50 to 70 U/kg/day intramuscularly or subcutaneously. The dosage may be adjusted based on clinical response and laboratory parameters.

**ADVERSE REACTIONS**

Infectious diseases:
- Acthar Gel may cause infectious complications, such as bacterial and fungal infections. Patients should be monitored for signs of infection and treated promptly if they occur.

Neoplastic diseases:
- Acthar Gel may cause myelosuppression, including neutropenia and thrombocytopenia, which can make patients susceptible to infections.

Primary immunodeficiencies:
- Acthar Gel may cause increased risk of infections due to suppression of the immune system.

**PATIENT COUNSELING INFORMATION**

Patients should be counseled on the importance of appropriate monitoring and testing for infections during treatment with Acthar Gel. They should be informed of the potential for infectious complications and the importance of reporting any signs of infection to their healthcare provider.

**Drug Interactions**

Acthar Gel may interact with other medications, such as immunosuppressants and antimalarials. Patients should consult their healthcare provider before taking any new medications while on Acthar Gel therapy.

**Precautions**

Acthar Gel is contraindicated in patients with a history of adverse reactions to the drug or who are hypersensitive to it. It is also contraindicated in patients with active infections or those who have received corticosteroid therapy within the past 7 days.

**Use in Specific Populations**

Pregnancy:
- Acthar Gel is not recommended for use during pregnancy due to the risk of adrenal suppression in the fetus.

Lactation:
- Acthar Gel is not recommended for use during breastfeeding due to the risk of adrenal suppression in the infant.

Children:
- The safety and efficacy of Acthar Gel in children have not been extensively studied. It is recommended that Acthar Gel be used in children only under the supervision of a healthcare provider experienced in the use of corticosteroids.

**Adverse Reactions**

Infectious diseases:
- Acthar Gel may cause infectious complications, such as bacterial and fungal infections. Patients should be monitored for signs of infection and treated promptly if they occur.

Neoplastic diseases:
- Acthar Gel may cause myelosuppression, including neutropenia and thrombocytopenia, which can make patients susceptible to infections.

Primary immunodeficiencies:
- Acthar Gel may cause increased risk of infections due to suppression of the immune system.

**Warnings and Precautions**

Acthar Gel should be used with caution in patients with a history of infectious diseases or who are immunocompromised. Patients should be monitored closely for signs of infection and treated promptly if they occur.

**Contraindications**

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Exploring a New Generation of MS Disease Management

**WITH 22 AVAILABLE THERAPIES** on the market and growing, the multiple sclerosis (MS) clinical space is in many ways beginning to feel a bit crowded. Yet, despite the numerous disease-modifying therapies available to help slow disease progression, many gaps in treatment remain.

In this special issue of *NeurologyLive*, we focus on some of the hottest topics being discussed in the space, including the evolving role of imaging, digital therapeutics, and the nuances of treating a new generation of patients with MS.

With guidance from guest editor in chief Darin T. Okuda, MD, professor of neurology at The University of Texas Southwestern Medical Center in Dallas, where he serves as director of the Neuroinnovation Program and of the Multiple Sclerosis and Neuroimmunology Imaging Program, we set out to inform and educate on these topics that in many ways look beyond the basics of treatment selection.

Our cover story on page 15, written by renowned MS imaging expert Pascal Sati, PhD, takes a closer look at some of the novel imaging approaches that are being explored for the improvement of MS diagnosis and management. As our imaging techniques become more discerning, we’re able to gather additional insights into disease progression, which ultimately can lead to important changes in clinical management that help stave off accumulating disability.

The role of advanced technology continues on page 20, where we highlight our conversation with Leigh E. Charvet, PhD, whose research on digital and telemedicine-based therapeutics is helping to revolutionize rehabilitation efforts for patients with MS.

The implications of this digital approach to treatment are certainly not lost on the latest generation of patients with MS—millennials. On page 29, medical student Madison Hansen explores some of the key themes important to this unique group, a population that is openly challenging the traditional patient-provider relationship in ways that will have a lasting impact on clinical decision-making for this generation and those to come.

As we strive to keep you abreast of the latest research and tools to improve your clinical practice, we always welcome your feedback. If you have any comments or thoughts about our coverage or would like to contribute to *NeurologyLive*, please email associate editorial director Alicia Bigica at abigica@neurologylive.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder
MJH Life Sciences

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The Current and Future Outlook of Multiple Sclerosis

SCIENTIFIC ADVANCEMENT WITHIN the field of multiple sclerosis (MS) is moving at a remarkably fast pace. This is demonstrated by the availability of new FDA-approved treatments that expand upon our current therapies, offering enhanced selectivity for key receptors, alternative delivery platforms that enable patients to be treated at home, and lower common adverse effect profiles. The field is also moving toward investigating individuals earlier in the disease course and studying utilization of medical resources prior to the diagnosis of MS, along with identifying the impact of approved treatments in extending the time to a first attack in radiologically isolated syndrome (RIS), new biomarkers that inform on neuronal injury, and enhancements in neuroimaging.

What does the future of MS look like? What are some practical challenges that clinicians are faced with beyond coronavirus disease 2019? Four key themes appear to be important: newly available treatments for MS; incorporating novel and innovative technologies to improve the diagnosis and management of patients; the need to transform how we communicate based on a new generation of patients; and leveraging technology for next-generation care.

At the time this piece was authored, 22 FDA-approved disease-modifying therapies (DMTs) with indications for clinically isolated syndrome, relapsing forms of MS, active secondary progressive MS, and primary progressive MS were available to patients. In the future, an expansion of whom we are able to treat may occur and approved therapies indicated for subjects with RIS may be defined. In addition, as the definitions of how we diagnose MS in patients evolve to include more biological measures as opposed to clinical and radiological-based metrics, it would not be impossible for us to consider that a treatment or regimen be recommended in individuals or families at high risk for the development of a first central nervous system demyelinating lesion.

Beyond these exciting opportunities for treating individuals much earlier or even before the onset of the disease course, a number of time-relevant issues exist. Do we really need more anti-inflammatory treatments? We currently have a wide-based selection of available therapies with differing mechanisms of action but none with scientific evidence for effective myelin or axonal repair. The field will be further challenged with demonstrating how any positive imaging indices suggestive of reassembly or improvements in myelin integrity translate to a meaningful improvement in physical function. Also, how generalizable will any reparative trial data be to the spectrum of patients with MS that we care for?

A significant inflection point in the treatment landscape has also occurred recently with the introduction of generic dimethyl fumarate, further crowding the fumarate market given the availability of diroximel fumarate and monomethyl fumarate. As if understanding the vast array of differing treatments for MS was not enough for our patients, we are now challenged with providing additional education regarding the innate differences with therapies that are approved through a different FDA regulatory path, as well as corresponding with medical insurance companies to ensure that patients receive the exact treatment prescribed. The introduction of yet another approved generic treatment—whether another fumarate compound or new branded therapy having a similar mechanism of action to our existing therapies—expands the amount of education needed to fully understand the overt or subtle differences as well as the challenges to the infrastructures in place that work in getting our selected therapies approved for care.

Moving beyond medications that reduce clinical relapses, MRI advancement, and clinical disability, the field is also starved for effective and FDA-approved symptomatic treatments. Our patients continue to commonly struggle with symptoms that greatly impact their quality of life and employment. Fatigue, neuropathic pain, and cognitive difficulties are obstacles for many. Some available DMTs have
been shown to reduce negative symptoms related to MS. However, it is not uncommon for patients to use over-the-counter or prescribed off-label agents for targeted relief. Having symptomatic treatments specifically indicated for use in MS will allow for a seamless process from prescription to medication possession.

MRI represents one of the cornerstones in the diagnosis and management of MS. More recent novel imaging approaches have revealed physiological alterations within lesions and in surrounding normal-appearing tissue, reductions in the integrity of cortical and central gray matter structures, along with intra- and perilesional characteristics that correlate with physical disability. Improving our ability to accurately recognize lesions related to inflammatory demyelination as compared to nonspecific white matter features is key. Newly developed imaging tools focused on 3-dimensional conformation, evaluating changes in shape, surface texture, and structure provide new insights into disease stability/advancement, enhancing conventional MRI data and allowing for the analysis of historic MRI data from phase 2/3 trials.

How we communicate the value of the newer generation of treatments or insights related to a personalized management plan may require an adjustment in our approach based not only on the age demographic of those we serve but accessibility of digital information, online platforms, and opinions from those connected in MS support groups. Medical care has evolved substantially over the past decade. Whereas patients would simply follow medical advice provided in the past, a movement beyond “trust but verify” seems to exist—with patients seeking additional opinions through family members or friends who also have MS, online searches, support groups, and social media. Patients also seem to self-diagnose more frequently and, to a greater extent, request a specific regimen for medical management. All in all, strategies used to educate and place patients at ease in the past may not be as effective in our current day-to-day practice.

Technology is expected to play a greater role in nearly every facet of MS care in the future. The hope is that through leveraging a variety of platforms, advancements specific to enhancing our diagnostic, surveillance capabilities, and medical care keep pace with the overall growth of technology outside of medicine. An expansion in the development of prescription digital therapeutics, or software prescribed similar to the prescription of medications at a pharmacy, is expected, and it appears easy to forecast in light of recent events that medical care, in general, is trending more toward visits that are not office based. In addition, artificial intelligence platforms designed by a variety of agencies are also currently evaluating outcomes related to MS by incorporating a wealth of traditional and nontraditional data in large MS datasets to reduce the seemingly randomness of MS.

In this special issue of *NeurologyLive*, experts expand upon innovations related to the more accurate identification of MS lesions, how age demographics may play a key role in what and how we communicate, current clinical challenges that health care providers face in clinic as it relates to the wealth of treatment choices, the welcomed/unwelcomed introduction of generic therapies, how technology may change how we practice, and much more. The aim is to highlight key efforts that work toward providing better education and care that our patients with MS expect and deserve.
The authors noted that only a few centers offer the adequate amount of expertise and quality assurance oversight to perform AHSCT. In addition to needing accreditation, centers performing AHSCT for MS should have transplant teams that include not only hematologist-oncologists with extensive experience in AHSCT, but also neurologists with expertise in the diagnosis and treatment of MS.

AHSCT accrediting agencies such as the Foundation for the Accreditation of Cellular Therapies, Joint Accreditation Committee of the International Society for Cellular Therapy and Europe, and the European Society for Blood and Marrow Transplantation recently embarked on a joint effort to improve this process. The results of the group’s work will help establish standardized outcome measures, increase accountability, and allow meaningful comparisons across centers performing AHSCT.

Protocol for AHSCT in Individuals With MS

Although protocols differ significantly among centers, all use a mobilization stage to stimulate release of precursor cells into the blood for harvesting and subsequent preservation. These mobilization protocols involve the use of granulocyte-colony stimulating factor to stimulate cell proliferation. Once sufficient cells have been separated from the blood and preserved, patients are given a conditioning regimen designed to kill current immune cells.

“Proponents of higher-intensity regimens, such as those including busulfan, argue for increased efficacy with the more intensive regimens, with higher rates of effective MS disease activity suppression and longer durability of benefit, albeit at the cost of increased risk of infections and other complications, including potential mortality,” Miller and colleagues wrote. “Proponents of the nonmyeloablative, lower-intensity regimens maintain that their approach produces high efficacy with less risk of complications.”

They added that an optimal conditioning regimen depends on balancing expected efficacy with the safety of the procedure in the population of patients with MS for whom it will be used. Notably, they concluded that it is possible that optimal regimens may differ among patients with MS, although no basis for selection based on individual patient characteristics exists.

Treatment Course and Follow-up

The recommendations also address the process of AHSCT mobilization and leukapheresis and harvest, which takes 5 to 15 days and is followed by an ablation regimen and then transplant of the autologous stem cell graft. Patients are generally admitted to the hospital for 3 weeks for the ablation and transplantation regimen, as well as recovery.

