Disproportionate Neurodegeneration in Black Patients With MS: The Need for Stratified Treatments

BY DARIN T. OKUDA, MD, FAAN, FANA
MAVENCLAD is administered in 2 treatment courses approximately 1 year apart. 1

RMS: relapsing multiple sclerosis.


- At-home oral administration 1
- A well-characterized safety and tolerability profile 2
- Lymphocyte depletion followed by repopulation, without continuous immunosuppression 1,3,4

MAVENCLAD® (cladribine) tablets is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

- MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant.

Only MAVENCLAD can deliver proven efficacy over 96 weeks with a maximum of 20 days of oral treatment.1,2

*Screening and monitoring should be performed before, during, and after treatment. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD demonstrated efficacy across endpoints

**ARR (primary endpoint)**1,2

![Relative Reduction in ARR at 96 weeks](image)

**EDSS progression**2

![Reduction in Risk of 3-Month Confirmed EDSS Progression](image)

**T1-Gd+ lesions**2

![Reduction in Median Number of T1-Gd+ Lesions](image)

**Active T2 lesions**2

![Reduction in Mean Number of T1-Gd+ Lesions](image)

ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; HR: hazard ratio; T1-Gd+: T1 gadolinium-enhanced.

*Includes data from studies of oral and parenteral forms of MAVENCLAD.

Significantly more patients taking MAVENCLAD achieved NEDA compared to placebo in a post hoc analysis of the high disease activity subgroup of CLARITY.5,6

A PATIENT WITH HIGH-DISEASE-ACTIVITY RMS MEETS THESE CRITERIA:6

- 2 relapses in the year before study entry, regardless of treatment status, OR
- 1 relapse in the year before study entry while on another DMT AND ≥1 T1-Gd+ or ≥9 T2 lesions

NEDA WAS DEFINED AS CLARITY PATIENTS WHO:5,6

- were relapse free
- had no 3-month sustained change in EDSS score
- had no new T1-Gd+ lesions
- had no active T2 lesions

NEDA: In the subgroup of patients with high disease activity:5,6

- MAVENCLAD: 44% of patients (n=59/135)
- PLACEBO: 9% of patients (n=13/144)

OR: 7.82 (4.03-15.19), P=0.04.

DMT: disease-modifying therapy; NEDA: no evidence of disease activity; OR: odds ratio.

PATIENTS HAD A MEAN DISEASE DURATION OF:5,6

- 4.75 years for placebo (standard deviation: 5.43)
- 3.94 years for MAVENCLAD (standard deviation: 4.92)

- Patients with high disease activity compared to the overall study population had a higher number of relapses during the 12 months prior to baseline

Learn more about MAVENCLAD, prescribed to 36,000+ patients globally in real-world settings, at MAVENCLAD.com/hcp

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed WARNING on the following pages.
IMPORTANT SAFETY INFORMATION (CONTINUED)

CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- Malignancies: Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reintroducing MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.
- Risk of Teratogenicity: MAVENCLAD may cause fetal harm when administered to pregnant women. Malformations and embryolethality may occur rarely after transfusion of nonirradiated blood.
- Hematologic Toxicity: In addition to lymphopenia, decreases in neutrophil counts and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hematoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- Risk of Graft-versus-Host Disease With Blood Transfusions: Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.
- Liver Injury: In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0.1% of placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.
- Hypersensitivity: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.
- Cardiac Failure: In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parental cladribine used for treatment indications other than multiple sclerosis.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed WARNING on the following pages.

Visit MAVENCLAD.com/hcp to learn more about the first and only short-course oral treatment.

Screening and monitoring should be performed before, during, and after treatment.
MAVENCLAD® (cladribine) tablets, for oral use

WARNING: MALIGNANCIES AND RISK OF TERATOGENICITY

Malignancies
Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD [see Contraindications (4) and Warnings and Precautions (5.2)].

Risk of Teratogenicity
MAVENCLAD is contraindicated for use in pregnant women and in women of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Maternal use of MAVENCLAD is not recommended in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Additional mechanisms of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant [see Contraindications (4), Warnings and Precautions (5.2), and Use in Specific Populations (8.1, 8.3)].

1 INDICATIONS AND USAGE
MAVENCLAD is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS. MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

4 CONTRAINDICATIONS
MAVENCLAD is contraindicated:

• in patients with current malignancy [see Warnings and Precautions (5.1)].
• in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. May cause fetal harm [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)].
• in patients infected with the human immunodeficiency virus (HIV) [see Warnings and Precautions (5.4)].
• in patients with active chronic infections (e.g., hepatitis or tuberculosis) [see Warnings and Precautions (5.4)].
• in patients with a history of hypersensitivity to cladribine [see Warnings and Precautions (5.8)].

5 WARNINGS AND PRECAUTIONS
5.1 Malignancies
Treatment with MAVENCLAD may increase the risk of malignancy. In controlled and extension clinical studies worldwide, malignancies occurred more frequently in MAVENCLAD-treated patients (10 events in 3,754 patient-years [0.27 events per 100 patient-years]), compared to placebo patients (3 events in 2,275 patient-years [0.13 events per 100 patient-years]). Malignancy cases in MAVENCLAD patients included metastatic pancreatic carcinoma, malignant melanoma (2 cases), ovarian cancer, compared to malignancy cases in placebo patients, all of which were curable by surgical resection (basal cell carcinoma, carcinoid tumor in situ [2 cases]). The incidence of malignancies in United States MAVENCLAD clinical study patients was higher than the rest of the world (4 events in 189 patient-years [2.2 events per 100 patient-years] compared to 0 events in United States placebo patients; however, the United States results were based on a limited amount of patient data. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years [see Dosage and Administration (2.2)]. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy (7 events in 790 patient-years [0.91 events per 100 patient-years]) calculated from the start of cladribine treatment in Year 3. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

5.2 Risk of Teratogenicity
MAVENCLAD may cause fetal harm when administered to pregnant women. Malformations and embryolethality occurred in animals [see Use in Specific Populations (8.1)]. Advise women of reproductive potential a minimal risk to a fetus during MAVENCLAD dosing and for 6 months after the last dose in each treatment course.

In females of reproductive potential, pregnancy should be excluded before initiation of each treatment course of MAVENCLAD and prevented by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment [see Use in Specific Populations (8.1, 8.3)]. MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception.

5.3 Lymphopenia
MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course, and were lower with each additional treatment course. In patients treated with a cumulative dose of MAVENCLAD 3.5 mg per kg over 2 courses as monotherapy, 26% and 1% had nadir absolute lymphocyte counts less than 500 and less than 200 cells per microliter, respectively. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells per microliter; median time to recovery to at least 800 cells per microliter was approximately 28 weeks. Additive hematological adverse reactions may be expected if MAVENCLAD is administered prior to or concomitantly with other drugs that affect the hematological profile [see Drug Interactions (7.3)].

The incidence of lymphopenia less than 500 cells per microliter was higher in patients who had used drugs to treat relapsing forms of MS prior to study entry (32.1%), compared to those with no prior use of these drugs (23.8%).

Obtain complete blood count (CBC) with differential including lymphocyte count prior to, during, and after treatment with MAVENCLAD. [see Dosage and Administration (2.1, 2.3) and Warnings and Precautions (5.4) for timing of CBC measurements and additional instructions based on the patient’s lymphocyte counts and clinical status (e.g., infections)].

5.4 Infections
MAVENCLAD can reduce the body’s immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of placebo patients in clinical studies. The most frequent serious infections in MAVENCLAD-treated patients included herpes zoster and pyelonephritis [see Herpes Virus Infections]. Fungal infections were observed, including cases of coccidioidomycosis. HIV infection, active tuberculosis, and active hepatitis must be excluded before initiation of each treatment course of MAVENCLAD [see Contraindications (4)].

Consider a delay in initiation of MAVENCLAD in patients with an acute infection until the infection is fully controlled.

Initiation of MAVENCLAD in patients currently receiving immunosuppressive or myelosuppressive therapy is not recommended [see Drug Interactions (7.1)]. Concomitant use of MAVENCLAD with these therapies could increase the risk of immunosuppression.

Tuberculosis
Three of 1,478 (0.2%) cladribine-treated patients in the clinical program developed tuberculosis. All 3 cases occurred in regions where tuberculosis is endemic. One case of tuberculosis was fatal, and 2 cases resolved with treatment.

Perform tuberculosis screening prior to initiation of the first and second treatment course of MAVENCLAD. Latent tuberculosis infections may be activated with use of MAVENCLAD. In patients with tuberculosis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Hepatitis
One clinical study patient died from fulminant hepatitis B infection. Perform screening for hepatitis B and C prior to initiation of the first and second treatment course of MAVENCLAD. Latent hepatitis infections may be activated with use of MAVENCLAD. Patients who are carriers of hepatitis B or C virus may be at risk of irreversible liver damage caused by virus reactivation. In patients with hepatitis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Hepatitis B Virus Infections
In controlled clinical studies, 6% of MAVENCLAD-treated patients developed a herpes viral infection compared to 2% of placebo patients. The most frequent types of herpes viral infections were herpes zoster infections (2.0% vs. 0.2%) and oral herpes (2.5% vs. 1.2%). Serious herpes zoster infections occurred in 0.2% of MAVENCLAD-treated patients.

Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.

The incidence of herpes zoster was higher during the period of absolute lymphocyte count less than 500 cells per microliter, compared to the period when the patients were not experiencing this degree of lymphopenia. Administer anti-herpes prophylaxis to patients with lymphocyte counts less than 200 cells per microliter.

Patients with lymphocyte counts below 500 cells per microliter should be monitored for signs and symptoms suggestive of infections, including herpes infections. If such signs and symptoms occur, initiate treatment as clinically indicated.中断 interruptions or delay of MAVENCLAD until resolution of the infection.

Progressive Multifocal Leuкоencephalopathy
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No case of PML has been reported in clinical studies of cladribine in patients with multiple sclerosis. In patients treated with oral cladribine, no fatal cases of PML were reported. In addition, based on preclinical indications, cases of PML have been reported in the postmarketing setting.

Obtain a baseline (within 3 months) magnetic resonance imaging (MRI) prior to initiating the first treatment course of MAVENCLAD. At the first sign or symptom suggestive of PML, withhold MAVENCLAD and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms.

Vaccinations
Administer all immunizations according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 8 weeks prior to starting MAVENCLAD, because of a risk of active vaccine infection [see Herpes Virus Infections]. Avoid vaccination with live-attenuated or live vaccines during and after MAVENCLAD treatment while the patient’s white blood cell counts are not within normal limits.

5.5 Hematologic Toxicity
In addition to lymphopenia [see Warnings and Precautions (5.3)], decreases in other blood cells and hematological parameters have been reported in MAVENCLAD clinical studies. Mild to moderate decreases in neutrophil counts (cell count between 1,000 cells per microliter and ≤ lower limit of normal [LLN]) were observed in 27% of MAVENCLAD-treated patients, compared to 13% of placebo patients whereas severe decreases in neutrophil counts (cell count below 1,000 cells per microliter) were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Decreases in hemoglobin levels, in general mild to moderate (hemoglobin
8.0 g per dl to < LLN) were observed in 26% of MAVENCLAD-treated patients, compared to 19% of placebo patients. Decreases in platelet counts were generally mild (cell count < 75,000 cells per microliter to < LLN) and were observed in 11% of MAVENCLAD-treated patients, compared to 4% of placebo patients. In clinical studies, these decreases were similar to or higher than the approved MAVENCLAD dosage, serious cases of thrombocytopenia, neutropenia, and pancytopenia (some with documented bone marrow hypoplasia) requiring transfusion and granulocyte-colony stimulating factor treatment have been reported [see Warnings and Precautions (5.6) for information regarding graft-versus-host disease with blood transfusion]. Obtain complete blood count (CBC) with differential prior to, during, and after treatment with MAVENCLAD [see Dosage and Administration (2.1, 2.5)].

5.6 Graft-Versus-Host Disease With Blood Transfusion

Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications. In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to decrease the risk of transfusion-related graft-versus-host disease. Consultation with a hematologist is advised.

5.7 Liver Injury

In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) considered related to treatment, compared to 0 placebo patients. Onset has ranged from a few weeks to several months after initiation of treatment with MAVENCLAD. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 20-fold the upper limit of normal, have been observed. These abnormalities resolved upon treatment discontinuation.

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to the first and second treatment course [see Dosage and Administration (2.1, 2.5)]. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with MAVENCLAD, as appropriate.

5.8 Hypersensitivity

In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD (e.g., dermatitis, pruritus) occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. One patient had a serious hypersensitivity reaction with rash, mucous membrane ulceration, throat, swelling, vertigo, diplopia, and headache after the first dose of MAVENCLAD.

If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine [see Contraindications (4)].

5.9 Cardiac Failure

In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately 1 week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling).

6. Adverse Reactions

The following serious adverse reactions and potential risks are discussed, or discussed in greater detail, in other sections:

Malignancies [see Warnings and Precautions (5.1)], Risk of Teratogenicity [see Warnings and Precautions (5.2)], Lymphopenia [see Warnings and Precautions (5.2)], Infections [see Warnings and Precautions (5.4)], Hematologic Toxicity [see Warnings and Precautions (5.5), Graft-Versus-Host Disease With Blood Transfusion [see Warnings and Precautions (5.6)], Liver Injury [see Warnings and Precautions (5.7)], Hypersensitivity [see Warnings and Precautions (5.8)], Cardiac Failure [see Warnings and Precautions (5.9)].