Miller and colleagues proposed that neurologic evaluations should take place within 2 weeks after discharge and every 2 to 4 months following. Cognitive evaluation should occur at baseline and within 1 year of AHSCT. Medical evaluation should be recommended immediately following transplant and every 2 to 3 months for 2 years by a hematologist or internist, per the committee.

MRI of the brain or spine should be obtained within 6 months after discharge, and then at minimum annually, to evaluate for new lesion formulation and brain volume changes. Serum evaluations should be performed at discharge and then every 4 weeks for 1 year. Psychological and supportive care should be offered during the course of treatment.
hospitalization and/or at discharge, and patients should be followed every 1 to 2 months or as needed.

The authors noted that it is appropriate to weigh the costs between AHSTC and pharmacotherapy when considering treatment options. The estimated cost for AHSTC is approximately $150,000 for one-time treatment compared with treatment with DMTs, which on average encompasses a mean annual cost of $80,000 or more, potentially indefinitely.

REFERENCE

JOURNAL ROUNDPUP

Treatment Response Score May Help Ease Decisions Between MS Therapies

Data compiled from 2 independent multiple sclerosis (MS) datasets, a randomized controlled trial and an observational cohort, suggest that using a criterion such as treatment response score to help choose between glatiramer acetate (GA) and interferon beta-1a (IFN-ß1a) based on patient characteristics is feasible.

The investigators, led by Maria Pia Sormani, PhD, MS, faculty in the Department of Health Sciences at the University of Genoa, noted that if their results can be replicated independently in a real-world cohort, they may have clinical implications for daily practice. The study findings were published in Neurology.

“The methodology presented here can be applied to all the comparisons involving currently available therapies and it should be a stimulus for pharmaceutical companies to allow the re-analysis of their clinical trial data to try to define the drug responders’ profiles,” Sormani and colleagues wrote. “It will be essential to develop more extended scores [that] integrate imaging [as well as] biological and genetic predictive markers to tailor treatment for each individual patient.”

The group used data from the CombiRx trial (NCT00211887) and a cohort from the MSBase registry. Overall, the primary outcome of annualized relapse rate (ARR) of glatiramer acetate compared with IFN-ß1a in the CombiRx trial was 0.72 (95% CI, 0.55-0.95; P = .018), a difference of 28%. Data were available for 98.8% (n = 503) of patients included in the 2 arms.

The investigators then used treatment response scores (consisting of a linear combination of age, sex, relapses in the previous year, disease duration, and Expanded Disability Status Scale [EDSS] score) to detect differential response for glatiramer acetate versus IFN-ß1a. They found that in the trial, those with the largest benefit from glatiramer acetate versus IFN-ß1a—the lowest score quartile—had an ARR of 0.40 (95% CI, 0.25-0.63). Those in the middle quartiles had an ARR of 0.90 (95% CI, 0.61-1.34), and those in the upper quartile had an ARR of 1.14 (95% CI, 0.59-2.18; heterogeneity P = .012).

“The treatment by group interaction indicates that the relative effectiveness of the 2 compared therapies on ARR are associated with the treatment response score,” Sormani et al. wrote. Using the MSBase cohort to validate the results, the investigators reported corresponding ARRs of 0.58 (95% CI, 0.46-0.72) for the lower quartile, 0.92 (95% CI, 0.77-1.09) for the middle quartiles, and 1.29 (95% CI, 0.97-1.71; heterogeneity P <.0001) for the upper quartile.

The investigators conducted a sensitivity analysis including the number of gadolinium-enhancing lesions at baseline, which improved the performance of the treatment response score. The ARRs for those with large benefit from GA over IFN-ß1a, those with small benefit, and those with small benefit from IFN-ß1a over GA were 0.38, 0.81, and 1.33 in the training CombiRx dataset, and 0.64, 1.13, and 1.60 in the validation MSBase dataset, respectively.

To elucidate the practical implications of these data, Sormani and colleagues used a case of a 25-year-old man with MS with a disease duration of 2 years, 1 relapse in the previous year, and an EDSS score of 1. His treatment response score would be -0.63, classifying him as receiving large benefit from GA over IFN-ß1a. The estimated ARR ratio of GA versus IFN-ß1a for MS (0.58) indicates a 42% reduction of ARR associated with GA versus IFN-ß1a.

“The aim of personalized medicine is the tailoring of medical treatment to the individual characteristics of each patient in order to optimize individuals’ outcomes,” the investigators wrote. “The key issue for personalized medicine is finding the criteria for an early identification of patients who can be responders or nonresponders to each therapy. This is now an important topic in MS, due to the availability of many effective drugs, making informed treatment decisions complex.”

REFERENCE

High-Dose Biotin Fails to Improve Disability in Progressive MS

Results from the SPI2 study (NCT02936037) suggest that high-dose, pharmaceutical-grade biotin (MD1003; MedDay Pharmaceuticals) does not significantly improve disability or walking speed in patients with progressive multiple sclerosis (MS) and cannot be recommended for the treatment of the disease.

The data show that for the primary outcome—a composite of the proportion of participants with confirmed improvement in Expanded Disability Status Scale (EDSS) score or timed 25-foot walk (TW25) at month 12 (confirmed at month 15)—just 12% of those treated with biotin (n = 19) improved compared with 9% of those in the placebo group (n = 29), for an odds ratio (OR) of 1.35 (95% CI, 0.81-2.26);
In total, the study included 642 participants randomly assigned to either 100-mg of oral biotin 3 times daily (n = 326) or placebo (n = 316).

In the prior MS-SPI study (NCT02220933), high-dose biotin appeared to improve disability outcomes over 12 months in patients with progressive MS. However, study author Bruce Cree, MD, PhD, MAS, clinical research director at the University of California, San Francisco Multiple Sclerosis Center, and colleagues noted that they did not anticipate a replication of the results from the smaller MS-SPI study.

“Given that SPI2 was a substantially larger trial done in a more diverse patient population, it seems more likely that the favorable observations from MS-SPI were due to a type 1 error rather than a type 2 error in SPI2,” they wrote. “Therefore, we conclude that biotin is ineffective in patients with progressive multiple sclerosis.”

Additionally, Cree et al confirmed high-dose biotin to have deleterious health consequences caused by interference on laboratory tests based on a biotin-streptavidin interaction. In this assessment, 25 inaccurate laboratory results were recorded, with the most common error being the mischaracterization of hyperthyroid in euthyroid participants.

For the EDSS component of the SPI2 primary end point, 22 patients (7%) in the biotin group and 20 (6%) in the placebo group reported a response (OR, 1.07; 95% CI, 0.57-2.02); for the TW25 component, 22 (7%) and 11 (3%) in each group, respectively, had a response (OR, 2.02; 95% CI, 0.98-4.39). In total, 5 participants in the biotin group and 2 in the placebo group improved on both components. The percentage change in mean TW25 between month 0 and month 15 was 20.7% (standard deviation [SD], 52.1) in the biotin group and 22.5% (SD, 53.4) in the placebo group, but the between-group difference (0.30) was not significantly different.

With regard to the secondary outcomes, 60 (18%) patients in the biotin group and 62 (20%) of the placebo group reported 12-week confirmed EDSS progression. The time-to-confirmed progression analysis revealed no significant differences between groups (hazard ratio [HR], 0.97; 95% CI 0.68-1.39), though a prespecified subgroup analysis revealed a possibly positive effect of biotin in patients with low body mass index (BMI) (≤25.6 mg/kg²) for an OR of 1.76 (95% CI, 1.05-2.95) that had a corresponding negative effect in those with high BMI (OR, 0.60; 95% CI, 0.36-1.00), though it was not significant.

Treatment-emergent adverse events (AEs) were reported in 277 (84%) of 331 participants in the biotin group and in 264 (85%) of 311 in the placebo group. At least 1 serious AE was reported by 87 (26%) and 82 (26%) participants, respectively, with 1 death recorded in the biotin group.

In addition to not meeting the primary or secondary end points, Cree and colleagues concluded that “exploratory analyses using biomarkers of neuronal injury, MRI markers of axonal integrity magnetic resonance spectroscopy, and a sensitive measure of ambulation found no differences between the treatment groups and exclude a neural protective role of biotin. Taken together, these results suggest no beneficial effect of MD1003 in patients with multiple sclerosis.”

REFERENCE
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Ponesimod Is Linked to Low Levels of Disease Activity, No Cardiac Safety Risks in Relapsing MS

Analyses presented at the 8th Joint ECTRIMS-ACTRIMS Meeting demonstrated the investigational drug’s ability to modify disease activity with a good safety profile.

By Marco Meglio

**DATA FROM A PHASE 2B core study (NCT01006265) and its extension study (NCT01093326) revealed that long-term treatment with 20-mg ponesimod (Janssen Pharmaceuticals) resulted in consistently low levels of disease activity across relevant clinical and MRI outcomes in patients with relapsing-remitting multiple sclerosis (RRMS).**

Among a cohort of 214 patients who were still on ponesimod treatment, annualized relapse rates for confirmed relapses in the 20-mg group were 0.154 (95% CI, 0.111-0.214), with 64.1% of patients remaining free of confirmed relapse.

The data presented at MS Virtual 2020: 8th Joint ECTRIMS-ACTRIMS Meeting, September 11-13, 2020, by Mark Freedman, MD, MSc, director of the multiple sclerosis research unit at Ottawa Hospital, showed that the Kaplan-Meier estimate of 6-month confirmed disability accumulation at week 432 was 20.4% (95% CI, 13.7%-29.7%) for those treated with ponesimod.

A total of 435 patients with RRMS received more than 1 dose of ponesimod (10, 20, or 40 mg per day) during the core and/or extension study. Notably, the 40-mg dose was discontinued during treatment period 1 of the extension study. During treatment period 2, patients received either the 10- or 20-mg dose, with the investigators eventually discontinuing the 10-mg dose. This was followed by open-label 20 mg in treatment period 3.

MRI outcomes showed a mean of 0.448 (95% CI, 0.305-0.657) T1 gadolinium-enhancing lesions per patient per scan, as well as a mean of 0.718 (95% CI, 0.523-0.985) new or enlarging T2 lesions per year.

No new safety signals emerged with ponesimod treatment; nasopharyngitis (30%), headache (24%), and upper respiratory tract infection (21%) were the most common treatment-emergent adverse events (TEAEs). Most of the serious AEs (SAEs) were reported in a single patient and no SAE was reported at an incidence of more than 1%.

Also presented at the meeting was an analysis of the drug’s cardiac safety profile, showing that treatment with the agent was associated with no increased risk for major cardiovascular (CV) events (myocardial infarction, stroke, or CV death) when compared with teriflunomide (Aubagio; Sanofi). In comparison, 3 major CV events occurred in the teriflunomide group.

The dataset was from the phase 3 OPTIMUM study (NCT02425644) and was presented by Till Sprenger, MD, a neurologist with DKD Helios Klinik Wiesbaden.

Among a cohort of 1131 patients who received treatment with either ponesimod (n = 565) or teriflunomide (n = 566), cardiac TEAEs that led to discontinuation occurred in 1 patient (0.2%) on ponesimod (cardiomyopathy) and 2 patients (0.4%) on teriflunomide (1 atrial fibrillation, 1 coronary artery insufficiency).

Patients included in the analysis were randomized 1:1 to ponesimod 20 mg or teriflunomide 14 mg for 108 weeks. Those on
ponesimod underwent a gradual 14-day titration that began with 2 mg, implemented to address first-dose cardiac effects. Blood pressure and 12-lead electrocardiogram measurements were used to assess cardiac safety.

Sprenger and colleagues noted that there was no association between clinically significant bradyarrhythmia events and patients who had their doses uptitrated. Additionally, none of those events were serious or led to discontinuation. No second degree or higher atrioventricular blocks were reported.

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**Ofatumumab Is Highly Effective in Treatment-Naïve Patients With Relapsing Multiple Sclerosis**

*Results in treatment-naïve patients were consistent with those of the overall study population in the ASCLEPIOS I and II trials.*

By Marco Meglio

**AN EVALUATION OF A SUBGROUP** population of treatment-naïve patients with relapsing-remitting multiple sclerosis from the phase 3 ASCLEPIOS I and II trials (NCT02792218 and NCT02792231) demonstrated that treatment with ofatumumab (Kesimpta; Novartis) was associated with low absolute relapse rates (ARRs), very low MRI lesion activity, and prolonged time to disability worsening, compared with treatment with teriflunomide (Aubagio; Sanofi).

The poster was presented at MS Virtual 2020: 8th Joint ECTRIMS-ACTRIMS Meeting, September 11-13, 2020, by Stephen L. Hauser, MD, the director of the University of California, San Francisco Weill Institute for Neurosciences and cochair of the steering committee for the ASCLEPIOS I and II studies.

Hauser and colleagues assessed key efficacy and safety outcomes in 615 newly diagnosed (within 3 years before screening), treatment-naïve (no prior disease-modifying therapy [DMT] use) patients who received ofatumumab or teriflunomide as a first-line therapy.

They found that compared with treatment with teriflunomide, treatment with ofatumumab reduced ARR by 50.3% (0.09 vs 0.18; *P* < .001); 3-month confirmed disability worsening (3mCDW) risk by 38% (10.1% vs 12.8%; *P* = .065); and 6-month CDW (6mCDW) by 46% (5.9% vs 10.4%; *P* = .044). The treatment was also superior in reducing gadolinium-enhancing T1 lesions per scan by 95.4% (0.02 vs 0.39; *P* < .001) and new or enlarging T2 lesions per year by 82.0% (0.86 vs 4.78; *P* < .001).

In total, 84.7% of patients who received ofatumumab experienced treatment-emergent adverse events (AEs) compared with 86.0% of teriflunomide-treated patients. Notably, serious AEs occurred in 7.0% and 5.3% of the groups, respectively.

Investigators reported no cases of malignancies in the newly diagnosed patients who were randomized to either drug. Both ofatumumab (56.1%) and teriflunomide (56.5%) were associated with comparable rates of infection, with no opportunistic infections reported. Serious infection rates were 1.9% and 0.7% in the ofatumumab and teriflunomide groups, respectively.

Hauser and colleagues concluded that ofatumumab is the first high-efficacy DMT that can be self-administered at home. In fact, more than 70% of RMS patients opted for self-injection at home after their fourth injection, and 98.8% of patients complied with injections of ofatumumab.

Ofatumumab was granted market approval by the FDA in August 2020 for the treatment of relapsing forms of MS in adults, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive MS.

Approval for the fully human anti-CD20 monoclonal antibody was supported by data from the same ASCLEPIOS I and II studies, which included more than 1800 patients. Full trial results indicated that ARRs for patients with MS who received ofatumumab in the ASCLEPIOS I and II trials were reduced by 51% (ofatumumab: 0.11; teriflunomide: 0.22; difference, −0.11; 95% CI, −0.16 to −0.06; *P* < .001) and 58% (ofatumumab: 0.10; teriflunomide: 0.25; difference, −0.15; 95% CI, −0.20 to −0.09; *P* < .001), respectively, with both differences achieving statistical significance (*P* < .001 for both).

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**RISK FACTORS FOR SEVERE COVID-19 INFECTION IN MULTIPLE SCLEROSIS**

Asaff Harel, MD, a neurologist at Lennox Hill Hospital, characterized the patterns of coronavirus disease 2019 infections in patients with multiple sclerosis and identified risk factors for severe infection.

*View video: neurologylive.com/ms-covid-19*

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For a full list of references, see the article on NeurologyLive.com.
Ozanimod Exhibits Long-Term Safety, Efficacy in Open-Label Extension

Along with being generally well tolerated, ozanimod was able to help most patients become relapse free without disability progression.

By Marco Meglio

INTERIM ANALYSIS FROM AN open-label extension of patients with relapsing forms of multiple sclerosis (RMS) enrolled in the DAYBREAK study (NCT02576717) showed an association between the use of ozanimod (Zeposia; Bristol Myers Squibb) and both low annualized relapse rate (ARR) and low counts of new or enlarging T2 and gadolinium-enhancing (GdE) lesions over time.1

Presented at MS Virtual 2020: 8th Joint ECTRIMS-ACTRIMS Meeting, September 11-13, 2020, senior author Bruce Cree, MD, PhD, MAS, clinical research director of the University of California, San Francisco (UCSF) Multiple Sclerosis Center and professor of clinical neurology at USCF Weill Institute for Neurosciences, and colleagues aimed to characterize the long-term safety and efficacy of ozanimod in patients with RMS.

At months 24 and 36, 79% and 75% of participants, respectively, were relapse free. A cohort of 2492 participants with a mean ozanimod exposure of 35.4 months (range, 0.03-50.2) revealed an adjusted ARR of 0.112 (95% CI, 0.093-0.135).

Patients were eligible for the extension trial if they had completed any phase 1, 2, or 3 trial of ozanimod previously. Investigators calculated the number of new/enlarging T2 and GdE MRI brain lesions for the subset of patients who entered the open-label extension from an active-controlled phase 3 trial.

Regardless of parent-trial treatment group, mean number of new/enlarging T2 lesions per scan at 24 months was similar (range, 1.57-1.90), as were the mean number of GdE lesions (range, 0.2-0.4). Confirmed disability progression was observed in 10.8% and 8.6% of participants at 3 and 6 months, respectively.

Available data on safety measures from 2039 participants showed that 81.8% of the population had a treatment-emergent adverse event (TEAE). Additionally, 9.5% of patients had a serious TEAE (SAE) and 56 (2.2%) discontinued due to a TEAE. Researchers also noted that similar rates of TEAEs and SAEs occurred when assessed by the parent-trial treatment group.

Nasopharyngitis (17.9%), headache (14.0%), upper respiratory tract infection (9.9%), and lymphopenia (9.6%) were among the most common TEAEs observed within the extension period. There were no serious opportunistic infections, and exposure-adjusted incidence rates of TEAEs and SAEs decreased over time.

Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator, was approved by the FDA for the treatment of adults with RMS, including clinically isolated syndrome, relapsing-remitting MS, and active secondary progressive MS, in March 2020.2

The approval of ozanimod was based on data from the phase 3 SUNBEAM (NCT02294058) and RADIANCE part B (NCT01628393) trials that included more than 2600 adults. The randomized, active-controlled studies compared ozanimod with interferon beta-1a (Avonex) on the primary end point of ARR.

Bristol Myers Squibb announced the commercial launch and availability of ozanimod in June 2020, making it the first and only S1P on the market that requires no first-dose observation.3

For a full list of references, see the article on NeurologyLive.com.

More on NeurologyLive.com

ADVANTAGES OF PONESIMOD AS AN S1P MODULATOR
Luc Truyen, MD, PhD, details what sets apart investigational agent ponesimod from other currently available FDA-approved treatments for MS.

View video: neurologylive.com/ponesimod-advantages

EARLY DATA ON CELL THERAPY FOR PROGRESSIVE MS
Jakob Dupont, MD, discusses phase 1 results for ATA188, an agent that targets cells infected by Epstein-Barr virus for progressive MS.

View video: neurologylive.com/cell-therapy-progressive-ms
Investigational Drug Targeting Epstein-Barr Virus Shows Promise for Progressive MS

Atara Biotherapeutics’ allogeneic EBV-targeted T-cell therapy, ATA188, is well tolerated in phase 1 study, with a dose identified for the randomized placebo-controlled portion of the trial.

By Matt Hoffman

PRELIMINARY PHASE 1 SAFETY DATA (NCT03283826) on the investigational, off-the-shelf, allogeneic Epstein-Barr virus (EBV)-targeted T-cell therapy ATA188 (Atara Biotherapeutics) suggest that the agent is well tolerated in adults with progressive forms of multiple sclerosis (MS).

The findings include data from patients dosed up to April 2020 (n = 25), each of whom received at least 1 dose of ATA188. Ultimately, no adverse events (AEs) worse than grade 3 were reported. In total, 2 treatment-emergent serious AEs were noted: a grade 2 incidence of muscle spasticity, which was not related to therapy, and a grade 3 incidence of MS relapse, which was considered possibly related to treatment.

The data were presented at MS Virtual 2020: 8th Joint ECTRIMS-ACTRIMS Meeting, September 11-13, 2020, by Amit Bar-Or, MD, the Melissa and Paul Anderson President’s Distinguished Professor of Neurology, Perelman School of Medicine, University of Pennsylvania.

“[ATA188] was very well tolerated, and the good news is that we are not seeing [intolerance] even with the longer-term dosing of patients with these cells going out to 21 months, 24 months. We’re not seeing augmentation of safety issues,” Jakob Dupont, MD, executive vice president and head of global research and development, Atara Biotherapeutics, told NeurologyLive. “One [important] aspect of ATA188 is that it’s a very specific treatment. These T cells are really directed against only EBV-expressing infected cells, and because of that, we don’t have a lot of off-target toxicity.”

As well as the generally low-grade AEs that were observed, there were no dose-limiting toxicities, cytokine release syndrome, graft-vs-host disease, or infusion reactions reported. “With a lot of cell therapies, whether it’s [chimeric antigen receptor T-cell therapy] or whatever it may be, you can see neurological symptoms, you can see cytokine release syndrome and so forth, and we really don’t see those types of effects with our treatment because of, again, the specificity of our EBV T cells. They’re not directed against the patient’s own self-antigens, if you will,” Dupont noted.

The first part of the study included 4 cohorts of patients who received escalating doses to determine the recommended dose for the second part of the trial. The participants were followed for 1 year, and then given the option to participate in a 4-year open-label extension (OLE) at the recommended dose, which was determined by Cohort 3.

In addition to the safety measures, sustained disability improvement (SDI)—defined as improvement in Expanded Disability Status Scale (EDSS) score or Timed 25-Foot Walk at 2 or more consecutive time points—was assessed, as were Fatigue Severity Scale, 12-item MS Walking Scale, and MS Impact Scale-29 (physical) scores, and whole-brain volume. The efficacy end points were assessed in all 4 cohorts (n = 24) at the 6-month mark, and in the first 3 cohorts (n = 17) at 12 months.

A higher proportion of patients who were treated with ATA188 showed SDI with an increasing dose. At 6 and 12 months, 6 and 5 patients met SDI criteria, respectively. This was driven by EDSS score in all but 2 patients at both time points. In cohorts 1, 2, and 3, every patient with SDI at the 6-month time point maintained that status through 12 months.

Additionally, those who achieved SDI at any time point maintained it at all future time points and tended to show improvements in fatigue, physical function, and MRI whole brain volume at 1 year. As of June 2020, OLE data from the 15-month time point were available for 4 individuals: 3 had SDI at 6 and 12 months that was maintained to that point.

“We are encouraged by what we’re seeing in the clinical trial because when we get into Cohort 3, we are seeing sustained disability improvement in these patients…this isn’t just 1 point in time where we’re seeing a patient doing better today,” Dupont said.

REFERENCE

MS Education Goes Virtual

NeurologyLive® recently partnered with the Consortium of Multiple Sclerosis Centers on 2 educational webinar programs for MS health care providers and patients.

AS PART OF ITS ONGOING Strategic Alliance Partnership, NeurologyLive® recently teamed up with the Consortium of Multiple Sclerosis Centers (CMSC) to cohost 2 virtual educational events for health care providers (HCPs) as well as patients with multiple sclerosis (MS).

The webcast-based programs took place in October and included multiple presentations from esteemed faculty across the spectrum of providers. The first program, a 1-day intensive event geared towards specialized MS nursing staff and advanced practice providers and their patients, titled “Differing Perspectives on Multiple Sclerosis Care,” offered 3 continuing education (CE) credits for nursing professionals based on evidence-based presentations made by 3 featured speakers: Denise Bruen, MSN, ANP-BC, MSCN; Stephanie Agrella, PhDc, MSN, RN, ANP-BC, MSCN; and Marie Namey, APRN, MSCN.