6.1 Clinical Trials Experience

Adverse Reactions in Study 1 With an Incidence of at Least 5% for MAVENCLAD and Higher Than Placebo

<table>
<thead>
<tr>
<th>MAVENCLAD (N=466)</th>
<th>Placebo (N=453)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>38</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>24</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
</tr>
<tr>
<td>Arthritis and arthritis</td>
<td>7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
</tr>
</tbody>
</table>

6.2 Drug Interactions With MAVENCLAD

7. Drug Interactions With MAVENCLAD (continued)

7.2 Interferon Beta

Clinical Impact
Concomitant use of MAVENCLAD with interferon beta did not change the exposure of cladribine to a clinically significant extent; however, lymphopenia risk may be increased [see Warnings and Precautions (5.2)].

Prevention or Management
Concomitant use is not recommended.

7.3 Hematotoxic Drugs

Clinical Impact
Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects [see Warnings and Precautions (5.5)].

Prevention or Management
Monitor hematological parameters.

7.4 Antiviral and Antiretroviral Drugs

Clinical Impact
Compounds that require intracellular phosphorylation to become active (e.g., lamivudine, zidovudine, stavudine, and zidovudine) could interfere with the intracellular phosphorylation and activity of cladribine.

Prevention or Management
Avoid concomitant use.

7.5 Potent ENT, CNT, and BCRP Transporter Inhibitors

Clinical Impact
MAVENCLAD dosing and for at least 1 week. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD.

Prevention or Management
Avoid co-administration of potent ENT, CNT3, or BCRP transporter inhibitors (e.g., ritonavir, etravirine, cobicistat, and elvitegravir).

7.6 Potent BCRP and P-gp Transporter Inhibitors

Clinical Impact
Concomitant use of MAVENCLAD with immunomodulatory, immunosuppressive, or myelosuppressive drugs may increase the risk of adverse reactions because of the additive effects on the immune system [see Warnings and Precautions (5.6)].

Prevention or Management
Concomitant use of myelosuppressive or other immunosuppressive drugs is not recommended. Acute short-term therapy with corticosteroids can be administered.

In patients who have previously been treated with immunosuppressive or other immunosuppressive drugs, consider potential additive effect, the mode of action, and duration of effect of the other drugs prior to initiation of MAVENCLAD.

7.7 Hormonal Contraceptives

Clinical Impact
It is currently unknown whether MAVENCLAD may reduce the effectiveness of systemically acting hormonal contraceptives.

Prevention or Management
Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course.
8 Use in Specific Populations
8.1 Pregnancy
Risk Summary
MAVENCLAD is contraindicated in pregnant women and in females and males of reproductive potential who do not plan to use effective contraception. There are no adequate data on the developmental risk associated with use of MAVENCLAD in pregnant women. Cladribine was embryolethal when administered to pregnant mice and produced malformations in mice and rabbits [see Data]. The observed developmental effects are consistent with the effects of cladribine on DNA [see Contraindications (4) and Warnings and Precautions (5.2)].

Data
Animal Data
When cladribine was administered intravenously (0.05, 1.5, or 3 mg/kg/day) to pregnant rabbits during the period of organogenesis, fetal growth retardation and malformations (including exencephaly and cleft palate) and embryofetal death were observed at the highest dose tested. An increase in skeletal variations was observed at all but the lowest dose tested. There was no evidence of maternal toxicity.

When cladribine was administered intravenously (0.02, 0.3, 1, and 3 mg/kg/day) to pregnant rabbits during the period of organogenesis, fetal growth retardation and a high incidence of craniofacial and limb malformations were observed at the highest dose tested, in the absence of maternal toxicity.

When cladribine was administered intravenously (0.05, 1.5, or 3.0 mg/kg/day) to mice throughout pregnancy and lactation, skeletal anomalies and embryolethality were observed at all but the lowest dose tested.

8.2 Lactation
MAVENCLAD is contraindicated in breastfeeding women because of the potential for serious adverse reactions in breastfed infants [see Contraindications (4) and Warnings and Precautions (5)]. Advise women not to breastfeed during dosing with MAVENCLAD and for 10 days after the last dose.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
In females of reproductive potential, pregnancy should be excluded before the initiation of each treatment course of MAVENCLAD [see Use in Specific Populations (8.1)].

Contraception
Females
Females of reproductive potential should prevent pregnancy by use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course. It is unknown if MAVENCLAD may reduce the effectiveness of the systemically acting hormonal contraceptives. Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course. Women who become pregnant during MAVENCLAD therapy should discontinue treatment [see Warnings and Precautions (5.2) and Drug Interactions (7.7)].

Males
As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected. Therefore, male patients of reproductive potential should take precautions to prevent pregnancy of their partner during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course [see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)].

8.4 Pediatric Use
The safety and effectiveness in pediatric patients (below 18 years of age) have not been established. Use of MAVENCLAD is not recommended in pediatric patients because of the risk of malignancies [see Warnings and Precautions (5.1)].

8.5 Geriatric Use
Clinical studies with MAVENCLAD did not include sufficient numbers of patients aged 65 or over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution is recommended when MAVENCLAD is used in elderly patients, taking into account the potential greater frequency of decreased hepatic, renal, or cardiac function, concomitant diseases, and other drug therapy.

8.6 Patients With Renal Impairment
The concentration of cladribine is predicted to increase in patients with renal impairment [see Clinical Pharmacology (12.3)]. No dosage adjustment is recommended in patients with mild renal impairment (creatinine clearance 60 to 89 mL per minute). MAVENCLAD is not recommended in patients with moderate to severe renal impairment (creatinine clearance below 60 mL per minute) [see Clinical Pharmacology (12.3)].

8.7 Patients With Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown [see Clinical Pharmacology (12.3)]. No dosage adjustment is recommended in patients with mild hepatic impairment. MAVENCLAD is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score greater than 6) [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the possible risk of malignancies, teratogenicity, lymphopenia, and other hematologic toxicity, infection, liver injury, hypersensitivity, and cardiac failure. Inform women that they cannot breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose. Instruct patients that MAVENCLAD is a cytotoxic drug and to use care when handling MAVENCLAD tablets.
Disproportionate Neurodegeneration in Black Patients With MS: The Need for Stratified Treatments

BY DARIN T. OKUDA, MD, FAAN, FANA

The content contained in this publication is for general information purposes only. The reader is encouraged to confirm the information presented with other sources. NeurologyLive™ makes no representations or warranties of any kind about the completeness, accuracy, timeliness, reliability, or suitability of any of the information, including content or advertisements, contained in this publication and expressly disclaims liability for any errors and omissions that may be presented in the publication. NeurologyLive™ reserves the right to alter or correct any error or omission in the information it provides in this publication, without any obligations. NeurologyLive™ further disclaims any and all liability for any direct, indirect, consequential, special, exemplary, or other damages arising from the use or misuse of any material or information presented in this publication. The views expressed in this publication are those of the authors and do not necessarily reflect the opinion or policy of NeurologyLive™.
Consistently Pushing the MS Care Paradigm Forward

THE MULTIPLE SCLEROSIS (MS) treatment paradigm has evolved greatly since the introduction of the A-B-C drugs in the early 1990s. The therapeutic toolbox has now grown to include more than 20 options for disease management across relapsing as well as primary- and secondary-progressive disease.

In addition, progress has been made in understanding the root pathology of MS and the subsequent identification of several key biomarkers of disease activity and progression, such as neurofilament light chain. But as pharmaceutical development has brought forth agents with novel mechanisms and more has been uncovered about MS, new markers to assess disease clinical course are needed. In this issue of *NeurologyLive®*, on page 35, Tirisham Gyang, MD, and Torge Rempe, MD, offer an updated look at the current roster of biomarkers for clinicians.

In addition to assessment needs, research and real-world data have pointed to significant disparities in care faced by patients based on racial and ethnic differences. These disparities are often associated with a more severe disease course and poorer outcomes, putting pressure on the medical community to address them in a timely manner. In our cover story on page 20, Darin T. Okuda, MD, FAAN, FANA, highlights some of these disparities faced by Black and African American patients with MS and the importance of a personalized assessment and treatment plan designed to address their more challenging disease course.

Despite these challenges for clinicians, the treatment pipeline remains robust, including a number of agents aimed at treating progressive forms of MS—a critical need—and several new options for relapsing MS. Many of these therapies offer new mechanisms of action, such as the highly anticipated Bruton tyrosine kinase (BTK) inhibitor class. One such BTK inhibitor, tolebrutinib, is currently being investigated for its effect on relapsing disease in the GEMINI 1 trial (NCT04410978), which this issue explores further on page 27.

Although these novel pharmaceutical therapies are helping move the field closer to truly being able to provide personalized medicine, the importance of a whole-body approach to health is becoming more apparent with emphasis on the comprehensive care model. On page 33, Robert W. Motl, PhD, explores the current evidence supporting the importance and benefits of exercise in patients with MS, and why exercise prescription should be a key component in care plans.

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 managing editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences™
Moving Toward a More Personalized MS Treatment Journey

Mitzi Joi Williams, MD

**FROM THE EDITOR**

**THIS IS INDEED AN EXCITING TIME** in the field of multiple sclerosis (MS). As treatment options continue to expand—now with over 20 therapies, including options for primary and secondary progressive disease—the science in the field is focusing more on other issues such as understanding and tracking disease progression, approaches to treatment initiation, and the roles of diet and exercise in pathogenesis and disease course. This issue of *NeurologyLive®* focuses on several of these topics.

There is an increasing volume of data characterizing the more severe disability seen in Black populations, but the roles of social determinants of health and underlying biology remain unclear. Our cover story, “Disproportionate Neurodegeneration in Black Patients With MS: The Need for Stratified Treatments” by Darin T. Okuda, MD, FAAN, FANA, examines evidence in the literature regarding both phenotype of MS in Black patients and imaging markers of early neurodegeneration. This piece highlights the importance of individualized treatment approaches but also raises important questions regarding how we approach therapeutic decision-making in populations that are known to have more aggressive disease. This extremely important topic emphasizes the dire need for increased diversity in clinical research to make results more generalizable and better understand disparate outcomes.

It has been well known that exercise provides cardiovascular benefit for patients living with MS, but the prescription of exercise training to help with specific symptoms of MS including fatigue and cognitive dysfunction is less well known. In the feature story “Exercise Training in Multiple Sclerosis” by Robert W. Motl, PhD, he discusses the role of exercise training in MS and our current understanding of its benefits. Motl also provides interesting perspective and a review of studies focused on exercise training as a disease-modifying intervention for MS, as well.

As treatments become more effective, it has become more imperative to track effectiveness, but also disease progression. Torge Rempe, MD, and Tirisham Gyang, MD, provide an overview of available and emerging biomarkers in MS in their feature article. This piece first describes the role of biomarkers and qualities of good biomarkers. The authors discuss current well-known markers such as MRI, cerebrospinal fluid oligoclonal bands, and optical coherence tomography and how they can be used in both diagnosis and evaluating treatment response. The article also covers emerging biomarkers such as glial fibrillary acidic protein and neurofilament light chain and the potential utility of these markers once they become more widely available in clinical practice.

As the therapeutic landscape becomes more complex, it becomes even more imperative that we engage in shared decision-making with our patients and their care partners to create the best individualized treatment plan possible. This plan should include early intervention with disease-modifying therapy, although there is not sufficient evidence to fully support escalation therapy versus early high-efficacy therapy. As evidence unfolds focused on the effects of diet, the gut microbiome, exercise, and comorbidities, these issues will also become more integral in initial and ongoing treatment plans.

We have not yet attained the ability to practice precision medicine in MS, but the scientific community is moving us closer to this goal. As we set our sights on moving past preventing disability to examining clinically definite improvement and reaching no evidence of disease activity as a treatment goal for our patients, we need a comprehensive approach to treatment that focuses not only on disease-modifying...
therapy but also modifiable risk factors and wellness. Improving health outcomes for all ethnic groups and better understanding MS characteristics in minority populations will also play a key role in improving health equity in these populations but will hopefully lead to discoveries that allow us to increase quality of care for all people living with MS.
INDICATION
MAYZENT® (siponimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION
Contraindications
- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

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

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

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

No cases of progressive multifocal leukoencephalopathy (PML) were reported in MAYZENT clinical trials; however, they have been observed in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, MAYZENT should be discontinued.

Cases of herpes viral infection, including one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, have been reported. Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting MAYZENT. If VZV antibodies are not present or detected, then VZV immunization is recommended and MAYZENT should be initiated 4 weeks after vaccination.

Use of live vaccines should be avoided while taking MAYZENT and for 4 weeks after stopping treatment.

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

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.
MAYZENT is
THE FIRST
AND ONLY
oral DMT studied and proven to delay disability progression in a more progressed RMS population, including active SPMS.1,2*

THE DUAL MOA OF MAYZENT
targets S1P1,5—2 key receptors thought to play a role in RMS inflammation and neurodegeneration.1,3,6

WITH INTERIM EXPLORATORY DATA
UP TO 5 YEARS
from an open-label extension study aiming to evaluate long-term safety and tolerability, as well as efficacy measures; patients who completed the core part of the study either continued on MAYZENT or switched from placebo to MAYZENT.7,8†‡

The mechanism by which siponimod exerts therapeutic effects on MS is unknown but may involve reduction of lymphocytes in the CNS.1

ARR=annualized relapse rate; CDP=confirmed disability progression; CNS=central nervous system; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; MOA=mechanism of action; MS=multiple sclerosis; RMS=relapsing MS; S1P=sphingosine 1-phosphate; SDMT=Symbol Digit Modalities Test; SPMS=secondary progressive MS.