Topics covered during the event, which was also produced in partnership with the International Organization of Multiple Sclerosis Nurses and supported by grants from Biogen, Bristol Myers Squibb, Genentech, and Novartis, included MS physiology and immunology; goals of disease-modifying therapies (DMTs), including updates on the newest FDA-approved treatments; and mental health concerns and management in patients with MS, as well as discussion on shared decision-making. The more than 150 live course attendees also reviewed several cases and engaged in a lively question-and-answer session with the nursing faculty.

The 3-hour nursing session was followed by a complimentary patient program for those living with MS and their caregivers. Notably, many of the HCPs who attended the nursing course chose to also attend the patient program, eager to understand more about the information being communicated to patients and the questions they had.

The patient program, also led by the nursing faculty, provided information on DMTs, how and why certain medications are chosen for certain patients, management of common MS symptoms, and mental health.

Exploring Alternative Treatments for MS

The second, 3-part program focused on educating HCPs on a hot topic in the MS community: cannabis use. Led by MS expert Allen C. Bowling, MD, PhD, director of the NeuroHealth Institute and clinical professor of neurology at the University of Colorado, and supported by an independent educational grant from Greenwich Biosciences, attendees could earn up to 3 CE credits through the virtual series.

Over the 3 sessions, Bowling addressed a broad swath of important topics pertaining to the pharmacology, efficacy, and safety of cannabis use in MS, including the role of the FDA and regulations around dispensaries, clinical trial data, and symptom management. The more than 500 registrants for the events put aside their preconceived notions to learn about differences in administration/consumption, potential drug interactions, and how to best address and educate their patients who are curious about or are using cannabis products to help manage their MS symptoms.

Those who missed out on the live virtual events can view the enduring materials and instructions on how to claim credit at NeurologyLive.com/virtual-events.

If your institution or organization is interested in learning more about the Strategic Alliance Partnership program, contact program coordinator Boris Sotnikov at bsotnikov@mjhlifesciences.com.

For more direct access to expert insight into multiple sclerosis, go to the NeurologyLive® “Multiple Sclerosis” Clinical Focus page.

Head to neurologylive.com/clinical/multiple-sclerosis
The Future of Multiple Sclerosis Imaging

Advanced imaging technology collides with artificial intelligence in what is shaping up to be a revolutionary period for the diagnosis and management of MS.

By Pascal Sati, PhD

BRAIN IMAGING RESEARCH in multiple sclerosis (MS) is experiencing an acceleration of technological progress. Fueled by the relentless pace of innovation in magnetic resonance imaging (MRI) and the recent outburst of artificial intelligence (AI), these advances are the crest of a new wave of scientific tools for the MS clinic.

Since its introduction nearly 3 decades ago, 2-dimensional (2D) multislice brain MRI sequences—such as proton-density, T2, fluid-attenuated inversion recovery (FLAIR), and T1 scans—have become the workhorses of any diagnostic or follow-up brain MRI exams for MS. The longevity of these scans, often referred to as conventional MRI, is explained by their high sensitivity in the detection of white matter lesions (WMLs) of the brain (represented as hyper- or hypointense focal areas) and their robust imaging on any 1.5-T and 3-T clinical scanners. However, recent advances in ultra-fast MRI sequences are about to completely transform the way these conventional brain scans are routinely acquired in hospitals and medical imaging centers.

Advances in Image Acquisition and Analysis

One of these new MRI sequences is simultaneous multislice (SMS), which collects multiple imaging slices concurrently.1 SMS can cut the scan time of conventional 2D multislice scans by a factor of 2 without degradation of image quality.2 Another technique, compressed sensing, collects and utilizes heavily undersampled data; this can reduce the scan time of any 2D or 3D anatomical scans by 20% to 50% while maintaining virtually equivalent image quality.3 Wave-controlled aliasing in parallel imaging is another technical breakthrough that combines an undersampling strategy with an efficient 3D encoding; this technique can massively accelerate any 3D T2, FLAIR, and T1 brain scan to reduce scan times to 1 to 2 minutes.4 Finally, AI-based image reconstruction techniques can improve the image quality of undersampled data, thus enabling shorter scans.5 This significant reduction in scan time will provide crucial benefits. First and foremost, patients will experience less discomfort as a result of a much shorter MRI exam, possibly as short as 10 minutes or even less. Second, a scan will be quickly repeated if motion affects image quality, enabling radiologists and neurologists to evaluate their patients’ images more consistently. Last, high-resolution 3D brain scans will replace conventional 2D brain scans, which produce thick-slice images, often containing large gaps between each slice. These important innovations will pave the way for widespread adoption of automated image analysis tools that provide invaluable information about MS disease activity.

Over the past decade, a multitude of image analysis techniques have been developed to automatically segment brain tissues and lesions using high-resolution 3D anatomical scans. These techniques rely on various approaches, including statistical methods (Method for Inter-Modal Segmentation Analysis6), machine-learning classifiers (Classification using DErivative-based Features7), and deep-learning algorithms (3D U-Net8). Currently, fully automated image analysis solutions powered by AI, including those from CorTechs Labs,9 Icometrix, and Quantib, are even offered as products that are approved for clinical use. Therefore, a flurry of imaging-based measures could be factored into the routine evaluation of patients with MS, including longitudinal volume changes of brain tissues, total/regional lesion load, and individual lesions.
Brain volume changes—which include whole-brain atrophy and regional brain atrophy (e.g., cortical atrophy, thalamic atrophy)—are particularly useful as a measurement of brain tissue loss and have become widely accepted measures of neurodegeneration; they are among the best predictors of physical and cognitive disability. Clinical trials evaluating new disease-modifying therapies (DMTs) for MS already incorporate brain atrophy measures as critical end points in their cohort studies. Further, ongoing efforts to improve the accuracy and reliability of these measures and build large normative reference data sets using cloud computing platforms will allow the ability to track brain atrophy routinely in individual patients. Tracking individual lesions, particularly the formation of new WMLs, is also useful to assess the biological response of a patient to DMTs targeting MS inflammatory activity. By automatically comparing a baseline 3D scan to a follow-up 3D scan, reliable detection of new lesions is now possible without using T1-enhancing lesions, thus preventing the repetitive use of macrocyclic and linear gadolinium-based contrast agents, a clinical practice that is being intensively debated because of possible safety concerns. Additionally, monitoring persistent WMLs will become clinically relevant as some of the chronic lesions slowly expand over time. These slowly expanding lesions are in the spotlight of MS investigators, as they are believed to reflect the demyelination and axonal loss as a result of a smoldering inflammation behind an intact blood-brain barrier. Investigators suspect that this chronic inflammation drives the disease worsening observed in patients with progressive MS. For this reason, an ongoing race exists in the MS pharmaceutical industry to deliver the first brain-penetrant therapy that could stop this smoldering inflammation.

Other features of MS lesions may also have clinical significance. Specific lesion morphological characteristics, such as shape and surface features extracted from high-resolution 3D brain MRI scans, could help differentiate MS lesions from nonspecific WMLs. Additionally, lesion phenotyping based on 3D morphology may open new avenues for developing outcome measures, which would reflect the biological activity of MS lesions such as myelin repair. Another feature, lesion intensity, is now assessed qualitatively in the clinic. As an example, chronic black holes that are known to be areas of permanent tissue destruction are defined as severely hypointense lesions on T1-weighted scans; however, depending on the type of MRI sequence and parameters of the T1 scan, the level of hypointensity can significantly change, thus hampering the proper identification of these black holes. A quantitative measure of the T1 signal, referred to as T1 relaxation time, would provide a standardized metric of black holes, enabling their robust discrimination in the clinic. Initially dedicated to research, quantitative MRI techniques measuring T1 and T2 relaxation times have been significantly improved in terms of accuracy, reproducibility, and overall workflow. Some of these techniques, such as MAGnetic resonance image Compilation (MAGIC), 2 inversion-contrast magnetization-prepared rapid gradient echo (MP2RAGE), and magnetic resonance fingerprinting, are moving into the realm of clinical imaging. These techniques may even become the workhorses of clinical MS brain protocols thanks in part to their additional capability of synthesizing multiple image contrasts simultaneously.

Innovative Imaging Biomarkers

The advances discussed so far rely on MRI techniques that produce conventional image contrasts (e.g., proton-density, T1, T2, and FLAIR). Unfortunately, these types of contrasts lack specificity regarding the underlying pathological mechanisms involved in the development of MS lesions. This poor specificity frequently complicates the evaluation of patients suffering from radiological mimics of MS, putting these patients at risk of receiving a misdiagnosis when there is an overreliance on MRI findings. Brain lesions related to comorbidities in patients with MS could be falsely interpreted as MS lesions and mislead treatment decisions. Therefore, a crucial need exists for MRI techniques to deliver biomarkers specific to MS pathology; currently, 2 extremely promising imaging biomarkers are in the research pipeline to help address this issue of specificity (FIGURE).

The first and most mature biomarker is the central vein sign (CVS), which corresponds to the presence of a small vein running centrally through a focal lesion. The perivenular formation of MS lesions is a well-known biological phenomenon initiated by the breakdown of the blood-brain barrier, which releases inflammatory cells that radially diffuse from the inflamed vein into the surrounding brain tissue leading to focal demyelination. Advanced MRI techniques sensitive to the magnetic properties of the brain can image these small veins thanks to the difference in magnetic susceptibility between venous blood and parenchymal tissue. One such technique is susceptibility-weighted imaging (SWI), which was initially developed to perform cerebral venograms. However, SWI scans acquire thick-slice images that do not allow adequate visualization of central veins running in a multitude of directions. For a more sensitive and robust detection of the CVS, optimized susceptibility-based techniques can be used instead. Indeed, T2*-weighted 3D echo-planar imaging (or T2*-3DEPI) and FLAIR (a combination of FLAIR and T2*) produce high-isotropic-resolution 3D images that facilitate the identification of brain lesions with central veins. From a clinical perspective, CVS will be helpful for the differential diagnosis of MS. Multiple clinical studies have recently demonstrated that patients with MS have a significantly higher proportion of brain lesions with CVS than patients with migraine, small vessel disease, neuromyelitis optica spectrum disorder, and other inflammatory vasculopathies. Encouraged by these results, an ongoing multicenter study is investigating the diagnostic potential of CVS in undiagnosed patients with typical or atypical onset. By comparing the current diagnostic criteria against the prediction based on CVS detection, this large-scale prospective study could demonstrate a significant gain in speed and accuracy of MS diagnosis. Another potential benefit of CVS could be the detection of the disease even before its clinical manifestation. Indeed, patients with radiological findings but without any history of clinical symptoms can have a significant proportion of their brain lesions with CVS, suggestive of subclinical MS disease.

The second biomarker is the so-called paramagnetic rim lesions (PRLs). Using the susceptibility-based MRI techniques introduced above, along with advanced quantitative susceptibility mapping post-processing techniques, investigators very recently demonstrated that some MS lesions possess a paramagnetic rim located at their edges. This rim appears to correspond to the accumulation of iron-laden...
Macrophages or microglia, which are thought to be the generation of the smoldering inflammation discussed previously. Although not all patients with MS have PRLs, those with PRLs clearly experience a more aggressive disease.

These findings point to the potential value of PRLs as a prognostic biomarker. In addition, PRLs appear to be very specific to MS lesions and may be a complementary biomarker for MS diagnosis. To prepare for future clinical use of these biomarkers, automated solutions for the detection of CVS and PRLs are already in development using probabilistic methods, as well as deep-learning algorithms (CVSnet and RimNet).

Advanced MRI Devices

Although imaging WMLs is the bread and butter of clinical MRI, cortical lesions are seen with increasing clinical importance and will become important radiological findings for predicting disease progression as well as evaluating new therapies for neuroprotection. Because of their specificity regarding MS pathology, cortical lesions are now part of the MRI diagnostic criteria for MS. However, in practice, these lesions remain difficult to detect reliably using conventional MRI scans. Newer techniques such as phase-sensitive inversion recovery and the very recent inversion-recovery susceptibility-weighted imaging with enhanced T2 weighting can improve the visualization of cortical lesions on 3T scanners, especially the detection of subpial lesions associated with cognitive decline and disease progression. Meanwhile, another powerful strategy for imaging cortical lesions with high sensitivity utilizes scanners with a stronger magnetic field, such as the 7-T scanner.

Seven-tesla MRI produces exquisite images of the human brain by achieving very high spatial resolution—on the order of hundreds of micrometers. This high-end imaging device has been intensively used in clinical research over the past 10 years to noninvasively investigate MS pathology developing in patients’ brains. This sustained research effort has brought new insights into the understanding of cortical and white matter MS lesions and sparked the discoveries of the CVS and PRLs. The recent FDA approval of the first 7-T MRI for clinical use is another major step forward for MS imaging, as it will enrich the clinician’s toolbox for diagnosing MS and speed up the clinical translation of future imaging biomarkers yet to be discovered with this cutting-edge imaging technology.

Without a doubt, MS imaging is set to undergo an exciting technological transformation. The next-generation MRI techniques discussed here will provide clinicians with an unprecedented wealth of information about this complex and multifaceted disease. By fully embracing these technological and scientific shifts on the horizon, neurologists will enhance their ability to diagnose earlier and more accurately, identify and anticipate the trajectory of the disease, and adapt treatment strategies to keep the irreversible progression of the disease at bay. Lastly, integrating rapidly innovative imaging biomarkers into the clinical trials of emerging drugs—especially those promoting neuroprotection and neurorepair—will help finally turn the tables on this debilitating disease. All in all, the future of MS imaging is very bright. For a full list of references, see the article on NeurologyLive.com

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HISPANIC PATIENTS MAY DEVELOP MORE AGGRESSIVE MS, MRI DATA INDICATE

MRI data collected by Carlos Perez, MD, and colleagues suggest that Hispanic patients are at greater risk for developing more aggressive forms of multiple sclerosis at earlier ages. Read article: neurologylive.com/hispanics-aggressive-ms
OPTIC NEURITIS

Steps Forward in the Management of Optic Neuritis

Two experts in neuro-ophthalmology discuss the advances in the identification and treatment of patients presenting with optic neuritis.

By Matt Hoffman

THE TREATMENT OF PATIENTS WITH multiple sclerosis (MS) often spans a multidisciplinary care team to adequately manage the disease's wide spectrum of symptoms and complications—such as the inflammation of the optic nerve, leading to optic neuritis and neuromyelitis optica (NMO).

Literature suggests that approximately half of patients receiving a diagnosis of MS will present with optic neuritis as the first sign of relapsing-remitting MS, whereas those with primary progressive MS are less likely to present with optic neuritis. A key identifier for neuro-ophthalmologists is pain accompanying eye movement, as well as swelling and other evidence of inflammation in the eye and optic nerve.

In a recent NeurologyLive® Peers & Perspectives series titled “Management of Optic Neuritis,” a pair of specialists in neuro-ophthalmology discussed the diagnosis, management, and treatment of these patients, including discussion on therapeutic advances and anti-myelin oligodendrocyte glycoprotein (MOG) disease.

Treatment and Patient Identification

Although physicians treating optic neuritis had previously been quite limited in what they had available to treat the symptom, there are now nearly 2 dozen treatments to utilize. Robert Sergott, MD, chief of neuro-ophthalmology at Wills Eye Hospital in Philadelphia, Pennsylvania, noted that some patients are still treated with injectable therapy, such as glatiramer acetate or interferon, but many are also treated with oral medications and intravenous infusions.

“While we can prevent a lot of relapses now, where MS therapy needs to move to is how we repair damage,” he said. That area, he added, will be the focus for the next decade in therapeutic development. Advancements in therapy over the past 20 years have shifted what happens in the management of acute optic neuritis—particularly the spectrum of disease with NMO.

“It used to be we would lump all inflammatory optic neuropathy together that looked somewhat like MS,” Rod Foroozan, MD, a neuro-ophthalmologist and associate professor at Baylor College of Medicine in Houston, Texas, said. “We now know that there are some variants and there’s a spectrum of disease. In the early to mid-2000s, a blood test became available for neuromyelitis optica,” Foroozan recalled, noting the discovery of a circulating IgG autoantibody reported in patients with NMO that was absent in those with MS, “which is an antibody to aquaporin 4, and that was a game changer because we could now define—by pathophysiology and identify with a blood test—those patients who were going to be at risk for a more progressive disease.”

Prior to the blood test becoming available, the general belief was that NMO was a variation of MS, despite the fact that the conditions differ greatly both diagnostically and therapeutically. In fact, Foroozan pointed out, some patients treated for NMO will not have an adequate response to traditional therapy for MS. Additionally, physicians were originally taught to only point to NMO if both optic nerves were involved.

Relatively soon after the identification of this antibody to aquaporin 4, physicians began to notice that individuals with more
severe optic nerve involvement, poor vision bilaterality, simultaneous involvement, or longer stretches of enhancement of the optic nerve—extending into the optic chiasma, for example—differed immunologically in how inflammation occurred. Sergott noted that patients who do not improve with steroids often lead him to be very suspicious of NMO. In these cases, plasmapheresis can be used and has been with dramatic success.

“NMO is a vicious disease. It’s just not a little worse demyelination,” Sergott said. “Beautiful work by Claudia Lucchinetti [MD,] from Mayo Clinic has shown that this is a vasculitis that has special preference for the optic nerve, the retina, an area of the brain near the start of the spinal cord called the medulla, the area postrema, and for long segments of the spinal cord.”

Sergott noted that every patient in question should receive an NMO titer and an anti-MOG titer. He pointed to potential identifying symptoms, including uncontrollable hiccups caused by inflammation in the area postrema in the medulla and, rarely, long-lasting itching, which can present prior to vision loss.

As for imaging, Sergott and Foroozan explained that patients with optic neuritis require imaging in the spinal cord—both cervical and thoracic—to find asymptomatic lesions that stretch over several segments of the cord.

“There are patients who will have what’s called seronegative NMO,” Sergott said. “That is, the blood test will be negative, but they’ll have these clinical features or the neuroradiological features, and that’s still NMO.”

MOG and Neuromyelitis Optica

Foroozan explained that research on MOG revealed that a group of patients with optic neuritis were very responsive to steroids. These patients were found to be MOG antibody positive. In his experience, about one-third of pediatric patients who develop optic neuritis will have MOG antibodies present.

“Exactly what their role is in the pathogenesis of optic neuritis is not clear, but it is a marker in a group of patients, and that includes pediatric patients who develop optic neuritis,” Foroozan said. “And they can signify in older patients a risk for recurrent optic neuritis or what was previously termed CRION, for chronic relapsing idiopathic optic neuritis. Now we have a spectrum of disease that initially was only considered to be MS and now it has branched into at least 2 other forms, MOG and NMO.”

Sergott noted that a common tip-off for MOG disease is swelling on fundoscopic examination when the patient is unable to see, identifiable as optic nerve swelling and hemorrhages. He and Foroozan agreed that admitting these patients quickly is often best to acquire the proper imaging and see response. The pair explained that after between 3 and 5 days of intravenous steroids, if there is no improvement, it is justifiable to conduct plasmapheresis.

“Especially for the pediatric cases routinely admitted, 1 of the things I’ll look for is an early response to treatment,” Foroozan said. “We talked about a lack of response as being a marker maybe for NMO. One of the things that we’ll see with MOG is a very rapid response. If you’re getting a visual recovery within 24 to 48 hours with IV steroids, I’m very suspicious for MOG.”

Additionally, he added, with MOG there is this tendency for a perineural enhancement pattern to appear on MRI. When there is enhancement of the optic nerve extending into the orbital fat or around the optic nerve sheath, instead of just the nerve itself, that can be a strong indicator of MOG, or at least another type of inflammatory optic neuropathy.

“When I was in medical school, before we had MRI and before we had a lot of things, we thought MS was a rare disease,” Sergott said. “That is not true, and that happened because of MRI. Anytime we get better technology, we become better clinicians and can more precisely treat patients. The teaching, 5 years ago, was that NMO and anti-MOG were rare. I think they’re common.”

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The Future Is Digital: Telemedicine Is Helping Open Doors to More Comprehensive Care in MS

As the adoption of telemedicine rises, the ability to incorporate digital- and telehealth-based therapies offers clinicians a unique opportunity to supplement the comprehensive care model.

By Matt Hoffman

THE RAPID ADOPTION OF TELEMEDICINE that has occurred over the course of the coronavirus disease 2019 (COVID-19) pandemic has shined an even brighter light on the already recognized care access challenges faced by patients with chronic, debilitating diseases such as multiple sclerosis (MS)—one that often requires repeat clinic visits and consults with a large team of health care professionals. With many of those visits now taking place virtually out of necessity, it has added support to the argument that there is a “clear and tremendous” need for more digital- and telehealth-based interventions in MS.

This has long been the focus of clinical neuropsychologist Leigh Charvet, PhD, of the division of MS at NYU Langone Health in New York, who told NeurologyLive® that when these digital interventions are brought home to patients, clinicians reach a much broader spectrum of people living with MS—a highly important facet for research. Access to these resources, she said, underscores the demand for symptomatic management and rehabilitation, areas of treatment that often fall second to relapse prevention despite their immense impact on patient quality of life. To learn more about the digital therapeutic landscape and telemedicine’s place in the future treatment of MS, NeurologyLive® spoke with Charvet in an interview.

Q: Can you describe the evolution of your research into digital, home-based interventions for patients with MS?
My entry into this world was with cognitive remediation, which we know that we need a lot of training to do. That’s probably one of the early therapies that has very well designed and accessible computer-based or online-based training. That was really our first entry into this, to send people computers to their home and supervise them remotely to complete our first trial. They did 60 sessions over 12 weeks, so you could just imagine that that wouldn’t have been able to be done if they were coming to clinic. In general, with cognition, we also think of what a lot of times we call the “invisible symptoms” that have such a burden on day-to-day living for so many people. That definitely includes fatigue, and things like pain, and emotional distress is another huge component for many of us. Our approach has been to evaluate computer-based or app-based interventions targeting these symptoms remotely, and we do that because we can reach many more people and provide the adequate number of treatment sessions.

Our particular focus moved from that cognitive rehabilitation trial to evaluating the use of noninvasive brain stimulation, in particular, something called transcranial direct current stimulation (tDCS). That’s in the world of noninvasive brain stimulation therapies, but it can be portable and wearable. We knew that we could reach people in their homes, so we developed a whole protocol where we do live video visits to help people self-administer, with supervision, tDCS. The idea with tDCS is it may be therapeutic on its own. For instance, it is approved in many countries for the treatment of depression, but we’re particularly interested in its ability to boost rehabilitative outcomes. The idea is that pairing the stimulation while you’re doing a training activity may boost the benefit of the training activity. We took our cognitive remediation that we had established and then added tDCS to that.
That also brought us into the world of some motor rehabilitation. For instance, there is an established at-home hand exercise program to strengthen and recover hand function, where we're actually adding tDCS to that right now in the clinical trial. We're also very interested in types of exercise, physical therapy, and aerobic exercise at home paired with the brain stimulation to see if we can boost the benefit of that training activity.

We're interested in its benefits for fatigue, in general. There are a lot of parameters on how to use it, and in our research program, we're sending it home. And with our absolutely amazing patient participants who are true collaborators, we've designed a platform where we can reach people in their homes and have the high volume of sessions and sample sizes needed to really evaluate these emerging therapeutics. In that work, what we've seen is that people are able to do what would seem on paper to be very complicated procedures in their homes with supervision. We've learned how to take on the technical burden on our side, and then guide people to be able to do these therapies very successfully in their homes.

**Q:** How easily could these interventions be incorporated into standard care that patients with MS receive?

I think we're pretty close to that, but there are a lot of these emerging therapeutics—and this is not specific to MS, especially as these things are computer-based—where there's a disconnect between a provider or therapist telling a patient, “Here's something that you can access that will help you,” and then the patient actually doing that. We all know that you should go to the gym every day, but if I don't have a personal trainer or somebody watching me, I'm not going to do it. It's hard to change the behavior. Because of the brain stimulation part with tDCS, we are live with patients through video visits every time. That's really helped to have that behavioral adoption of the daily treatments, and I think that is a critical ingredient, that there is this supervised, connected onboarding of these daily therapies. There are all these wonderful tools out there, and many of them need more research, but the uptake is not there yet, and I think that connection is necessary for wider-scale adoption and people truly benefiting from these therapies.