DISCOVER UP TO 5 YEARS OF INTERIM DATA AT
mayzenthcp.com

IMPORTANT SAFETY INFORMATION (CONT)

BRADYARRHYTHMIA AND ATRIOVENTRICULAR CONDUCTION DELAYS:
Prior to initiation of MAYZENT, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects.

MAYZENT was not studied in patients who had:
• In the last 6 months, experienced myocardial infarction,
unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
• New York Heart Association Class II-IV heart failure
• Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
IMPORTANT SAFETY INFORMATION (CONT)

Bradypnea and Atrioventricular Conduction Delays (cont):
- history or observed at screening, unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class la or Class III anti-arrhythmic drugs
Reinitiation of treatment (initial dose titration, monitoring effects on heart rate and AV conduction [ie, ECG]) should apply if ≥4 consecutive daily doses are missed.

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

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

Cutaneous Malignancies: Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator. Periodic skin examination is recommended. Monitor for suspicious skin lesions and promptly evaluate any that are observed. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended.

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

Fetal Risk: Based on animal studies, MAYZENT may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT therapy.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a sphingosine 1-phosphate (SIP) receptor modulator. Such events have not been reported for patients treated with MAYZENT in clinical trials. If patients develop any unexpected neurological or psychiatric symptoms, a prompt evaluation should be considered. If PRES is suspected, MAYZENT should be discontinued.

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

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

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

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

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

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


MAYZENT and the MAYZENT logo are registered trademarks of Novartis AG.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

©2021 Novartis

2/21

MKT-1400690

0.25 mg - 2 mg
MAYZENT® (siponimod) tablets, for oral use

Initial U.S. Approval: 2019

**BRIEF SUMMARY:** Please see package insert for full prescribing information.

1. **INDICATIONS AND USAGE**
   MAYZENT® is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2. **CONTRAINDICATIONS**
   MAYZENT® is contraindicated in patients who have:
   - A CYP2D6 *3/*3 genotype [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5) in the full prescribing information].
   - In the last 6 months experienced myocardiad infection, unstable angina, stroke, TIA, uncompensated heart failure requiring hospitalization, or Class III or IV heart failure.
   - Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker [see Warnings and Precautions (5.3)].

3. **WARNINGS AND PRECAUTIONS**

   **5.1 Infections**

   **Risk of infections.**
   MAYZENT® causes a dose-dependent reduction in peripheral lymphocyte count to 20% to 30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT® may therefore increase the risk of infections, some serious in nature [see Clinical Pharmacology (12.2) in the full prescribing information]. Life-threatening and rare fatal infections have occurred in association with MAYZENT®.
   
   In Study 1 [see Clinical Studies (14) in the full prescribing information], the overall rate of infections was comparable between the MAYZENT®-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infection were more common in MAYZENT®-treated patients. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT®-treated patients compared to 2.5% of patients receiving placebo.
   
   Before initiating treatment with MAYZENT®, results from a recent CBC (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.
   
   Initiation of treatment with MAYZENT® should be delayed in patients with severe active infection until resolution. Because of residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of MAYZENT®, vigilance for infection should be continued throughout this period [see Warnings and Precautions (5.12)].
   
   Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT® should be considered if a patient develops a serious infection.

   **Cryptococcal Infections**
   Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine 1-phosphate (SIP) receptor modulator. Rare cases of CM have also occurred with MAYZENT®. Physicians should be vigilant for CM in patients with symptoms or signs consistent with a cryptococcal infection and undergo prompt diagnostic evaluation and treatment. MAYZENT® treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

   **Herpes Viral Infections**
   Cases of herpes viral infection, including one case of reactivation of VZV infection leading to varicella zoster meningitis, have been reported in the development program of MAYZENT®. In Study 1, the rate of herpetic infections was 4.8% in MAYZENT®-treated patients compared to 3.0% of patients receiving placebo. In Study 1, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT®-treated patients compared to 0.7% of patients receiving placebo. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT® [see Vaccinations below].

   **Progressive Multifocal Leuкоencephalopathy (PML)**
   Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical associations associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

   No cases of PML have been reported in MAYZENT®-treated patients in the development program; however, PML has been reported in patients treated with an S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immuno compromised patients, polytherapy with immunomodulators). Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with MAYZENT® should be suspended until PML has been excluded.

   **Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies**
   Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects during such therapy [see Drug Interactions (7.1)].

   **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 MAYZENT® treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with MAYZENT®, following which initiation of treatment with MAYZENT® should be postponed for 4 weeks to allow the full effect of vaccination to occur.

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT® and for 4 weeks after stopping treatment [see Drug Interactions (7.1)]. Vaccinations may be less effective if administered during MAYZENT® treatment. MAYZENT® treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema

Macular edema was reported in 1.8% of MAYZENT®-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT®.

Continuation of MAYZENT® therapy in patients with macular edema has not been evaluated. A decision on whether to continue MAYZENT® should be based on an individual patient’s 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 diabetes mellitus are at increased risk of macular edema during MAYZENT® therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT®, the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. 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.

5.3 Bradycardia and Atrioventricular Conduction Delays

Since initiation of MAYZENT® treatment results in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of MAYZENT® [see Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.2) in the full prescribing information].

MAYZENT® was not studied in patients who had:

- In the last 6 months experienced myocardiad infection, unstable angina, stroke, transient ischemic attack (TIA), or uncompensated heart failure requiring hospitalization
- New York Heart Association Class II–IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second degree AV-block or higher grade AV-block (e.g., history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)]

**Reduction in Heart Rate**

After the first titration dose of MAYZENT®, the heart rate decrease starts within an hour, and the Day 1 decline is maximal at approximately 3–4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days, with maximal decrease from Day 1 baseline reached on Day 5–6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on Day 1, with the pulse declining on average 5–6 bpm. Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after Day 6 and reaches placebo levels within 10 days after treatment initiation.

In Study 1, bradycardia occurred in 4.4% of MAYZENT®-treated patients compared to 2.9% of patients receiving placebo. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, including dizziness or fatigue, and these symptoms resolved within 24 hours without intervention [see Adverse Reactions (6.1)]. Heart rates below 40 bpm were rarely observed.

Atrioventricular Conduction Delays

Initiation of MAYZENT® treatment has been associated with transient atrioventricular conduction delays that follow a temporal pattern as the observed decrease in heart rate during dose titration. The AV conduction delays manifested in most of the cases as first-degree AV block (prolonged PR interval on ECG), which occurred in 5.1% of MAYZENT®-treated patients and in 1.9% of patients receiving placebo in Study 1. Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at the time of treatment initiation with MAYZENT® in less than 1.7% of patients in clinical trials. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, rarely required treatment with atropine, and did not discontinue discontinuation of MAYZENT® treatment.

If treatment with MAYZENT® is considered, advice from a cardiologist should be sought:

- In patients with significant QT prolongation (QTc greater than 500 msec)
- In patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)]
- In patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block [see Contraindications (4)]

**Treatment-Initiation Recommendations**

- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.
- In all patients, a dose titration is recommended for initiation of MAYZENT® treatment to help reduce cardiac effects [see Dosage and Administration (2.2, 2.3) in the full prescribing information].
- In patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree (Mobitz type I) AV block, or a history of myocardial infarction or heart failure, if not concomitantly, ECG testing and first-dose monitoring is recommended [see Dosage and Administration (2.1, 2.4) in the full prescribing information and Contraindications (4)].
Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, MAYZENT is not recommended in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

Use of MAYZENT in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

Experience with MAYZENT is limited in patients receiving concurrent therapy with drugs that decrease heart rate (e.g., beta-blockers, calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate, such as ivabradine and digoxin). Concomitant use of these drugs during MAYZENT initiation may be associated with severe bradycardia and heart block.

For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing MAYZENT treatment. If the resting heart rate is greater than 50 bpm under chronic beta-blocker treatment, MAYZENT can be introduced. If resting heart rate is less than or equal to 50 bpm, beta-blocker treatment should be interrupted until the baseline heart rate is greater than 50 bpm. Treatment with MAYZENT can then be initiated and treatment with a beta-blocker can be reinitiated after MAYZENT has been up-titrated to the target maintenance dosage [see Drug Interactions (7.3)].

For patients taking other drugs that decrease heart rate, treatment with MAYZENT should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate [see Dosage and Administration (2.4) in the full prescribing information].

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

If a titration dose is missed, or if 4 or more consecutive daily doses are missed during maintenance treatment, reinitiate Day 1 of the dose titration and follow titration monitoring recommendations [see Dosage and Administration (2.2, 2.3) in the full prescribing information].

5.4 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MAYZENT-treated patients as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV1 from baseline compared to placebo was 88 mL [95% confidence interval (CI): -139, -37] at 2 years. The mean difference between MAYZENT-treated patients and patients receiving placebo in percent predicted FEV1 at 2 years was 2.8% (95% CI: -4.5, -1.0). There is insufficient information to determine the reversibility of the decrease in FEV1 after drug discontinuation. In Study 1, five patients discontinued MAYZENT because of decreases in pulmonary function testing. MAYZENT has been tested in MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The changes in FEV1 were similar in this subgroup compared with the overall population. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated.

5.5 Liver Injury

Elevations of transaminases may occur in MAYZENT-treated patients. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of MAYZENT therapy.

In Study 1, elevations in transaminases and bilirubin were observed in 10.1% of MAYZENT-treated patients compared to 3.7% of patients receiving placebo, mainly because of transaminase [alanine aminotransferase/aspartate aminotransferase/gamma-glutamyltransferase (ALT/AST/GGT)] elevations.

In Study 1, ALT or AST increased to three and five times the upper limit of normal (ULN) in 5.6% and 1.4% of MAYZENT-treated patients, respectively, compared to 1.5% and 0.5% of patients receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of MAYZENT. In clinical trials, MAYZENT was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic dysfunction.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should have liver enzymes checked. MAYZENT should be discontinued if significant liver injury is confirmed.

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 MAYZENT, caution should be exercised when using MAYZENT in patients with a history of significant liver disease.

6 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 practice. A total of 1737 MS patients have received MAYZENT at doses of at least 2 mg daily. These patients were included in Study 1 [see Clinical Studies (14) in the full prescribing information] and in a Phase 2 placebo-controlled study in patients with MS. In Study 1, 67% of MAYZENT-treated patients completed the double-blind part of the study, compared to 59% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of MAYZENT-treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in MAYZENT-treated patients in Study 1 were headache, hypertension, and transaminase increases.

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate at least 1% higher than in patients receiving placebo.
nance treatment, reinitiate Day 1 of the dose titration and follow titration monitoring recommen-

If a titration dose is missed, or if 4 or more consecutive daily doses are missed during mainte-

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were

Periodic skin examination is recommended for all patients, particularly those with risk factors for

risk of basal cell carcinoma (BCC). In Study 1, the incidence of BCC was 1.0% in MAYZENT-treated

5.6 Cutaneous Malignancies

5.7 Increased Blood Pressure

6 ADVERSE REACTIONS

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) were observed in patients treated with MAYZENT [see Warnings and Precautions (5.4)].

Vascular Events

Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.0% of MAYZENT-treated patients compared to 2.6% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

Respiratory Effects

The following adverse reactions have occurred in less than 5% of MAYZENT-treated patients but at a rate at least 1% higher than in patients receiving placebo: herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block (1st and 2nd degree), ashen, and pulmonary function test decreased [see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)].

Seizures

In Study 1, cases of seizures were reported in 1.7% of MAYZENT-treated patients, compared to 0.4% in patients receiving placebo. It is not known whether these events were related to the effects of MS, to MAYZENT, or to a combination of both.

Elevations of transaminases may occur in MAYZENT-treated patients. Recent (i.e., within last 2 years) elevations occurred within 6 months of starting treatment. ALT levels returned to normal within 10 days of stopping treatment in some patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients compared to placebo patients.

In Study 1, ALT or AST increased to three and five times the upper limit of normal (ULN) in 5.6% of patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients compared to placebo patients.

The risk of basal cell carcinoma is increased in MAYZENT-treated patients, and an increased risk of cutaneous malignancies has also been reported in association with another S1P modulator [see Warnings and Precautions (5.6)].

7 DRUG INTERACTIONS

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

MAYZENT 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 (5.10)].

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with MAYZENT after alemtuzumab is not recommended. MAYZEN can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

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

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

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradicardia. If treatment with MAYZENT is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltia-

zern), or other drugs that may decrease heart rate (e.g., vabradine, digoxin) [see Warnings and Precautions (5.5) and Drug Interactions (7.3)]. If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

7.3 Beta-Blockers

Caution should be applied when MAYZENT is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of MAYZENT [see Warnings and Precautions (5.3)]. Beta-blocker treatment can be initiated in patients receiving stable doses of MAYZENT [see Clinical Pharmacology (12.2) in the full prescribing information].

7.4 Vaccination

During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination [see Warnings and Precautions (5.1)].

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT [see Warnings and Precautions (5.1)].

7.5 CYP2C9 and CYP3A4 Inhibitors

Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recom-

mended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhib-

itor (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inhibitors.

7.6 CYP2C9 and CYP3A4 Inducers

Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause strong CYP2C9 and moderate or strong CYP3A4 induction is not recom-

mended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual induc-

er (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP3A4 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended. In Study 1, the incidence of BCC was 1.0% in MAYZENT-treated patients with CYP3A4*11 and 2/3 genotype [see Clinical Pharmacology (12.3) in the full prescribing information].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman [see Data]. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital, and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recom-

mended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscar-

riage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The back-

ground risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post-implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, only the dose with fetuses available for evaluation. A no-effect dose for adverse effects on embryo-fetal development in rats was not identified. Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose (RHD) of 1.5 mg/day.