**Q:** What kind of barriers to adoption of these therapies have you experienced from both patients and the clinical community?

There are 2 types of pushback: 1 is awareness. Raising awareness for your patients of this tool does not mean that they’ll use it and benefit from it. That's a common experience for a provider. Maybe [the provider] is aware of the tool, they refer their patients who then have the tool, but they hear, “Oh, I looked at it twice, and I didn't do it.” There's that critical period of structured onboarding, how to use it, in order to have an adequate evaluation. I think that causes premature dismissal of some things that are actually of great therapeutic benefit. Second, despite moving the dial on the acceptability of telehealth at a lightning rate because of COVID-19, there's always been the pushback of “people can't do that.” [Excuses like]

**Q:** Do you anticipate that more MS centers will adopt these interventions for at least some patients as they are validated?

Well, the short answer is absolutely. But I think what you raised is the critical piece, in terms of validation. What happens is, you have a glut of apps and online programs, and some are very science based. They take what we know from in-person therapy and make it into a digital therapeutic for access. Others are very different, and it's hard for the consumer—it's hard for the researcher—to tell the difference sometimes between what is what. We need carefully controlled clinical trials to guide our use because nobody wants to tell anybody to use something, to put the time into something, that hasn't been demonstrated to be worth their time. I don't think it would replace anything that we do now. We have our provider care, our nursing support, our social worker support, our therapists—physical, occupational, all kinds of therapists that we work with. That's already comprehensive care on-site, but this would supplement it because we know that so many people in between these visits still have significant burden of disease, primarily with these symptoms for which there aren't any tools to readily manage them. Therefore, access to these digital therapeutics might fill that need.

**Q:** How might these digital and telehealth approaches influence data collection for the study of the MS population?

It will absolutely have a positive effect in getting therapies evaluated for what we call pragmatic practical use, so very downstream. For very good reasons, clinical trials have that rigorous enrollment eligibility criteria because it's a different set of questions. We're on the total opposite end of the spectrum in that we want to reach as many people living with MS as possible, to have these tools evaluated. Then we can see that maybe there's a segment or something that wouldn't benefit from them, but let us find out by including everybody. We're much more focused on inclusion, and in that, we've been able to demonstrate that it's very important for evaluation of these types of therapies—any kind of tele- or digital therapeutics—to include the broadest spectrum of people living with MS as possible. That's important for so many reasons. There's a segment of people living with MS who are left out of a lot of clinical trials right now, and they face even more burden to get to a clinic visit to receive some type of therapy for a trial. We've been encouraged by being able to reach so many more people than are typically reached in a clinical trial to evaluate these therapies.
ZEPOSIA—a focused on what counts

ZEPOSIA was studied in the largest number of patients with RMS in 2 pivotal head-to-head trials against an active comparator (N=2659)²,³a:

**POWERFUL Efficacy**³a

- Proven superior in reducing relapses vs Avonex³c
- Proven superior in reducing GdE and T2 lesions vs Avonex

**COMPARABLE Safety Profile vs Avonex**

- Consistently low discontinuation rates vs Avonex
- Comparable rates of serious infections and malignancies vs Avonex

**The FIRST AND ONLY SIP With No First-Dose Observation Required**¹,³d

- Full Prescribing Information for ZEPOSIA has NO FIRST-DOSE OBSERVATION required
- NO genetic testing required
- NO ophthalmic testing required for most patients⁶,e

**Study designs:** SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-µg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, respectively). **Secondary endpoints:** ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.¹,³

**Adverse reactions:** Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. **Serious infections:** The rate of serious infections at 1 year for ZEPOSIA was 11% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. **Malignancy rates:** The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.¹,³

**Indication:** ZEPOSIA 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 who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.
**IMPORTANT SAFETY INFORMATION (CONTINUED)**

**Infections:** ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA.

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (SIP) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA.

- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another SIP receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

- Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with SIP receptor modulators and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued.

- In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

- Use of live attenuated vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

**A relapse was defined as the occurrence of new or worsening neurological symptoms persisting for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.**

**Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations.** Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation.

**For patients with a history of uveitis or macular edema, an ophthalmic assessment is required.** An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.

**Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA.**

ARR=annualized relapse rate; CBC=complete blood count; ECG=electrocardiogram; GdE=gadolinium enhancing; RMS=relapsing multiple sclerosis; SIP=sphingosine-1-phosphate; VZV=varicella-zoster virus.
IMPORTANT SAFETY INFORMATION (CONTINUED)

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for these individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class 1a or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome, or sinoatrial heart block

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease.

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA.

Increased Blood Pressure: Increase in systolic pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

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

Macular edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: 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 while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended.

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

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA.

Most common Adverse Reactions (≥ 4%): upper respiratory infection, urinary transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Please see Important Safety Information and Brief Summary of all Prescribing Information.
ZEPOSIA® (ozanimod) capsules, for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE
ZEPOSIA 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.

2 DOSAGE AND ADMINISTRATION
2.1 Assessments Prior to First Dose of ZEPOSIA
Before initiation of treatment with ZEPOSIA, assess the following:
- Complete Blood Count
- Obtain a recent blood count (CBC), including lymphocyte count [see Warnings and Precautions (5.5)].

Cardiac Evaluation
Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought [see Warnings and Precautions (5.4)].

Liver Function Tests
Obtain a recent liver function test (i.e., within the last 6 months) transaminase and bilirubin levels [see Warnings and Precautions (5.3)].

Ophthalmic Assessment
In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula [see Warnings and Precautions (5.6)].

Current or Prior Medications
- If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].
- Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction [see Warnings and Precautions (5.2) and Drug Interactions (7.2)].

Vaccinations
Test patients for antibodies to varicella zoster virus (VZV) before initiating ZEPOSIA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with ZEPOSIA [see Warnings and Precautions (5.3)].

If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

2.2 Dosing Information

Maintenance Dosage
After initial titration (see Treatment Initiation), the recommended maintenance dosage of ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8.

ZEPOSIA capsules should be swallowed whole and can be administered with or without food.

Treatment Initiation
Initiate ZEPOSIA with a 7-day titration, as shown in Table 1 [see Warnings and Precautions (5.2)].

| Table 1: Dose Titration Regimen |
| Days 1-4 | 0.23 mg once daily |
| Days 5-7 | 0.46 mg once daily |
| Day 8 and thereafter | 0.92 mg once daily |

2.3 Reinitiation of ZEPOSIA After Treatment Interruption
If a dose of ZEPOSIA is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen [see Dosage and Administration (2.2)].

If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

4 CONTRAINDICATIONS
ZEPOSIA is contraindicated in patients who:
- In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure [see Warnings and Precautions (5.2)].
- Have the presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker [see Warnings and Precautions (5.2)].
- Have severe untreated sleep apnea [see Warnings and Precautions (5.2)].
- Are taking a monoamine oxidase (MAO) Inhibitor [see Drug Interactions (7.7)].

5 WARNINGS AND PRECAUTIONS
5.1 Infections
Risk of Infections
ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of a reversible sequestration of lymphocytes in lymphoid tissues [see Clinical Pharmacology (12.2)]. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA.

Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. In Study 1 and Study 2, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA was similar to that in patients who received interferon (IFN) beta-1a (35% vs 34% and 1% vs 0.8%, respectively). ZEPOSIA increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes zoster [see Adverse Reactions (6.1)].

The proportion of patients who experienced lymphocyte counts less than 0.2 x 10^9/L was 3.3%. These values generally returned to greater than 0.2 x 10^9/L while patients remained on treatment with ZEPOSIA. After discontinuing ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)].

Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Because the elimination of ZEPOSIA after discontinuation may take up to 3 months, continue monitoring for infections throughout this period.

Herpes Viral Infection
In Study 1 and Study 2, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients who received IFN beta-1a. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (SIP) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA (see Vaccinations below).

Cryptococcal Infection
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with SIP receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. ZEPOSIA treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progressing over days to weeks, and include progressive weakness on one side of the body, clumsy gait, loss of visual acuity, ataxia, and personality changes.

PML has been reported in patients treated with SIP receptor modulators and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

If PML is confirmed, treatment with ZEPOSIA should be discontinued.

Prior and Concomitant Treatment with Anti-neoplastic, Immunosuppressive, or Immune-modulating Therapies
In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for the treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Vaccinations
Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA, following which initiation of treatment with ZEPOSIA should be postponed for 4 weeks to allow the full effect of vaccination to occur.

No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Vaccinations may be less effective if administered during ZEPOSIA treatment.

If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA.

5.2 Bradycardia and Atrioventricular Conduction Delays
Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA [see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)].

ZEPOSIA was not studied in patients who had:
- A myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months
- New York Heart Association Class III / IV heart failure
- Cardiac conduction or rhythm disorders, including sick sinus syndrome, significant QT prolongation (QTc > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that in the opinion of the treating investigator could jeopardize the patient's health
- Other pre-existing stable cardiac conditions without clearance from a cardiologist
- Severe untreated sleep apnea
- A resting heart rate less than 55 beats per minute (bpm) at baseline

Reduction in Heart Rate
Initiation of ZEPOSIA may result in a transient decrease in heart rate. In Study 1 and Study 2, after the initial dose of ZEPOSIA 0.23 mg, the greatest mean decrease from baseline in heart rate of 1.2 bpm occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. With continued up-titration, the maximal heart rate effect of ozanimod occurred on Day 8. The utility of performing first-dose cardiac monitoring when initiating ZEPOSIA in patients with characteristics similar to those studied in clinical trials of ZEPOSIA is unclear. Heart rates below 40 bpm were not observed. Initiation of ZEPOSIA without titration may result in greater decreases in heart rate [see Dosage and Administration (2.2)].
In Study 1 and Study 2, bradycardia was reported on the day of treatment initiation in 0.6% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.8% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

5.3 Liver Injury
Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain transaminase and bilirubin levels, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. In Study 1 and Study 2, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients who received IFN beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ZEPOSIA and 3.1% of patients who received IFN beta-1a. The median time to an elevation of 3-fold the ULN was 6 months. The majority (79%) of patients continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2 to 4 weeks. In clinical trials, ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked, and ZEPOSIA should be discontinued if significant liver injury is confirmed. Individuals with an AST or ALT greater than 1.5 times ULN were excluded from Study 1 and Study 2. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA, caution should be exercised when using ZEPOSIA in patients with a history of significant liver disease.

5.4 Fetal Risk
There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm (see Use in Specific Populations (8.1)). Because it takes approximately 3 months to eliminate ZEPOSIA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA (see Use in Specific Populations (8.1)).

5.5 Increased Blood Pressure
In Study 1 and Study 2, patients treated with ZEPOSIA had an average increase of approximately 1 to 2 mm Hg in systolic pressure over patients who received IFN beta-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment and persisted throughout treatment. Hypertension was reported as an adverse reaction in 3.9% of patients treated with ZEPOSIA 0.92 mg and in 2.1% of patients who received IFN beta-1a. Two patients treated with ZEPOSIA in Study 1 and one patient treated with interferon (IFN) beta-1a in Study 2 experienced a hypertensive crisis that was not clearly influenced by a concomitant medication. Blood pressure should be monitored during treatment with ZEPOSIA and managed appropriately.