When siponimod (0, 0.1, 1, or 5 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryolethality and increased incidences of fetal skeletal variations were observed at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose (0.1 mg/kg) for adverse effects on embryo-fetal development in rabbits is less than that in humans at the RHD.

When siponimod (0, 0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual matura-

tion were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal develop-

ment in rats was not identified. The lowest dose tested (0.03 mg/kg) is less than the RHD, on a mg/m^2 basis.

8.2 Lactation

Risk Summary

There are no data on the presence of siponimod in human milk, the effects of MAYZENT on the breastfed infant, or the effects of the drug on milk production. A study in lactating rats has shown excretion of siponimod and/or its metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for MAYZENT and any potential adverse effects on the breastfed infant from MAYZENT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Before initiation of MAYZENT treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with MAYZENT [see Use in Specific Populations (8.1)]. Since it takes approximately 10 days to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period [see Warnings and Precautions (5.8)].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Oral administration of siponimod (0, 5, 15, or 50 mg/kg/day) to young rats from postnatal day 25 to 70 resulted in mortality, lung histopathology (alveolar/interstitial edema, fibrin, interstitial mixed cell infiltration) and decrease in body weight gain at the mid and high doses. Neuro- behavioral impairment (decreased acoustic startle response) was observed at the high dose but was reversible by the end of the recovery period. Decrease in immune function (T-cell dependent
antibody response) was observed at all doses and had not fully recovered by 4 weeks after the end of dosing. A no-effect dose for adverse effects in juvenile animals was not identified.

8.5 Geriatric Use
Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 CYP2C9 Genotype
Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4% to 0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod [see Dosage and Administration (2.3) and Clinical Pharmacology (12.5) in the full prescribing information].

10 OVERDOSAGE
In patients with overdosage of MAYZENT, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed [see Warnings and Precautions (5.3, 5.7) and Clinical Pharmacology (12.2) in the full prescribing information].

There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body. The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

MAYZENT is a registered trademark of Novartis AG
© Novartis
T2021-04
A special protocol agreement with the FDA allowed for both ULTIMATE 1 and 2 to be conducted, and a combined total of 1094 patients in 10 countries were enrolled. In both studies, the investigators administered a 450-mg dose of ublituximab via 1-hour intravenous infusion every 6 months. This followed an infusion on day 1 of the trial of 150 mg over the course of 4 hours and another infusion on day 15 of 450 mg over 1 hour. Teriflunomide was administered via 14-mg oral tablets that were taken once a day. The investigators randomized patients in both trials 1:1 to either agent and then assessed the ARR at 96 weeks.

In ULTIMATE 1, treatment with ublituximab resulted in an ARR of 0.076 compared with 0.188 for those treated with teriflunomide, representing a relative reduction of 60% (ARR ratio, 0.406; 95% CI, 0.268-0.615; P < .0001). In ULTIMATE 2, ARRs at 96 weeks were 0.091 and 0.178 in the ublituximab and teriflunomide groups, respectively, equating to a 49% relative reduction (ARR ratio, 0.509; 95% CI, 0.330-0.784; P < .0022).

The total number of T1 gadolinium (Gd)-enhancing lesions were reduced with ublituximab treatment by 97% and 96% relative to teriflunomide treatment in ULTIMATE 1 and 2, respectively (P < .0001). Additionally, investigators observed relative reductions of 92% and 90% for new or enlarging T2 lesions by treatment with ublituximab in ULTIMATE 1 and 2, respectively (P < .0001).

Both trials reported similar numbers of adverse events, with the most common being infusion-related reaction (IRR), headache, nasopharyngitis, and lymphopenia. No patients treated with teriflunomide had grade 4 severity of IRRs, compared with 0.2% of those in the ublituximab group at weeks 1 and 3. Serious adverse events occurred in 6.2% of patients in the teriflunomide group and in 9.5% in the ublituximab group, with the most common being infections and infestations as well as nervous system disorders.

Three deaths occurred during the trial, all in the ublituximab group, and were the results of encephalitis, salpingitis, and pneumonia. Investigators noted that the pneumonia case was potentially related to treatment and saw no cases of progressive multifocal leukoencephalopathy.

---

**Biologics License Application Submitted for Relapsing MS Anti-CD20 Antibody**

*By Abby Reinhard*

A biologics license application (BLA) has been submitted to the FDA by TG Therapeutics for the use of ublituximab as treatment for patients with relapsing forms of multiple sclerosis (RMS). Ublituximab, an investigational glycoengineered anti-CD20 monoclonal antibody, was evaluated in 2 independent, identical, phase 3, randomized, global, multicenter trials, ULTIMATE 1 and ULTIMATE 2 (NCT03277261; NCT03277248), which compared the efficacy of the treatment with teriflunomide (Aubagio; Sanofi/Genzyme).1,2

Results from the double-blinded, active controlled trials were announced earlier this year at the 7th Congress of the European Academy of Neurology, which took place on June 19 through 22. The study investigators concluded that ublituximab had met its primary end point in significantly reducing annualized relapse rate (ARR) and MRI parameters over a 96-week period, when compared with teriflunomide (P < .005 in each trial).1,3

---

**Ocrelizumab Demonstrates Real-world Long-term Safety up to 7 Years**

*By Marco Meglio*

Pooled real-world data from more than 5000 patients with multiple sclerosis (PwMS) treated with ocrelizumab (Ocrevus; Genentech) showed that the therapy was associated with a favorable and manageable safety profile, without any emerging safety concerns over a 7-year follow-up.

The study investigators pulled safety data for ocrelizumab, an FDA-approved treatment for patients with relapsing MS (RMS) or primary progressive forms of MS (PPMS), from 11 clinical trials. These included the controlled treatment and open-label extension periods of phase 2 and 3 trials as of January 2020, and assessed outcomes including adverse events (AEs), serious AEs (SAEs), and AEs leading to treatment discontinuation.
At data cutoff, 5680 PwMS (RMS, n = 4376; PPMS, n = 1304) had been exposed to treatment for a total of 11,424 patient-years (PYs) over a period of up to 7 years. More than 50% of patients had received at least 5 doses of ocrelizumab and 28% of patients had received at least 10 doses. After the investigators had pooled the data, the rates of AEs (248 per 100 PY; 95% CI, 246-251) and SAEs (7.3 per 100 PY; 95% CI, 7.0-7.7) in all patients with RMS or PPMS remained consistent with the rates observed in controlled treatment programs (CTPs) of the phase 3 trials. The investigators concluded that these findings provide class III evidence that long-term, continuous treatment with ocrelizumab is safe in patients with RMS and PPMS.

Among the cohort, 3.19% (n = 181) of patients discontinued ocrelizumab treatment due to an AE over the 7-year stretch compared with 3.35% and 6.17% of those in the placebo and interferon beta-1a groups, respectively, over a period of up to 3 years during the CTP. Malignancies (n = 40, mandatory discontinuation), infusion-related reactions (IRR; n = 33) mostly occurring at the first infusion, and infections (n = 27, majority nonserious) were the most common AEs leading to discontinuation among all ocrelizumab-exposed populations.

A total of 26 fatalities were recorded among patients treated with ocrelizumab; this corresponded to a rate of 0.14 per 100 PY (95% CI, 0.09-0.21), which was consistent with the rate observed at the end of the CTP and similar to rates observed for comparators. Although IRRs were among the most common AEs reported in the CTPs of the phase 3 trials, the rates of IRRs in the all-exposed population decreased with subsequent infusions.

Despite fluctuations over the 7-year period, the rate of serious infections (SIs) among both patients with RMS and PPMS never showed meaningful year-on-year variation. The incidence of these SIs was infrequent, represented by a rate of 2.01 per 100 PY (95% CI, 1.81-2.23). Urinary tract infections (0.30 per 100 PY; 95% CI, 0.23-0.39), pneumonia (0.30 per 100 PY; 95% CI, 0.22-0.39), and cellulitis (0.14 per 100 PY; 95% CI, 0.09-0.21) were among the most common SIs observed for patients treated with ocrelizumab.

The crude incidence rate of all malignancies, including nonmelanoma skin cancer (NMSC), was 0.46 per 100 PY (95% CI, 0.37-0.57). Furthermore, examination of all malignancies and female breast cancer was not suggestive of causal or of time-dependent or cumulative dose-dependent exposure effect. The data also showed that the standardized incidence rate of all malignancies, excluding NMSC, was 0.23 per 100 PY (95% CI, 0.15-0.39). Additionally, the age-standardized incidence rate of female breast cancer was 0.13 per 100 PY (95% CI, 0.08-0.32) for patients who received ocrelizumab.

Minimal immunogenicity was observed over a period of 6.5 years, with a total of 24 patients testing positive for treatment-emergent antidrug antibodies. “Long-term follow-up and postmarketing studies will continue to monitor the safety of long-term treatment with [ocrelizumab] in increasing numbers of patients,” the study authors concluded.

### Epilepsy Is Associated With Disability Progression in Multiple Sclerosis

**By Abby Reinhard**

Findings from a recent study published in *Multiple Sclerosis Journal* show that the secondary progressive disease course of multiple sclerosis (MS), age, and disability were associated with a 5-year prevalence of epilepsy. Data also showed that patients with both MS and epilepsy (MSE+) had greater levels of disability and faster disease progression in the first year of MS compared with patients with MS without epilepsy (MSE−) during a mean evaluation period of 17.6 years.

The trial included a total of 31,052 patients from the German Multiple Sclerosis Register (GMSR), of whom 633 had had MSE+ documented within the past 5 years at the time of study. Data showed a significant association between 5-year prevalence of epilepsy and increase in age, disease duration, and Expanded Disability Status Scale (EDSS) score (all P < .001). Epilepsy was associated with age (odds ratio [OR] per 10 years, 1.12; 95% CI, 1.05-1.19), MS disease duration (OR per 10 years, 1.40; 95% CI, 1.30-1.50), and EDSS score (OR per point, 1.29; 95% CI, 1.24-1.33).

Further analysis revealed an epilepsy association with disease course and sex. Using relapsing-remitting MS as a reference, the investigators identified an association between epilepsy and secondary progressive MS (OR, 2.23; 95% CI, 1.86-2.67) and primary progressive MS (OR, 1.19; 95% CI, 0.85-1.62). They also found a moderate association between male sex and prediction of epilepsy (OR, 1.11; 95% CI, 0.94-1.32). When they performed the multivariate logistic regression analysis, age, disease course, and sex were no longer significantly associated; however, disease duration (OR per 10 years, 1.28; 95% CI, 1.15-1.42) and EDSS score (OR per point, 1.30; 95% CI, 1.24-1.37) remained significantly associated.

When analyzing the MSE+ group (n = 550) and the matched control MSE− group (n = 5500) in a long-term comparison over a mean period of 17.6 years, investigators found that patients with MSE+ were more likely to have brainstem, motor, and cerebellar symptoms, as well as bladder dysfunction and depression during the onset of MS. During the first year of disease, the MSE+ group had a significantly higher EDSS score than the MSE− group, at 2.0 and 1.5 points, respectively (P < .001). Mean score difference increased after 15 years, growing from a 0.5-point gap to an 0.8-point gap between the MSE+ group and MSE− group, at 4.0 and 3.2 points, respectively. At final follow-up those in the MSE+ group had a lower employment status (40%) than those in the MSE− group (65%).

The investigators noted limitations of the register-based study, including the risk of additional heterogeneity due to data being collected from multiple centers and the introduction of bias if missing values are not entirely random. Additionally, the GMSR recorded epilepsy without including additional information about the prevalence of epileptic seizure, alternative causes, or an imaging parameter.
TOP TWEETS

TSC Alliance | @tscallliance
Check out @tscalliance Chief Scientific Officer @StevenRobertson and Board Chair @PeterCriso of UMMC talk about current care standards in TSC and the future of TSC research. Our thanks to @neurology_live for hosting this important Roundtable Discussion.
WATCH: neurologylive.com/tsc-roundtable

CC Nevada & Keep Memory Alive | @CCNevadaKMA
Jessica Caldwell, PhD, director of the @womensalz Prevention Center at #CCNevada, discussed her new study and the current knowledge of the role genetics play in Alzheimer disease risk. Read her interview with @neurology_live.
READ: neurologylive.com/nv-caldwell

Stanford Neurology & Neurological Sciences | @Stanford_Neuro
Gregory W. Albers, MD, shares his insight into the development & clinical use of RapidAI [and] findings of the pivotal DIFFUSE study, as well as the future use of AI in stroke and neuromaging. Listen to this podcast @neurology_live.
LISTEN: neurologylive.com/mm-ep-48

AASM Membership | @AASMmembership
In conversation with @neurology_live, AASM member Lynn Marie Trotti, MD, MSc, discussed the potential for the new AASM hypersomnolence guideline to educate providers treating patients with #SleepDisorders.
WATCH: neurologylive.com/trotti-guidelines

Jenny Majersik | @JMajersik
It was an honor to talk about something so important to our profession. RT: Jennifer Majersik, MD, MS, sat down with NeurologyLive to discuss a recent report on the ne...
Disproportionate Neurodegeneration in Black Patients With MS: The Need for Stratified Treatments

Identifying the best treatment strategy for Black or African American patients who are at risk for a more challenging clinical course is of great importance and represents a key unmet need in our field.

By Darin T. Okuda, MD, FAAN, FANA

TAILORING TREATMENT AND SURVEILLANCE recommendations to the individual patient serves as an attractive goal in the effective management of any medical condition. Commonly, therapeutic approaches and preventive measures are recommended based on patient age with the hope that these interventions will help to improve long-term outcomes. Other key factors include disease severity, genetic markers from tumors that may inform on therapeutic response, and comorbid conditions. The incorporation of such data aims to improve our ability to more effectively deliver care that minimizes morbidity and mortality. Yet despite all the advances in modern medicine up to this point, very few treatment recommendations are stratified based on race and ethnicity. Ethnicity is a much deeper issue than it may seem, representing more than who people are, going beyond genetics and involving shared cultural, behavioral, or religious characteristics. Consequently, these factors can shape a variety of outcomes including treatment response, the time course of disease behavior, and clinical outcomes. Given this, having a goal of “ethnicity-based” medication labels may be less ideal and focusing on effectively identifying and treating individuals with higher risks within a group may serve as the better strategy. But is this concept more relevant in the management of disease affecting the brain and spinal cord than other conditions involving less eloquent structures within the human body? Many neuroimmunologists specializing in the care of autoimmune disorders of the central nervous system believe so.

Multiple sclerosis (MS) is an autoimmune condition leading to inflammatory injury within the central nervous system that may result in irreversible neurological disability. An increase in risk for acute inflammatory events within the brain and spinal cord is present in younger individuals. Preventing permanent neurological disability while preserving quality of life serves as important measure of success. An early understanding of who may be at risk for a more challenging disease course in the future remains elusive, and the search for clinical, imaging, blood, and spinal fluid biomarkers is a current focus of investigators in the field. At present, disease localization and severity and the temporal profile of clinical and MRI exacerbations serve as coarse measures on which opinions regarding disease severity are based.

The incidence of MS in women appears to be higher in African American individuals than in White, Hispanic, and Asian individuals. In addition, the current scientific literature reveals that risk for the outcome of neurological disability may be influenced by race and ethnicity. Some Black or African American patients with relapsing MS may experience a more aggressive disease course than others. However, collectively, these individuals experience a higher frequency of clinical relapses, a greater propensity for clinical attacks at the optic nerves and spinal cord, a lower probability for full recovery following a relapse, and a more accelerated accrual of neurological disability than White patients.

In addition to clinical differences between groups, Black or African American patients with MS also appear to possess imaging.
indicators suggestive of more aggressive disease. Accelerated rates of brain atrophy along with retinal nerve fiber layer and ganglion cell inner plexiform layer atrophy were observed in African American patients when compared with White patients. An increase in the rate of cerebellar atrophy also appears to be present. Higher T2-lesion volumes and lower magnetization transfer ratio (MTR) values, suggestive of a decline in tissue integrity, in normal-appearing grey and white matter were also found to be lower in comparison with White patients with MS.

Are there earlier and more subtle signs of early neurodegeneration in individuals, with no current neurological impairments, that enable the identification of Black or African American patients with MS who are at greater risk for future disability? Recently, investigators in the field have been focused on volumetric outcomes involving the whole brain, cortical grey matter, and deep brain structures such as the thalamus to answer this question. The observation of a reduction in global or regional measures of volume within the brain suggests tissue compromise. More recently, the use of 3-dimensional (3D) conformational metrics—an approach centered on the study of shape, structure, and surface texture—has provided new information into how MS lesions and anatomical structures may change over time. This approach also offers insights into the pattern of injury or neurodegenerative change that is not observed through conventional imaging techniques. In the study of the medulla-upper cervical spine using a conventional MRI sequence commonly acquired in clinical practice and in research trials, both the ventral and dorsal compartments of this region of interest exhibited greater rates of atrophy in African American patients with MS compared with those in White patients, despite both groups having Expanded Disability Status Scale scores of 0.0. Interestingly, the rate of change at the dorsal surface, but not the ventral surface, was found to be more advanced in African American patients. The early reductions in tissue integrity affecting this region may have an early impact on the cuneate fasciculi and gracile or cuneate nuclei mediating sensation at the upper and lower body, respectively; the medial vestibular nuclei affecting head and eye movements; and the posterior longitudinal fasciculus controlling visceral motor and sensory signals, along with the area postrema that is vital in the control of autonomic functions. Why early involvement here is seen in African American patients with MS and not in White patients is not entirely clear but may be explained by the selective vulnerability of this posterior segment to autoimmune injury and early neurodegeneration. The resulting effect on clinical outcomes is not yet known, but these data are suggestive of early alterations in tissue integrity well before the onset of definitive neurological impairments.

One explanation for observed changes may involve secondary degeneration from nearby inflammatory lesions. Volume changes may also be the result of microanatomical inflammation and eventual scarring that remains below the resolution of our current MRI techniques. A global neurodegenerative process favoring specific structures such as the supratentorial white matter, cortex, deep grey matter, brainstem, or spinal cord may also be possible.

Identifying the most appropriate treatment strategy for Black or African American patients, given their risk as a group for a more challenging clinical course, is of great importance. It also represents a key unmet need in our field. The current FDA-approved disease-modifying therapies are known to be more similar in terms of having an effect during the inflammatory phase of MS, but are less similar in producing remarkable effects in reducing neurological disability and confirmed disability improvement. Understanding the reasons behind observed volume differences from different CNS structures is important, as it may inform clinicians on treatment decisions. Based on available scientific data, obvious inflammatory injuries, punctuated by the presence of contrast-enhancing and new T2-lesion formation on MRI, and neurodegenerative features defined by atrophy of tissue appear present. Whether whole brain atrophy or regional volume changes within the cortical grey matter, thalamus, brainstem, and other structures represent a separate neuropathological process is not entirely clear. In some individuals with MS, a greater likelihood for early neurodegeneration may also exist in distinct tissue types over others (ie, brainstem over whole brain, etc).

That neurological disability could be reversed or the risk for future neurological impairments be prevented earlier is an ambitious yet achievable goal. Overall, Black or African American patients remain severely underrepresented in MS clinical trials. Post hoc analyses have been performed to evaluate the effect of treatment in non-White groups. Natalizumab was found to significantly reduce the annualized relapse rate by 60% as well as the mean number of gadolinium-enhancing and new or enlarging T2-weighted lesions. In the review of data related to treatment response, when African American patients with MS were exposed to interferon beta-1a administered once per week intramuscularly, a significantly higher number developed MRI advancement compared with White patients. Investigators also observed an increase in relapses and lower rates of no evidence of disease activity. These data are meaningful, but it is important to highlight that the number of included participants for these poststudy analyses was small and genetic ancestry data were not uniformly captured. Based on these findings, we need to improve our inclusion of non-White groups within large clinical trials, as published data involving therapeutic efficacy and safety for our available treatments may not be entirely generalizable to all patients we care for.

Given the data presented here, should we consider not only the use of higher efficacy treatments but a deviation from our clinical surveillance recommendations when treating Black or African American people with MS? If such patients have a greater likelihood of more aggressive disease, why have we not been more vocal in formally modifying our surveillance recommendations for care? It would seem logical that a higher MRI frequency and shorter interval of time between clinical visits be recommended. An increase in the utilization of health care resources would also be expected if disability milestones were achieved earlier. Furthermore, less is known about how other concomitant medical conditions may be affecting disease severity in MS along with reported symptoms.

It should also be underscored here that the current diagnostic criteria for MS are deficient in providing guidance to patients who are non-White, yet these criteria are still being used as a means for diagnosis. Efforts specific to the focus of Black or African American patients may lead to opportunities for the earlier recognition of
disease that would enable health care providers to intervene earlier so that neurological impairment risk could be reduced or prevented. To achieve this goal, effective access to treatment is critical. At present, all health care customers are faced with treatment algorithms created by pharmacy benefit managers and insurers, which frequently limit access to MS treatments prescribed by the health care team. Now may be the right time to consider using a new platform that allows for higher-risk groups to have easier access to higher-efficacy treatments for MS, regardless of the disease’s current clinical course.

Significant scientific opportunities exist for identifying the most effective treatments for patients with MS who are Black or African American. Many questions remain unanswered, and the scientific data are unclear as to whether long-term outcomes in MS are improved through the early use of high-efficacy MS treatments or whether conventional approaches are sound based on quantified risk-benefit ratios. The hope one day is to have more refined knowledge specific to race and ethnicity such that our suggested treatments could mirror the Joint National Committee recommendations for the management of hypertension in adults. The inclusion of not only other races and ethnicities but of those who are admixed would be equally valuable. Additionally, given recent world events, it is vital that health care providers realize that many other challenges exist beyond science. After all, the best MS treatment may not be one that is most effective in suppressing inflammatory disease and neurodegeneration, but one that a person is willing to take—as prescribed.

REFERENCES


Cure CMD has led the design and release of a comprehensive mobile app focused on Congenital Muscular Dystrophy (CMD), designed by a member of our community, for the community.

Cure CMD is the place for all the latest news and updates in CMD care and research. We are dedicated to advancing research toward treatments for CMD, and to improving the lives of affected individuals and their families. By engaging the community at all points in our work — science, outreach, education, and engagement — we ensure our activities are responsive to the community and fulfill the need for work that is exclusively focused on CMD.
Advanced Practice Providers’ Perspectives on Optimal Multiple Sclerosis Management

In a NeurologyLive® Peer Exchange series, experts on the care of patients with multiple sclerosis offer recommendations for selecting and sequencing therapies used to treat patients with relapsing disease.

By Matt Hoffman

OVER THE COURSE OF THE PAST DECADE, the care of patients with multiple sclerosis (MS) has evolved rapidly, with the need for a more comprehensive care model taking hold. Aside from clinical disease progression, this patient population faces many additional challenges brought on by MS, including cognitive and mobility issues among others.

This shift has widened the scope of the MS team, providing a bigger role for the advanced practice providers (APPs) to offer their insight and expertise on patient management. As such, the perspective of nurse practitioners and physician assistants has become more essential to the ongoing conversations surrounding clinical care decisions.

In a recent NeurologyLive® Peer Exchange, a group of APPs came together to offer their views on the care of patients with MS, decisions in therapeutic approach, and several other topics. Moderated by Amy Perrin Ross, MSN, MSCN, APN, CNRN, Neuroscience Program coordinator at Loyola University Medical Center, a portion of the conversation focused on looking at nontherapeutic lifestyle interventions that can be applied to MS care regimens, as well as assessments of what the future holds for patients.

Lifestyle Interventions to Manage MS

Nontherapeutic approaches in MS management can include several interventions, ranging from diet and exercise to vitamin supplementation. These interventions are mostly leveraged as complementary methods, aimed at adding value to the benefit derived from a given patient’s disease-modifying therapy (DMT) regimen.

Specifically, Patricia Melville, MSN, MSCN, RN, NP-C, a nurse practitioner at the Multiple Sclerosis Comprehensive Care Center, Stony Brook Neurosciences Institute, noted the importance of addressing diet in patient conversations. Although the topic often comes up several times over the course of a patient visit, she explained that it can be tricky to navigate.

“There is no scientifically validated diet that we can speak to our patients about [adopting],” Melville said. “What I generally recommend is that they eat a healthy, well-balanced, and sensible diet; eliminate—or at least minimize—proinflammatory foods such as red meat; increase fruits, vegetables, [and] whole fiber; and minimize processed foods and…foods high in sugar and…salt. Hydration is critically important. Many of our patients, particularly if they have bladder problems, will limit the number of fluids that they take in.”

She added that, inevitably, these conversations often lead to discussion about vitamin D intake. Its role in the immune system is apparent. Thus it is important to make patients aware of the
need to measure their level of vitamin D and how they can boost their diet with it through food or a supplement, which may be prescribed occasionally. Stephanie Agrella, PhD, APRN-BC, a nurse practitioner specializing in MS at Central Texas Neurology Consultants, agreed, adding that she often has discussions about the Mediterranean diet and its cardiovascular benefits.

“Then maybe touching on some of the research regarding more of an anti-inflammatory diet is another discussion that we can talk about,” Agrella said. “I also highlight vitamin D and the importance of it, not only in the immune system’s ability to function, but also in its effects that could potentially happen in the setting of MS. Highlighting the fact that this is something they have control over then motivating them to take that control can be helpful for them.”

Exercise is another lifestyle facet in MS that is often brought into patient conversations. Christen Kutz, PhD, PA-C, director of research and head of the Huntington’s Disease Clinic at Colorado Springs Neurological Associates, pointed out that most patients are aware of the need for exercise. But emphasizing its importance in increasing their strength and balance, helping prevent falls, and improving spasticity is worthwhile.

“Potentially, it can even improve bowel or bladder function, it can help with fatigue, and it can help with mood,” Kutz said. “As far as what exercise we advise, that oftentimes depends on the patient’s physical and cognitive abilities, but we have a lot of patients that enjoy yoga or tai chi, just being outside walking, swimming, biking, or hiking. I have one patient that likes to do Zumba videos online. Whatever they find enjoyable that helps with their overall health and well-being is good.”

Ultimately, even something is better than nothing when it comes to exercise, according to Bryan Walker, MHS, PA-C, a physician assistant in the Department of Neurology at Duke University School of Medicine. “That’s where I tell my patients to start off—with getting up and walking around their home. Even if it’s with an assisted device, or a walker, it’s going to be better than just sitting there not doing anything,” Walker said.

For those individuals who have fewer mobility challenges, Walker noted that exercise can be as simple as a 20-minute walk most days of the week. Study findings have suggested that even light housework offers benefits to patients, he added. He also expressed his belief in the advantages of activities that work on not only core strength, but balance, flexibility, and stretching.