Certain foods that may contain very high amounts (i.e., more than 150 mg) of tyramine could cause severe hypertension because of potential tyramine interaction in patients taking ZEPOSIA, even at the recommended doses. Because of an increased sensitivity to tyramine, patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

5.6 Respiratory Effects
Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV₁) were observed in patients treated with ZEPOSIA as early as 3 months after treatment initiation. In pooled analyses of Study 1 and Study 2, the decline in absolute FEV₁, from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV₁, at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and % predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a (60 mL, 95% CI (-110, -10); 1.4%, 95% CI: (-2.6, -0.2)), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV₁ or FVC after drug discontinuation. One patient discontinued ZEPOSIA because of dyspnea. Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

5.7 Macular Edema
S1P modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a.

An ophthalmologic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA. Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus
Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.8 Posterior Reversible Encephalopathy Syndrome
Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In controlled clinical trials with ZEPOSIA, one case of PRES was reported. Should a ZEPOSIA-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Drugs
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 while at the same time minimizing risk of disease reactivation, when initiating ZEPOSIA. Initiating treatment with ZEPOSIA after treatment with alentuzumab is not recommended (see [Drug Interactions (7.1)]).

5.10 Severe Increase in Disability After Stopping ZEPOSIA
Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment. Patients should be observed for a severe increase in disability upon ZEPOSIA discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping ZEPOSIA
After discontinuing ZEPOSIA, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months (see Clinical Pharmacology (12.2)). Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA (see Drug Interactions (7.1)).

6. ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Infections [see Warnings and Precautions (5.1)]
- Bradycardia and Atrioventricular Conduction Delays [see Warnings and Precautions (5.2)]
- Liver Injury [see Warnings and Precautions (5.3)]
- Fetal Risk [see Warnings and Precautions (5.4)]
- Increased Blood Pressure [see Warnings and Precautions (5.5)]
- Respiratory Effects [see Warnings and Precautions (5.6)]
- Macular Edema [see Warnings and Precautions (5.7)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.8)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Drugs [see Warnings and Precautions (5.9)]
- Severe Increase in Disability After Stopping ZEPOSIA [see Warnings and Precautions (5.10)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The safety of ZEPOSIA was evaluated in two randomized, double-blind, active comparator-controlled clinical studies in which 882 patients received ZEPOSIA 0.92 mg [see Clinical Studies (14)]. Table 2 lists adverse reactions that occurred in at least 2% of ZEPOSIA-treated patients and greater than comparator. The most common adverse reactions that occurred in at least 4% of ZEPOSIA-treated patients and greater than in patients who received IFN beta-1a were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.
Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a* (Pooled Study 1 and Study 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ZEPOSIA 0.92 mg (n=882) %</th>
<th>IFN beta-1a 30 mcg Intramuscularly Once Weekly (n=885) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infection*</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Hepatic transaminase elevation*</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.

# 7. Drug Interactions

## 7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

ZEPOSIA has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration [see Warnings and Precautions (5.1)].

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects [see Warnings and Precautions (5.9)].

Because of the characteristics and duration of alentuzumab immune suppressive effects, initiating treatment with ZEPOSIA after alentuzumab is not recommended.

## 7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That may Decrease Heart Rate

### 7.2.1 ZEPOSIA

ZEPOSIA has not been studied in patients taking QT prolonging drugs.

Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with ZEPOSIA should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties [see Warnings and Precautions (5.2)]. If treatment initiation with ZEPOSIA is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought.

### 7.2.2 Vaccination

During, and for up to 3 months after, discontinuation of treatment with ZEPOSIA, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ZEPOSIA treatment and for up to 3 months after discontinuation of treatment with ZEPOSIA [see Warnings and Precautions (5.2)].

### 7.4 Strong CYP2C8 Inhibitors

Co-administration of ZEPOSIA with strong CYP2C8 inhibitors increases the exposure of the active metabolites of ozanimod [see Clinical Pharmacology (12.3)], which may increase the risk of ZEPOSIA adverse reactions. Therefore, co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.

### 7.5 Breast Cancer Resistance Protein (BCRP) Inhibitors

Co-administration of ZEPOSIA with BCRP inhibitors increases the exposure of the active metabolite of ozanimod [see Clinical Pharmacology (12.3)], which may increase the risk of ZEPOSIA adverse reactions. Therefore, co-administration of ZEPOSIA with inhibitors of BCRP (e.g., cyclosporine, eltrombopag) is not recommended.

### 7.6 Strong CYP2C8 Inducers

Co-administration of ZEPOSIA with strong CYP2C8 inducers (e.g., rifampin) reduces the exposure of the major active metabolites of ozanimod [see Clinical Pharmacology (12.3)], which may decrease the efficacy of ZEPOSIA. Therefore, co-administration of ZEPOSIA with strong CYP2C8 inducers should be avoided.

### 7.7 Monoamine Oxidase (MAO) Inhibitors

Co-administration of ZEPOSIA with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, metabolites of ozanimod may inhibit MAO [see Clinical Pharmacology (12.3)]. The potential for a clinical interaction with MAO inhibitors has not been studied; however, the increased risk of nonselective MAO inhibition may lead to a hypertensive crisis. Therefore, co-administration of ZEPOSIA with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors.

## 7.8 Adrenergic and Serotonergic Drugs

Because an active metabolite of ozanimod inhibits MAO-B in vitro, there is a potential for serious adverse reactions, including hypertensive crisis. Therefore, co-administration of ZEPOSIA with MAO inhibitors or over-the-counter medications that can increase norepinephrine or serotonin (e.g., opioid drugs, selective serotonin reuptake inhibitors [SSRIs], selective norepinephrine reuptake inhibitors [SNRIs], tricyclics, tyramine) is not recommended. Monitor patients for hypertension with concomitant use. Opioid Drugs

Serious, sometimes fatal reactions have been precipitated with concomitant use of opioid drugs (e.g., meperidine and its derivatives, methadone, or tramadol) and MAOIs, including selective MAO-B inhibitors. Although a small number of patients treated with ZEPOSIA were concomitantly exposed to opioids, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration.

## 8. Use in Specific Populations

### 8.1 Pregnancy

#### Risk Summary

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women. In animal studies, administration of ozanimod during pregnancy produced adverse effects on development, including embryolethality, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity. In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures [see Data]. The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

#### Data

**Animal Data**

Oral administration of ozanimod (0.2, 1, 5 or 5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/delayed ossification), and reduced fetal body weight at the highest dose tested. Maternal toxicity was not observed. At the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Oral administration of ozanimod (0.2, 0.6, or 2.0 mg/kg/day) to female rabbits during organogenesis resulted in a marked increase in embryofetal mortality at the highest dose tested and increased fetal malformations (mailed blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, plasma ozanimod exposure (AUC) was approximately 2 times that in humans at the MRHD, plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0.2, 0.7, or 2 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycle) and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day), adverse effects on postnatal development, plasma ozanimod exposure (AUC) was 30 times that in humans at the MRHD, plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

#### 8.2 Lactation

**Risk Summary**

There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

Following oral administration of ozanimod, ozanimod and/or metabolites were detected in the milk of lactating rat at levels higher than those in maternal plasma.
ZEPOSIA® (ozanimod) capsules, for oral use

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZEPOSIA and any potential adverse effects on the breastfed infant from ZEPOSIA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Before initiation of ZEPOSIA treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for contraception during treatment with ZEPOSIA [see Use in Specific Populations (8.1)]. Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing age should also use effective contraception for 3 months after stopping ZEPOSIA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ZEPOSIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of the ozanimod major active metabolites is unknown [see Clinical Pharmacology (12.3)]. Use of ZEPOSIA in patients with hepatic impairment is not recommended.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of ozanimod (0, 8, 25, or 80 mg/kg/day) to Tg.rastH2 mice for 26-weeks resulted in an increase in hemangioma and hemangiosarcoma (combined) in males and females at the mid and high doses tested.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to rats for 2 years resulted in no increase in tumors. At the highest dose tested (2 mg/kg/day), plasma exposure (AUC) for ozanimod was approximately 100 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Mutagenesis

Ozanimod was negative in a battery of in vitro (Ames, mouse lymphoma tk) and in vivo (rat micronucleus) assays. Metabolite CC112273 was negative in vitro (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an Ames assay, and positive in an in vitro chromosomal aberration assay in human (TK6) cells but negative in an in vivo rat micronucleus/comet assay.

Impairment of Fertility

Oral administration of ozanimod (0, 0.2, 2, or 30 mg/kg/day) to male and female rats prior to and during mating and continuing through gestation day 7 resulted in no adverse effects on fertility. At the highest dose tested (30 mg/kg/day), plasma ozanimod exposure (AUC) was approximately 1600 times that in humans at the maximum recommended human dose (MRHD) (0.92 mg/day); plasma AUCs for metabolites, CC112273 and CC1084037, at 30 mg/kg/day were 13 and 3 times, respectively, those in humans at the MRHD.

17 PATIENT COUNSELING INFORMATION

Advisers the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Infections

Inform patients that they may be more likely to get infections, some of which could be life-threatening, when taking ZEPOSIA and for 3 months after stopping it, and that they should contact their healthcare provider if they develop symptoms of infection [see Warnings and Precautions (5.1)]. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection. Advise patients that some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with ZEPOSIA. If immunizations are planned, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA. Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ZEPOSIA.

Cardiac Effects

Advise patients that initiation of ZEPOSIA treatment may result in a transient decrease in heart rate. Inform patients that to reduce this effect, dose titration is required. Advise patients that the dose titration is also required if a dose is missed for 1 day or more during the first 14 days of treatment [see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)].

Liver Injury

Inform patients that ZEPOSIA may increase liver enzymes. Advise patients that they should contact their healthcare provider if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine [see Warnings and Precautions (5.3)].

Pregnancy and Fetal Risk

Inform patients that, based on animal studies, ZEPOSIA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with ZEPOSIA and for 3 months after stopping ZEPOSIA. Advise a female patient to immediately inform her healthcare provider if she is pregnant or planning to become pregnant [see Warnings and Precautions (5.4)].

Respiratory Effects

Advise patients that they should contact their healthcare provider if they experience new onset or worsening dyspnea [see Warnings and Precautions (5.6)].

Macular Edema

Advise patients that ZEPOSIA may cause macular edema, and that they should contact their healthcare provider if they experience any changes in their vision. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema may be increased [see Warnings and Precautions (5.7)].

Posterior Reversible Encephalopathy Syndrome

Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological consequences [see Warnings and Precautions (5.8)].

Severe Increase in Disability After Stopping ZEPOSIA

Inform patients that severe increase in disability has been reported after discontinuation of a S1P receptor modulator like ZEPOSIA. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of ZEPOSIA [see Warnings and Precautions (5.10)].

Immune System Effects After Stopping ZEPOSIA

Inform patients that ZEPOSIA continues to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3 months after the last dose [see Warnings and Precautions (5.11)].

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Summit, NJ 07901

Patent: www.celgene.com/therapies

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Managing MS in Millennials

Effectively navigating the nuances of this unique patient population will ultimately help drive innovative solutions for this generation and those to come.

By Madison Hansen

THE ONSET OF MULTIPLE SCLEROSIS (MS) is commonly seen between age 20 and 40 years, making the millennial generation (aged 24-39 years in 2020) the most likely generation to develop MS in the coming years. As a cohort, millennials manage their health differently from the generations before them and thus will value and expect different things when it comes to their MS care. Furthermore, these differences may create new challenges for the health care team. Current MS practice must adapt to engage this unique generation and create innovative solutions tailored to their specific needs and desires. Doing so could afford this generation better prognostic outcomes as a result of increased engagement and disease management.

Shared Decision-Making

The defining quality of the millennial generation is their use of technology, although some may describe it as a dependence. Millennials are digital natives, meaning they are the first generation to grow up with the internet, and they integrate technology throughout multiple aspects of their everyday lives. Ninety-three percent of millennials own a smartphone, and nearly 100% use the internet. Furthermore, the millennial generation is the most educated generation yet, with 36% of millennial women and 29% of millennial men holding at least a bachelor’s degree as of 2017.

MADISON HANSEN

After graduating from Harvard with a degree in neurobiology, Hansen joined the research team at the Clinical Center for Multiple Sclerosis at UT Southwestern Medical Center. There, she led the Digital Healthcare Program and has created mobile applications that enhance patient education, augment disease surveillance, and improve patient diagnostic tools. Hansen also led the investigation of a novel imaging study that examined MS lesions in 3D to enhance their classification and our current understanding of disease progression. Her most recent research focuses on the millennial MS patient and how to best deliver MS care to this unique generation. Hansen is currently pursuing a joint MD/MPH degree at Dell Medical School in Austin, Texas.