“To tie back into diet, that’s also important. You are what you eat, and the fuel you put in your tank is going to be important to figure out what type of energy you’re going to have,” Walker said. “There has been a lot of input recently on the MIND [Mediterranean-DASH Intervention for Neurodegenerative Delay] diet, [referring] to Pat’s point earlier. [This involves] avoiding certain things that we know are not great for us and introducing things that are more beneficial and healthier for us. Eating healthily is expensive, but there are ways to do that for every budget. These things are important. When you start to think about…fatigue and cognition, [for example,] there are interventions that patients can [make] themselves to help with both.”

Looking Ahead at Managing MS

As the field of MS care advances toward the ultimate goal of offering precision intervention, the integration of a more holistic approach is essential. Incorporating facets of care such as nonpharmacologic interventions in diet, exercise, physical and occupational therapy, and neuropsychiatric care should be considered. Additionally, more investigations into the effect of such strategies and whole-patient approaches will help these efforts bear fruit.

With all of that in mind, no clinician can predict the future evolution of care, but examining the trends over the past few years may lend some insight into at least the near future. Ross asked each member of the panel to “take out [your] crystal ball and think about what the future looks like with MS.”

“The future is looking bright. We have so much research that’s been done just in MS over the past 25 years or more,” Agrella said. “It’s brought us 19 different therapies. We have a variety of different administration options. We have a variety of different mechanisms of actions that we can provide to our patients. As more research is done in the field—specifically looking at those biomarkers, remyelination, neuronal repair, and neuropilament light chains—it will help us expand our knowledge base, likely expand our treatment options, and ultimately benefit our patients’ outcomes.”

Walker agreed, noting that the MS field will likely “borrow” ideas and advances from efforts to address similar demyelinating disorders, particularly regarding the importance of the complete cascade of disease. “We’re going to be rehashing some of the old and maybe tweaking some of what we have now, and we’re going to be looking at what some of the other possible interventions are that could take us to the next step,” he said.

Kutz expressed her desire to further elucidate the root causes of MS to build out a more complete understanding of the disease’s pathophysiology. As for treatments, she is particularly excited about the trials of remyelination agents, the new class of Bruton tyrosine kinase inhibitors, and the potential for cell-based therapies to enter the landscape. For Melville, advancing care for progressive MS offers a particular challenge for the future. The variety in choice of available agents for relapsing disease induces a look into the need for more biomarkers, with the goal of individualizing therapies for specific patients.

“I’m hoping for prevention of damage. Once we identify that the cascade has started, what can we do beyond our current DMTs to hold the disease in its tracks? People are always talking about remyelination and how important that is. I agree that it is, but...if we let axonal transection continue to progress, what are we going to remyelinate?” Ross said. “My hope is that we move along the continuum somewhere in the concept of prevention and what we can do to at least stop this disease in its tracks if not reverse things, with respect to the future. That offers a great deal of opportunity for hope for patients, and that’s incumbent upon us.”

You can view the entire series, Optimal Management of Relapsing Multiple Sclerosis: Advanced Practice Providers’ Perspectives, at www.neurologylive.com/ms-app.
The Historically Fast Progress Made in NMOSD Care

Bruce Cree, MD, PhD, MAS, FAAN, shared his perspective on the history of clinical care for neuromyelitis optica spectrum disorder and the effect generated by 3 recent FDA approvals.

By Matt Hoffman

DESPITE THE MEDICAL COMMUNITY’S AWARENESS of the disease since the 1890s, the treatment of neuromyelitis optica spectrum disorder (NMOSD) only began to evolve—at an almost unprecedented pace—with the discovery of aquaporin-4 in the early 2000s. After just 15 years, the thousands of US patients with the rare disorder have been introduced to 3 novel therapies with high rates of efficacy, beginning with the 2019 approval of eculizumab (Soliris; Alexion Pharmaceuticals).

Very little of the history of NMOSD has been recorded, and a similar level of understanding existed about its pathogenesis and distinction from multiple sclerosis (MS) until the late 1990s. Bruce Cree, MD, PhD, MAS, FAAN, clinical research director at the University of California, San Francisco (UCSF) Multiple Sclerosis and Neuroinflammation Center and professor of clinical neurology at UCSF Weill Institute for Neurosciences, explained that until the early 2000s, NMOSD was frequently misdiagnosed as MS and patients often were treated with therapies that worsened their condition.

To find out more about the history of the clinical care of patients with NMOSD and the effect this recent influx of therapeutic options has had on this population and those providing care, NeurologyLive® inquired further with Cree. He offered his expert insight into the work that has laid the foundation for these recent advances and his perspective on the new therapies.

Q: NeurologyLive®: With 3 new therapies being approved in recent years, how would you describe the current state of care for NMOSD?

The remarkable aspect of this story is that in a relatively short period of time, we’ve gone from a disease that had no proven therapies to a disease that has 3…. Backing it up a little bit, it wasn’t even that long ago that there was an ongoing debate as to whether NMO was a distinct disease entity or not. Now it is clearly recognized as being distinct from MS, [although] it shares some clinical features for sure. It is a central nervous system autoimmune disease, just like MS. But we have learned so much about NMO pathogenesis that has been incredibly informative for drug development.

Q: What aspects of that work have driven the field to this point?

Some of the earliest work began with work that Claudia F. Lucchinetti, MD, had done at Mayo Clinic, where she identified the presence of antibodies and complement within pathological lesions and NMO. That led to some of us thinking that perhaps NMO was a B-cell–mediated disorder where antibodies and complement were involved. [And] that led to the initial treatment with rituximab in a patient with NMO in 2002, [in whom] we saw a remarkable recovery—an almost Lazarus-like treatment response.

Subsequent to that, an antibody that is strongly associated with NMO, the NMO IgG antibody that is directed against aquaporin-4, was identified by Vanda A. Lennon, MD, PhD, and colleagues, also at Mayo Clinic. That was around 2006, and it was the start of our real understanding that NMO was a distinct disorder from MS and that there was a pathogenic antibody involved. Work done by Jeffrey Bennett, MD, PhD, and others demonstrated clearly that this NMO antibody that recognizes aquaporin-4 was pathogenic and caused very similar lesions histopathologically with astrogial injury in animal models. Additional work done later again showed the presence
of complement within these lesions, and then it became increasingly clear that the aquaporin-4 antibody was capable of fixing complement.

That led to the idea that perhaps by complement inhibition, we would be able to have an impact in NMO. Work by many others has also shown that the inflammatory aspect of NMO, which is much more inflammatory than MS, is at least in part mediated by high levels of expression of IL-6. Studies looking at the CSF [cerebrospinal fluid] in patients who had a huge NMO attack showed high levels of IL-6, a proinflammatory cytokine that helps recruit additional inflammatory cells to the central nervous system. This led to the idea that perhaps by inhibiting IL-6 through initially tocilizumab, and now through satralizumab (Enspryng; Genentech), that that might be a strategy for an impact in NMO, as well.

All of this has led to the development of inebilizumab (Uplizna; Horizon), a B-cell depleting antibody therapy; satralizumab, an IL-6 receptor blocker; and eculizumab, a terminal complement inhibitor, [for the treatment of] NMO—and all 3 products work. And not only do they work, but they work incredibly well with respect to therapeutic efficacy, certainly stunningly. All these drugs offer a 70% [and greater effectiveness] on attack reduction, and those kinds of effects are uncommon in medicine. A lot of the time we were excited by relatively small changes, but here all 3 of these drugs have a tremendous clinical effect and therapeutic benefit for patients. It’s gone from a disease that, when I first started my work in NMO 20 years ago, was very difficult to treat [to this]. It was often likened to malignancies of the central nervous system in terms of bad outcomes and was a disease that would cause a lot of blindness, paralysis, and even death. And we’ve gone from that state now to having drugs that work unbelievably well. This is an extraordinarily exciting development for science. It’s the many years of work that have taken us from what was considered by many [to be] an incurable, fatal illness to a disease that now has not 1, not 2, but 3 FDA-approved treatments. It’s really remarkable. There are many, many people whose work has contributed to these products’ development, as well as the basic science and translational science that led to [their] development.

Q: What has been the effect on the day-to-day care of patients? Have these therapies made an impact thus far?

That is an evolving story, for sure….Part of the challenge with drug development in this disease space is that [NMOSD] is a relatively uncommon illness. So getting drugs to patients can be quite a challenge. [It involves] identifying the patients who need treatment, then selecting appropriate treatment for [those patients], and then getting it authorized through an insurance provider.

Now, as exciting and wonderful as it is to have 3 highly effective drugs available, there are, [as I said,] challenges with getting these medications to patients. All 3 drugs are extraordinarily expensive. That is a major barrier to access, not surprisingly. We’re seeing a gradual uptake [in] use of these products, but I think a lot of people who manage MS care are still using empirically derived therapies like mycophenolate mofetil, azathioprine, and rituximab, as well as daily chronic prednisone for the treatment of NMO.…Patients [with a new diagnosis] think they’re going to be offered, …more frequently, the newer treatments, but there are still major barriers of access that have to be overcome.

I personally do think that drugs that have gone through the rigorous of clinical trials [and for which] you can really explain to a patient what the actual efficacy and safety profile is…have a clear advantage over empirically derived off-label therapies [for which] you say, “Well, we think it works, but we don’t really know for sure.” I definitely have a bias in that regard, just generally speaking. If there’s nothing available then…there’s nothing available. And then, of course, you’re going to use whatever you can. When you have FDA-approved drugs that have gone through the process, I think you have to, at the very least, discuss those treatments with your patients and not simply rely on older therapies that have been around for a while that you have more comfort and familiarity with.

Two of the products were also launched during the pandemic. I would say that that has been a major inhibitor because normally when a product is launched, there’s some fanfare around it and you get to hear about it at meetings. That element has simply been missing from this entire experience, and I think that is a challenge. Getting the word out, having clinicians become familiar with the use of the drugs [and] what their ins and outs are, [is important]—each of them has unique features with respect to the route of administration, frequency of administration, and what you need to know about the products to provide them safely. Each of these drugs takes a little bit of effort to get physicians up to speed with them. The fact that all of this occurred during the pandemic has been a real inhibitor in getting that kind of medical education out.

REFERENCES
Tolebrutinib Adds to the Growing Momentum of BTK Inhibitors in MS

By Marco Meglio

IN A PHASE 2B SETTING, tolebrutinib demonstrated dose-dependent reduction of GdE lesions among patients with relapsing-remitting multiple sclerosis (MS) or relapsing secondary progressive MS (SPMS).

In clinical trials that have featured patients with relapsing MS (RMS), SPMS, and primary progressive MS (PPMS), Sanofi's tolebrutinib has become a well-traveled investigational agent in the MS pipeline. In December 2020, the National Multiple Sclerosis Society announced that the Bruton tyrosine kinase (BTK) inhibitor would be evaluated in 2 phase 3 trials, GEMINI 1 and GEMINI 2 (NCT04410978; NCT04410991).1

Each study includes 900 participants, aged 18 to 55 years, with various forms of RMS. GEMINI 1, a randomized, double-blind study, is evaluating the safety and efficacy of 60-mg oral tolebrutinib in comparison with oral teriflunomide (Aubagio; Sanofi Genzyme), an already FDA-approved therapy. Patients in the study are randomly assigned to receive either treatment for up to 3 years (FIGURE).

By acting as a BTK inhibitor, tolebrutinib is designed to reduce the activation of B cells, immune cells that play a role in the response that affects the brain and spinal cord in MS. “If you look at the compound itself, you have to look at brain penetration as one aspect. You have to look at specificity and potency as well,” Erik Wallström, MD, PhD, senior vice president and global head of the Neurology Department at Sanofi Genzyme, told NeurologyLive®.

“We do think tolebrutinib is a nice combination of those. It’s not the most selective, but it’s quite selective. It’s one of the most brain penetrant and quite potent. That combination makes us believe that we can achieve levels in the brain that are pharmacologically relevant,” Wallström added.

The trial’s primary outcome measure is the annualized adjudicated relapse rate. Other secondary outcome measures include confirmed disability worsening (CDW), time to onset of CDW, total number of new and/or enlarging T2 hyperintense lesions, and total number of gadolinium-enhancing (GdE) T1 hyperintense lesions. Investigators will also assess quality of life, safety, and laboratory biomarkers of immune and nervous system activity.

There has been a sizeable amount of data on tolebrutinib up to this point. In August, findings from a phase 2b study (NCT03889639) showed that treatment with the agent was well tolerated and had a dose-dependent reduction in the number of new GdE lesions among patients with relapsing-remitting MS or relapsing SPMS. This was a 16-week, double-blind, placebo-controlled, crossover, dose-finding trial that assigned 130 participants to tolebrutinib 5 mg (n = 33), 15 mg (n = 32), 30 mg (n = 33), and 60 mg.2

Cohort 1 received tolebrutinib for 12 weeks, then matched placebo for 4 weeks, whereas those in cohort 2 received 4 weeks of placebo followed by 12 weeks of tolebrutinib. An exponential model showed a dose-response relationship between tolebrutinib and new GdE lesions, which was used to reject the null hypothesis of a flat dose-response curve (test statistic, 2.47; P = .03). The 60-mg dose was the most efficacious, with an observed mean number of lesions of 0.13 (standard deviation [SD], 0.43) compared with 1.03 (SD, 2.50) for placebo. Furthermore, 28 of the 31 participants (90%) who received the 60-mg dose had no new GdE lesions after 12 weeks of treatment, compared with 44 of 59 participants (75%) in the cohort 2 placebo period observed at week 4.

At the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, October 13 to 15, 2021, additional data from the 1-year open-label extension of the phase 2b study were presented. The trial investigators observed no new safety signals among the 125 patients enrolled, and the most common treatment-emergent adverse events were headache (10%), COVID-19 (9%), upper respiratory tract infection (8%), and nasopharyngitis (7%).

“Those data look quite aligned with the phase 2b data, which is good, because we don’t want surprises,” Wallström said. He went on to explain how dose finding has been crucial for tolebrutinib’s development. “An observation that one should keep in mind when looking at BTK inhibitors across the class is that those findings are not trivial. It was [somewhat a case of] ‘You may have surprises.’ With the 60-mg dose, we’re quite confident based on the phase 2 data. We’ve also looked at exposure vs MRI effects.”

Sanofi is conducting multiple trials of tolebrutinib including HERCULES (NCT04411641), a phase 3 study that assesses the drug in up to 1290 patients with nonrelapsing SPMS. PERSEUS (NCT04458051) is another phase 3 study testing the efficacy of the agent in 990 adults with PPMS. Both studies are anticipated to be completed in August 2024.
INDICATION
KESIMPTA 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
Contraindication: KESIMPTA is contraindicated in patients with active hepatitis B virus infection.

WARNINGS AND PRECAUTIONS
Infections: An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections; some have been fatal in patients treated with other anti-CD20 antibodies. The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until resolved.

Consider the potential increased immunosuppressive effects when initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
GRACE

Make KESIMPTA your 1st choice for RMS

POWER
In two Phase 3 pivotal clinical trials vs teriflunomide, KESIMPTA demonstrated:
• Significant reduction in ARR of up to nearly 60% vs teriflunomide (P<0.001)1,2,3
• Profound reduction in mean number of Gd+ T1 lesions per scan of up to 98% (P<0.001)1,2,3
• Superior reduction in mean number of new or enlarging T2 lesions per year of up to 85% (P<0.001)1,2,3
• Significant risk reduction in 3-month CDP of 34% (P=0.002) and 6-month CDP of 32% (P=0.01)12,3

PRECISION
• A targeted and precisely delivered B-cell therapy1,3,4
Safety
• Favorable safety profile similar to teriflunomide as demonstrated in 2 pivotal trials1

FLEXIBILITY
• The first once-monthly (20 mg), SC, B-cell therapy administered at home or anywhere5,6,7,8

Study Design: ASCLEPIOS I and II were 2 identical randomized, active-controlled, double-blind Phase 3 studies in patients with RMS, approximately 40% of whom were DMT treatment naive. Patients were randomized to double-dummy subcutaneous KESIMPTA (20 mg every 4 weeks) or oral teriflunomide (14 mg daily) for up to 30 months. Primary endpoint was ARR. Key MRI endpoints were number of Gd+ T1 lesions, and annualized rate of new or enlarging T2 lesions. A key clinical endpoint was reduction in risk of 3-month CDP. Treatment duration was variable based on end of study criteria. Maximum duration 120 weeks, median duration 85 weeks.
ARR=annualized relapse rate; CDP=confirmed disability progression; DMT=disease-modifying therapy; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging; RMS=relapsing multiple sclerosis; SC=subcutaneous.
*Primary endpoint: relative reduction in adjusted ARR vs teriflunomide of 51% (0.11 vs 0.22) in ASCLEPIOS I and 59% (0.10 vs 0.25) in ASCLEPIOS II.
†Key clinical and MRI endpoints: reduction in mean number of Gd+ T1 lesions per scan vs teriflunomide of 98% (0.01 vs 0.45) in ASCLEPIOS I and 94% (0.03 vs 0.51) in ASCLEPIOS II; reductions in T2 lesions vs teriflunomide of 82% (0.72 vs 4.00) in ASCLEPIOS I and 85% (0.64 vs 4.15) in ASCLEPIOS II; reduced risk in 3-month CDP vs teriflunomide of 34% (15.0 vs 10.9) and 6-month CDP of 32% (8.1 vs 12.0) in pooled populations from both trials.
‡The precise mechanism by which KESIMPTA exerts its therapeutic effects is unknown.
§The initial dose period consists of 20 mg SC doses at Weeks 0, 1, and 2.
¶KESIMPTA Sensoready® Pens must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming, do not shake.
IMPORTANT SAFETY INFORMATION (cont)
WARNINGS AND PRECAUTIONS (cont)

Hepatitis B Virus: Reactivation: No reports of hepatitis B virus (HBV) reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with ofatumumab at higher intravenous doses for chronic lymphocytic leukemia (CLL) than the recommended dose in MS and in patients treated with other anti-CD20 antibodies.

Infection: KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. Perform HBV screening in all patients before initiation of KESIMPTA. Patients who are negative for HBsAg and positive for HB core antibody (HBcAb+) or are carriers of HBV (HBsAg+), should consult liver disease experts before starting and during KESIMPTA treatment.

Progressive Multifocal Leukoencephalopathy: No cases of progressive multifocal leukoencephalopathy (PML) have been reported for KESIMPTA in RMS clinical studies; however, PML resulting in death has occurred in patients being treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. In addition, JC virus infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. If PML is suspected, withhold KESIMPTA and perform an appropriate diagnostic evaluation. If PML is confirmed, KESIMPTA should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to starting KESIMPTA for inactivated vaccines. The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy: For infants whose mother was treated with KESIMPTA during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines. If the B-cell count has not recovered in the infant, do not administer the vaccine as having depleted B-cells may pose an increased risk in these infants.

Injection-Related Reactions: Injection-related reactions with systemic symptoms occurred most commonly within 24 hours of the first injection, but were also observed with later injections. There were no life-threatening injection reactions in RMS clinical studies.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If injection-related reactions occur, symptomatic treatment is recommended.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Fetal Risk: Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose.

Most common adverse reactions (>10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions.

Please see additional Important Safety Information on the previous page and Brief Summary of full Prescribing Information on the following pages.

KESIMPTA, the KESIMPTA logo, and SENSOREADY are registered trademarks of Novartis AG.
5.1 Infections
An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections, including serious bacterial, fungal, and new or reactivated viral infections; some of these infections have been fatal in patients treated with other anti-CD20 antibodies. In Study 1 and Study 2 [see Clinical Studies (14) in the full prescribing information], the overall rate of infections and serious infections in patients treated with KESIMPTA was similar to patients who were treated with teriflunomide (51.6\% vs 52.7\%, and 2.5\% vs 1.8\%, respectively). The most common infections reported by KESIMPTA-treated patients in the randomized clinical relapsing MS (RMS) trials included upper respiratory tract infection (39\%) and urinary tract infection (10\%). Delay KESIMPTA administration in patients with an active infection until the infection is resolved.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants
When initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA, consider the potential for increased immunosuppressant effects [see Drug Interactions (7.1) and Clinical Pharmacology (12.2) in the full prescribing information]. KESIMPTA has not been studied in combination with other MS therapies.

Hepatitis B Virus

Reactivation
There were no reports of HBV reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment) and in patients treated with other anti-CD20 antibodies.

Infection
KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients being treated with ofatumumab for CLL (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). HBV screening should be performed in all patients before initiation of treatment with KESIMPTA. At a minimum, screening should include Hepatitis B surface antigen (H BsAg) and Hepatitis B Core Antibody (H BcAb) testing. These can be complemented with other appropriate markers as per local guidelines. For patients who are negative for HBsAg and positive for HB core antibody [H BcAb+] or are carriers of HBV [H BsAg+], consult liver disease experts before starting and during treatment with KESIMPTA. These patients should be monitored and managed following local medical standards to prevent HBV infection or reactivation.

Progressive Multifocal Leuкоencephalopathy
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.

Although no cases of PML have been reported for KESIMPTA in the RMS clinical studies, PML resulting in death has occurred in patients being treated with ofatumumab for CLL (at substantially higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). In addition, JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. At the first sign or symptom suggestive of PML, withhold KESIMPTA and perform an appropriate diagnostic evaluation. Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is confirmed, treatment with KESIMPTA should be discontinued.

Vaccinations
Administer all immunizations according to the labeling. If PML is confirmed, treatment with KESIMPTA should be discontinued.

The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion [see Clinical Pharmacology (12.2) in the full prescribing information].

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy
In infants of mothers treated with KESIMPTA during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered, as indicated, prior to recovery from B-cell depletion, but an assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted.

5.2 Injection-Related Reactions

In Study 1 and Study 2, systemic and local injection reactions were reported in 21\% and 11\% of patients treated with KESIMPTA compared to 10\% and 6\% of patients treated with teriflunomide who received matching placebo injections, respectively [see Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information].

Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection, but were also observed with later injections. Symptoms observed included fever, headache, myalgia, chills, and fatigue, and were predominantly (99.8\%) mild to moderate in severity. There were no life-threatening injection reactions in RMS clinical studies.

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain. Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical studies. The first injection of KESIMPTA should be performed under the guidance of an appropriately trained healthcare professional. If injection-related reactions occur, symptomatic treatment is recommended.

5.3 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 7.7\% of patients treated with KESIMPTA compared to 3.1\% of patients treated with teriflunomide in RMS clinical trials [see Adverse Reactions (6.1)]. Treatment was discontinued because of decreased immunoglobulins in 3.4\% of patients treated with KESIMPTA and in 0.8\% of patients treated with teriflunomide. No decline in immunoglobulin G (IgG) was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

5.4 Fetal Risk

Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail elsewhere in the labeling:

• Infections [see Warnings and Precautions (5.1)]
• Injection-Related Reactions [see Warnings and Precautions (5.2)]
• Reduction in Immunoglobulins [see Warnings and Precautions (5.3)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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.

Approximately 1500 patients with RMS received KESIMPTA in clinical studies. In Study 1 and Study 2, 1682 patients with RMS were randomized, 946 of whom were treated with KESIMPTA for a median duration of 85 weeks; 33% of patients receiving KESIMPTA were treated for up to 120 weeks [see Clinical Studies (14.1) in the full prescribing information]. The most common adverse reactions occurring in greater than 10% of patients treated with KESIMPTA and more frequently than in patients treated with teriflunomide were upper respiratory tract infections, injection-related reactions (systemic), headache, and injection-site reactions (local). The most common cause of discontinuation in patients treated with KESIMPTA was low immunoglobulin M (3.3\%), defined in trial protocols as IgM at 10% below the lower limit of normal (LLN).

Table 1 summarizes the adverse drug reactions that occurred in Study 1 and Study 2.

Table 1: Adverse Reactions in Patients with RMS with an Incidence of at Least 5% with KESIMPTA and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>KESIMPTA 20 mg</th>
<th>Teriflunomide 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Upper respiratory tract infections*</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Injection-related reactions (systemic)</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Injection-site reactions (local)</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Blood immunoglobulin M decreased</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, trachitis.
6.2 Immunoegenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ofatumumab products may be misleading.

Treatment induced anti-drug antibodies (ADAs) were detected in 2 of 914 (0.2%) KESIMPTA-treated patients; no patients with treatment enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient; however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of KESIMPTA.

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

Concomitant usage of KESIMPTA with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with KESIMPTA.

When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of potential additive immunosuppressive effects when initiating KESIMPTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies (see Data).

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to ofatumumab in utero, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA in utero until B-cell recovery occurs [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2) in the full prescribing information].

Following administration of ofatumumab to pregnant monkeys, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans (see Data).

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.

8.2 Lactation

Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3) in the full prescribing information].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of KESIMPTA did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger subjects.

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
U.S. License No.: 1244
KESIMPTA and SENSOREADY is a [registered] trademark of Novartis AG.
T2020-112
Exercise Training and Multiple Sclerosis

In line with the push for more comprehensive care, literature suggests that patients with multiple sclerosis benefit from physical therapy interventions to help manage disease symptoms.

By Robert W. Motl, PhD

**MULTIPLE SCLEROSIS (MS),** an immune-mediated disease of the central nervous system (CNS) with secondary neurodegenerative processes in its pathogenesis, has a prevalence approaching 1 million adults in the United States.\(^1,^2\) MS is clinically characterized by relapses, lesions in the CNS, and progression of neurological disability. Those clinical expressions are brought about by periods of inflammatory demyelination and transection of axons as well as neurodegeneration involving loss of trophic support of neurons. The disease pathogenesis and resulting damage are expressed as dysfunction, such as walking and cognitive impairment, and in symptoms, such as fatigue and depression, that compromise quality of life (QOL) and full participation.

There has been a steadily increasing body of research on the outcomes of exercise training among individuals with MS.\(^3\) Exercise training is defined as planned, structured, and repetitive physical activity undertaken over periods of time with the objective of improving outcomes such as fitness, function, symptoms, and QOL. This paper provides an overview of exercise training and its outcomes, safety, and prescription in MS, and serves as an overview and reference for investigators and clinicians interested in the benefits, safety, and prescription of exercise training in MS.