Their education and tech savviness enable millennials to leverage technology to better manage their health. In fact, 55% of millennials said they believed health-related information on the internet is as reliable as information from medical professionals, more than any
other generation. Providers should value this personal motivation to seek out health information and continue to encourage patients’ self-learning. The advantages of easily accessing a multitude of information from a wide variety of sources on the internet, however, must be balanced with an understanding of the differing degrees of validity between sources. Less than half of millennials were concerned with finding false or misleading health data on the internet, the lowest percentage among all generations. Pointing patients toward trusted sources of information is an important first step to help encourage a credible knowledge source for these patients and to create a shared knowledge base between patient and provider. Equipping millennial patients in this way will emphasize their autonomy and facilitate shared decision-making between the patient and provider.

Building Trust to Enhance Patient Counseling

Current trends demonstrate an overall lack of trust in medical doctors by millennials; less than half of millennials were very satisfied with information from their doctor. Additionally, millennials were the least likely generation to respond, “I always listen to my doctor(s)” compared with other generations. Medical providers can build trust by understanding the communication strategies that millennials prefer.

As digital natives, millennials expect easy accessibility, rapid turnaround, and direct communication. Easy online appointment scheduling, short wait times, and online patient portals where patients can access their results and communicate directly with providers are examples of baseline logistics that health care providers can implement to start off on the right foot with their millennial patients. Millennials also value medical information directly from their peers: 4 out of 10 millennials trust their peers more than they trust medical professionals when it comes to their health. Providers can build off this heightened trust in social circles by utilizing young adult patient support groups to allow millennial patients with MS to share their experiences and learn from their peers. Highly vested in social media platforms, this generation could transform patient advocacy both locally and globally.

Using social media as a way to engage millennial patients with MS can be effective if done correctly. Millennials do, however, have a healthy dose of skepticism when it comes to health information on social media specifically. While 67% of Americans reported seeing health information on social media, only 35% said the information was even “mostly accurate.” Curated social media content from providers and clinics should emphasize the validity of the content by referencing studies, citing a trusted school or research organization, or including explanations directly from a medical professional. Consistency in communication style and content is key to bridging the gap between millennial patients and health care providers.

It would be a disservice to all patients not to note the complex impact of race on mistrust in the medical profession specifically. Ramifications from historic unjust medical practices continue to influence current medical practice, exemplified by the decreased participation in clinical trials by minorities due to the influence of the US Public Health Service Syphilis Study at Tuskegee (commonly known as the Tuskegee Syphilis Study). Because the millennial generation is the most diverse population in America, with minorities making up almost half of the population, mistrust in medical providers and medical institutions may be heightened within the millennial cohort. It is imperative for providers to understand the history of racism in American medicine and the complex ways in which it influences patients today. Establishing a shared understanding of these health injustices with millennial patients can help rebuild trust one patient at a time.

Cost Considerations

Millennials are the most cost-conscious generation yet, and understandably so; millennials have higher levels of student loan debt, poverty, and unemployment rates than the 2 previous generations—Generation X and baby boomers—had at the same stage of their life cycles. This economic strain leads millennials to often cut corners when it comes to their health care, a dangerous trend when diagnosed with a chronic, progressive disease like MS. More than half of millennials admit to delaying or avoiding medical treatment due to cost. It is well known that the cost of MS care is substantial, and MS-specific health care costs have been shown to increase with disease severity. Those with mild to moderate disease severity spent an average of $30,000 on health care costs per year compared with $100,000 per year for those with severe disability. Therefore, a key strategy to decreasing overall costs for millennial patients is emphasizing disease prevention. For example, although disease-modifying therapies (DMTs) often account for the majority of MS-related health care costs due to their high price tags, an effective DMT is a patient’s best resource for preventing the frequency and severity of relapses and for slowing disease progression. Emphasizing the cost-saving strategy of disease prevention from the day of diagnosis is important to encourage millennials with MS to invest in their health care. As new DMTs continue to be developed, often with greater efficacy at the expense of higher costs, it is imperative for providers to navigate costs with millennial patients when making treatment decisions. Treatment plans need to be individualized and align with each patient’s unique values and goals, as well as financial feasibility. These cost conversations should be initiated by providers to demonstrate a common understanding of the immense financial burden that an MS diagnosis entails. There is also a clear, increased need for financial advisers within MS practices to help millennial patients financially plan for lifelong MS health care costs.

Focus on Mental and Behavioral Health

Millennials report the worst mental and behavioral health outcomes compared to any prior generation. Compounding these trends is the increased prevalence of mental health disorders among the MS population in general. Patients with MS are 3 times more likely to experience anxiety or depression compared with the general population. Furthermore, inequity in mental and behavioral health prevalence has been seen among different demographics. In a survey of 1500 individuals, people who identify as LGBTQ+ were 3 times more likely to experience a mental health condition. Black and Hispanic respondents were more likely to experience every mental and behavior symptom assessed in the study compared with the study population as a whole.
Because millennials are the most diverse generation to date, MS providers should understand the increased burden of mental health on this generation as well as the unique experience of specific millennial demographics. Increased collaboration with mental health providers is imperative to providing quality MS care to millennial patients. Incorporating standardized depression and anxiety assessments into clinic workflow can equip providers to track mental health outcomes in their patient populations over time and serve as a launching point for provider-initiated conversations about mental health. Quality MS care must not only treat this unpredictable disease, but also adequately address the multiple disease sequelae experienced by patients, including mental and behavioral health.

Conclusions
Millennials are a technologically savvy, cost-conscious, diverse, and educated population who experience unique financial and mental health burdens compared with previous generations. Their distinctive characteristics drive change across multiple different sectors, including health care, and these changes create ripple effects across all generations. For example, millennials’ demand for technology has led Generation X and baby boomers to increasingly adopt technological platforms in their own lives. Early analysis of the youngest generation, Generation Z (those born after 1996), signal similar preferences to millennials, only heightened. MS care not only needs to adapt to better serve millennial patients with MS, but to adequately serve all generations past, present, and future. Innovative solutions geared specifically toward millennials will allow for increased patient engagement now and in the years to come.

For a full list of references, see the article on NeurologyLive.com

More on NeurologyLive.com

Fenebrutinib and BTK Inhibition in Progressive MS
Stephen L. Hauser, MD, spoke to the advantages of having agents that can be used across the spectrum of multiple sclerosis and the role disease progression plays early on.

View video: neurologylive.com/fenebrutinib-ms
Navigating an Expanding Treatment Toolbox for MS

“Is more always better?”: The age-old question is more relevant than ever as clinicians and patients alike navigate an increasingly crowded MS treatment landscape.

By Bhupendra O. Khatri, MD, FAAN

Ever since the approval of interferon beta-1b (Betaseron; Bayer) in 1993, there has been unprecedented growth in the number of disease-modifying therapies (DMTs) for multiple sclerosis (MS). We currently have 22 FDA-approved therapies with several more in the pipeline waiting to enter the market in the next few years. For a disease that has no known cause, no reliable biomarker to measure its activity, and no way of predicting which drug will work the best for a given patient, managing so many drugs for a single disease becomes a daunting task for both general neurologists and MS specialists.

The words of William Osler (1849-1919), the father of modern medicine and one of its greatest icons, have much wisdom: “A young physician starts life with 20 treatments for each disease, while the old physician ends life with 1 treatment for 20 diseases.” This is more relevant now than ever as we try to identify the most appropriate drug for each of our patients with MS, what and when to start, and when to switch. Our challenge is to balance the benefits against the potential adverse effects of high-efficacy drugs vs low- or moderate-efficacy drugs. Understanding the mechanism of action(s) of these drugs with their variable effects on the immune cells is crucial not only when initiating the drug therapy but also when switching the drug. The threshold for each has become quite low as we keep expanding the list of drugs from which to choose.

I cannot overstate the impact of these therapies on functional outcomes in patients with MS. I have been caring for patients with MS since before the first DMT was approved, and I can say with certainty that these drugs have made a huge difference in the way patients now lead their lives. I often tell my patients that MS is not what it used to be. They can now lead productive, healthy lives and achieve their goals. While it was not uncommon to see patients with MS in wheelchairs or using walkers before the first DMT was approved, now, I rarely see such patients. While there has not been a scientific study to prove this point, many senior MS experts I have spoken to agree that all the MS DMTs have improved patients’ quality of life.

For this to quality-of-life improvement to occur, however, physicians need to be proactive. We need to be guided by the patient’s prognostic criteria and then prescribe the most effective therapy as early as possible. Waiting until patients are clinically worse or their MRIs show increased disease burden may be too late. As such, physicians have an increased impetus to act swiftly in initiating a therapy as soon as the diagnosis is made to “save the brain.” Just as in stroke, time is of the essence in the management of MS. Inappropriate or delayed treatment can lead to irreparable harm. Some experts have posited, and I believe with some truth, that “in this day and age, if MS patients do not do well, it is more likely the fault of the treating physicians rather than of the disease’s progression.”

All of this places added stress on an already overworked physician. Physician burnout due to administrative overload is at record high. A recent study published in the Annals of Family Medicine showed that, for every hour physicians spend with a patient, they spend 2 hours doing administrative work, leaving little time for them to study the latest research updates. It is not unusual for physicians to return home from work late in the evening and spend the little time left in the day logging into the electronic health...
Higher prices translate to higher out-of-pocket costs for some patients, especially those with high-deductible health plans, resulting in high-priced therapies becoming inaccessible to some. Results of a recent National Multiple Sclerosis Society survey showed that 40% of respondents had “altered or stopped” DMTs for their MS due to high cost, and more than half were concerned about being able to continue to afford their medication in the coming years.4

Generic medicines tend to cost less than their brand-name counterparts because they do not have to repeat animal and clinical studies that were required of the brand-name medicines to demonstrate safety and effectiveness. However, does it always make sense to choose a generic over the brand-name drug? For biological and complex nonbiological medications, this would be difficult to prove without a controlled study. Success in the development of a generic drug depends on the maker’s ability to offer a similar, safe, and effective product at a cost saving. Introduction of a generic version of Copaxone, which is among the most frequently prescribed MS drugs, did very little to lower the cost of that medicine.2

An increase in the effective treatment armamentarium for MS is now capable of shutting down disease activity, but it has also propelled us to a threshold of a new frontier to conquer. For a disease that is highly heterogeneous and unpredictable, a personalized treatment is highly desirable. To provide better indicators for prognosis and treatment response, we need biomarkers that are readily available, reliable, and economical, and we need pharmacogenomics to help us navigate to the most appropriate therapy for a given patient. While the current DMTs prevent new lesion formation on MRI, they do not prevent delayed chronic neurodegeneration or bring about regeneration. Indeed, we may have reached a ceiling effect in our current class of drugs and will need to divert our efforts to repair and regeneration, which are the greatest unmet needs in MS therapy.

This is what I foresee as the next frontier to conquer in our fight against MS. ■

For a full list of references, see the article on NeurologyLive.com

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RECOMMENDATIONS PUBLISHED FOR STEM CELL TRANSPLANT IN MULTIPLE SCLEROSIS

The National Medical Advisory Committee of the National MS Society published recommendations on the use of autologous hematopoietic stem cell transplant for multiple sclerosis, pointing out areas of continued controversy and issues requiring further exploration.

View article: neurologylive.com/MS-stem-cells
Even patients taking a DMT can experience MS fatigue\(^1,2\)

This symptom is highly prevalent, can occur early in the disease course, and may worsen over time\(^1,2\).

The American Academy of Neurology (AAN) recommends using a validated fatigue rating instrument when identifying and managing fatigue.

The measurement of both maintenance and improvement of fatigue over a 12-month period may be useful when evaluating fatigue in patients with MS\(^3\).

Discover potential mechanisms of MS fatigue, how to recognize it, and the effect it can have on your patients.

Visit MoreToMS.com/more to learn more.

MS = multiple sclerosis; DMT = disease-modifying therapy.

References:

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