**Scope of Exercise Benefits in MS**

Consistent evidence exists for the benefits of exercise training in individuals with MS.\(^4,^5\) One recent review provided a quantitative synthesis of 20 randomized controlled trials (RCTs) and reported that exercise training improved muscular and cardiorespiratory fitness in patients with MS.\(^5\) Other meta-analytic reviews have reported that exercise training has been associated with improvements in symptomatic fatigue, depression, pain, and cognition.\(^7-^10\) Some meta-analyses have reported beneficial effects of exercise training on balance and walking function in patients with the disease.\(^11,^12\) An older meta-analysis has reported beneficial effects of exercise training interventions on QOL outcomes among patients.\(^13\)

Importantly, one group of investigators provided a literature review on the topic of exercise as a disease-modifying therapy by first identifying metrics for evaluating disease modification and progression in MS (ie, relapse rate, neurological disability and its progression, brain lesion volume, and neuro-performance outcomes of walking and cognition), and then reviewing evidence for exercise as a disease-modifying therapy (DMT).\(^14\) The evidence indicated that exercise was associated with reduced relapse rate, neurological disability and progression, and lesion volume, and further yielded improved neuro-performance, particularly walking outcomes. Of note, one review of 26 RCTs that included 1295 participants with MS reported relapse rates of 4.6% and 6.3% for exercise and control conditions, respectively; those rates yielded a relative risk of relapse for exercise training of 0.73 compared with control conditions (ie, 27% reduction in relapse rate for exercise training).\(^15\)

Overall, we can classify the evidence regarding exercise training effects on outcomes in MS using the International Classification of Functioning, Disability, and Health (ICF) model (FIGURE).\(^16\) The existing evidence demonstrated a pattern of smaller effects of exercise on outcomes when moving from body structure and function through activity performance. This is logical, as body structure and function represent more proximal outcomes associated with adaptations as a result of exercise itself, whereas activity performance (ie, participation) is a more distal outcome that is likely not the direct result of exercise training. This is consistent with models of exercise and physical activity effects on QOL in aging.\(^17\) There is obviously a need for considerable work in the areas of disease pathogenesis, activities, and participation within the ICF framework for providing a complete picture of exercise in MS.
Safety of Exercise in MS
The safety profile of exercise has been described in a recent review of exercise in individuals with MS, and this is critical for informing decisions and recommendations regarding its safety. To that end, the systematic review focused on adverse events (AEs) reported in RCTs of exercise training in MS. The investigators searched electronic databases for RCTs of exercise training in MS; they calculated the rate of AEs, and the relative risk of AEs for exercise training versus control. Twenty-six studies were reviewed that included 1295 participants. The rate of AEs was 1.2% and 2.0% for control and exercise, respectively. The relative risk of AEs for exercise training was 1.67, and the risk of AEs was no different when compared with evidence from the general population of adults who participate in exercise. The most common AEs involved musculoskeletal issues (eg, low back and joint pain) associated with resistance exercise training. This evidence should reduce uncertainty regarding the safety profile of exercise training in MS, and there are current efforts for updating the safety profile of exercise training in MS based on research published over the past 10 years.

Prescription of Exercise in MS
Two primary resources on the prescription of exercise in people with MS have recently been summarized by the National Multiple Sclerosis Society. One set of guidelines was developed based on a systematic literature review of exercise training interventions in MS. The resulting guidelines suggest that patients with MS who have mild or moderate disability should engage in at least 30 minutes of moderate-intensity aerobic activity 2 times per week and strength training exercises for major muscle groups 2 times per week. The aerobic and resistance exercise training can be performed on the same day, but should be separated by 24 hours (ie, not performed on consecutive days). This prescription should yield fitness benefits and possibly reduce fatigue, improve mobility, and improve components of health-related QOL. Importantly, these guidelines have not been formally tested, and require evaluation before broad application, particularly among those who have advanced disability with MS.

The other set of guidelines was developed through a scoping review of existing resources on exercise prescriptions in individuals with MS, stroke, and Parkinson disease (PD) to provide resources that are uniformly recognizable by health care practitioners and patients with these diseases. This paper, in particular, synthesized resources that reported aerobic and resistance training guidelines for patients with MS, stroke, and PD. Regarding MS, the systematic search yielded 10 eligible resources from electronic databases and textbooks or websites of major organizations. Data were extracted (exercise frequency, intensity, time, and type) and synthesized into recommendations per disease. Exercise guidelines for MS consistently recommended 2 to 3 days per week of aerobic training (per session, 10-30 minutes at moderate intensity) and 2 to 3 days per week of resistance training (maximum per session, 1-3 sets of between 8-15 repetitions). The frequency ranges between 2 to 3 days per week and should generally start with 2 days and progress toward 3 days per week over time. The duration of the exercise bouts ranges between 10 and 30 minutes and should gradually progress from 10 to 30 minutes over time. The intensity should be moderate and range between 11 to 13 on the 20-point rating of perceived exertion scale, or between 40% and 60% peak oxygen consumption or peak heart rate. The overall progression should start with increases in either duration or frequency. Progression in intensity should be based on the tolerability of the individual with MS, only after duration and frequency are well tolerated. This harmonizing of exercise guidelines provides a prescriptive basis for health care providers, exercise professionals, and those living with MS regarding disease-specific exercise programming. Importantly, these guidelines still require verification for benefits and safety before their broad application, particularly among those with advanced MS disability.

Summary
Overall, there is increasing evidence for the role of exercise in managing the MS disease pathophysiology, functions, and symptoms and for optimizing QOL and participation outcomes. Further, evidence exists for the safety and prescription of exercise in MS. Nevertheless, there are exciting opportunities for research on exercise and neuroplasticity in MS, as well as a need for developing a strong knowledge base regarding exercise training in patients with advanced stages of the disease. Such research will provide a comprehensive knowledge base for the promotion of exercise by health care providers as an approach for managing MS itself and the many consequences of this disease.

For a full list of references, see the article on NeurologyLive.com
The State of Biomarkers in Multiple Sclerosis

By Torge Rempe, MD; and Tirisham Gyang, MD

__IN THE FIELD OF__ multiple sclerosis (MS) there has been an ongoing search for ideal biomarkers to aid in the diagnosis of MS, prognostication, evaluation for ongoing subclinical disease activity, assessment for evidence of progressive disease, determination of adequate treatment response, and guiding the choice of safe disease-modifying therapies (DMTs). A biomarker should, therefore, ideally correlate with disease activity, progression, and treatment effects. The utility of a biomarker is also determined by its cost effectiveness, safety, practicality, and availability in routine clinical practice. The value of a biomarker is its ability to predict, correlate, and serve as a surrogate for a clinical state or outcome. The relevance of reliable biomarkers has strong clinical implications and affects the timeliness of diagnosis; the selection of safe, personalized, and effective DMTs; and the characterization of the phenotypic profile of a patient with MS.

In this outline, we present a selection of different established and novel biomarkers that are expected to have increasing clinical applications in coming years.

**Laboratory Biomarkers**

**Oligoclonal bands**

The detection of oligoclonal immunoglobulin bands in the cerebrospinal fluid (CSF) by isoelectric focusing on the absence of corresponding bands in the serum indicates an intrathecal production of antibodies. As 2 or more isolated oligoclonal bands (OCBs) are present in more than 95% of persons with MS (PwMS),¹ such presence of isolated OCB has been included in the 2017 modified McDonald diagnostic criteria as a substitute for the criterion of dissemination in time. Further, the absence of isolated CSF OCB has a high negative predictive value for MS.²,³ However, the presence of OCB is not specific to MS⁴ and can be found in a variety of inflammatory (autoimmune and paraneoplastic encephalitides, neuromyelitis optica, systemic lupus erythematosus, neurologic Behcet disease, neurologic Sjögren syndrome) and infectious (herpes encephalitis, neuroborreliosis, neurocysticercosis) central nervous system (CNS) diseases.³ High-positive results (≥10 isolated OCB in the CSF) also have a prognostic value as they have been shown to correlate with higher annualized clinical and radiographic relapse rates.⁵ The clear downside of OCB as a biomarker is that for clinicians to obtain CSF, patients need to undergo an invasive procedure.

**Neurofilament light chains**

Neurofilament light chains (NfLs) are neuronal cytoskeletal components involved in axonal transport and can be detected in the setting of axonal or neuronal damage. Although they are nonspecifically elevated in response to neuroaxonal damage, they are considered a promising surrogate marker for clinical and radiographic disease activity in MS. Even though their concentration is significantly lower in serum compared with CSF (approximately 1:200), NfLs can now be detected and quantified in the serum with the help of ultrasensitive single molecule arrays. Given a good correlation between serum and CSF levels, NfLs have significant potential as a serologic biomarker.⁶-⁸ High and increasing serum NfL levels have been shown to correspond to clinical (Expanded Disability Status Scale [EDSS]) and radiographic evidence of disease activity (number of gadolinium-enhancing lesions, new or enlarging T2/fluid-attenuated inversion recovery [FLAIR] lesions, increased brain and spinal cord atrophy rates).⁹,¹⁰ They can serve as a marker of treatment response with a demonstrated decrease of NfL levels in response to treatment with a variety of DMTs and after autologous hematopoietic stem cell transplantation.⁷,¹¹ Baseline NfL levels are also potential biomarkers of prognostication as PwMS...
with lower NFL baseline levels are less likely to develop disability (EDSS, ≥ 4) and transition to secondary progressive MS.\textsuperscript{12}

Data from phase 3 trials in progressive disease show that high baseline NFL concentrations are associated with higher atrophy rates and disability worsening. Compared with placebo, a significant decrease in NFL has been shown with different DMTs in their respective phase 3 trials for primary progressive (ocrelizumab, fingolimod) and secondary progressive (natalizumab, siponimod) MS. This contrasts with the primary clinical end point, which was not reached with 2 of the trialed medications (natalizumab and fingolimod). This could put into question the clinical value of NFL levels at least as a tool of measurement of treatment response in progressive disease.\textsuperscript{13-17} Nonetheless, the utility of serum NFL as a biomarker appears high and with expected availability in different commercial laboratories, their use in clinical practice will likely become more frequent.

Glial fibrillary acidic protein
Another promising serological biomarker candidate is the astrogial cytoskeletal glial fibrillary acidic protein (GFAP) as a surrogate marker of reactive astrogliosis with good correlations of GFAP CSF and serum concentrations. Higher GFAP serum levels have been shown to be associated with disease severity, duration, and progressive disease course. In particular, GFAP may have potential as a disease severity marker in progressive disease.\textsuperscript{18-20}

Ocular Biomarkers

Ocular coherence tomography
Ocular coherence tomography (OCT) is the most established and promising ocular biomarker in MS. Its clear advantage is its relative cost efficiency and availability, which makes it easy to obtain baseline and repeat assessments in the clinic setting. Retinal nerve fiber layer (RNFL) thinning has been repeatedly shown to be more severe in progressive compared with relapsing-remitting MS (RRMS),\textsuperscript{21-25} and in advanced stages of the disease.\textsuperscript{22} Furthermore, RNFL thinning correlates with clinical scores (EDSS, MS functional composite) as well as atrophy in magnetic resonance imaging (MRI).\textsuperscript{26,27} and is associated with an increased risk of disability worsening.\textsuperscript{28}

Eye-tracking devices
Novel eye-tracking devices also could become a future biomarker as they can detect subclinical efferent dysfunction in both saccades and smooth pursuit that correlates to clinical scores (EDSS, timed 25-ft walk).\textsuperscript{29-31}

Magnetic Resonance Imaging
T2/FLAIR hyperintense lesions and gadolinium-enhanced T1 lesions have been long recognized as an important biomarker for the diagnosis of MS and subsequent monitoring for ongoing disease activity. In the setting of a single clinical attack consistent of a typical MS syndrome, a diagnosis of clinically definite MS can be achieved by radiographic determination of dissemination in space (≥ 2 of the following specific areas of the CNS: periventricular, juxtacortical/cortical, infratentorial, and spinal cord) and time (coexistence of enhancing and nonenhancing lesions or interval development of a new lesion in MRI).\textsuperscript{2}

Central vein sign
The vein located in the center of MS lesions can frequently be determined by MRI, especially in periventricular lesions. Evidence is growing that this “central vein sign” has the potential to be a useful biomarker to distinguish MS lesions from other white matter lesions.\textsuperscript{32}

Paramagnetic rim lesions
Paramagnetic rim lesions are another finding that can help differentiate MS lesions from white matter lesions of a different etiology.\textsuperscript{29} Furthermore, they are a potential biomarker of chronic inflammation with decreased lesion volume shrinkage and increased interval development of T1 hypointensity. Histopathologically, they are the correlate of iron-laden inflammatory myeloid cells located at the rim of chronic demyelinated lesions.\textsuperscript{34}

Spinal cord
Spinal cord MRI can be an important prognostic tool as the presence of spinal cord lesions is associated with a higher MS risk in clinically isolated syndrome and a higher risk for development of MS-related disability.\textsuperscript{35,36} Furthermore, the presence of baseline spinal cord lesions is associated with later development of secondary progressive MS.\textsuperscript{37}

Monitoring
MRI is a sensitive monitoring tool to evaluate for subclinical disease activity and adequate response to DMT. The goal of “no evidence of disease activity” is determined by the absence of 3 measures (NEDA-3): clinical relapses, clinical disability progression, and the radiographic absence of new T2 and/or gadolinium-enhanced T1 lesions. However, the absence of accelerated brain volume loss has been proposed as an important fourth criterion (NEDA-4).\textsuperscript{38} The determination of brain and spinal cord (mean upper cervical cord area) atrophy by segmentation tools has indeed become a common radiographic research metric for progressive MS trials. However, even though volumetric assessments are now commercially available, their utility in clinical practice is still severely limited due to significant noise and a high degree of variability across scanners and segmentation tools.

Guiding Treatment Choice, Safety, and Treatment Effectiveness
More than 20 DMTs are approved for use in different MS phenotypes, and these drugs come with a wide degree of variability in their mechanism of action. When considering DMT options, factors such as efficacy, tolerability, safety, and long-term outcomes are typically assessed. Biomarkers are often employed to determine the safety, biologic effects, and efficacy of DMTs prior to initiation and during therapy.
**John Cunningham virus antibody index**

Natalizumab, a humanized antibody to α4 integrin, prevents the entry of lymphocytes into the CNS and was approved for the treatment of RRMS in 2004. Not long after its approval, an association with progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the John Cunningham virus (JCV), emerged and led to the voluntary withdrawal of the drug from the market in 2005. After careful investigation of PML risk factors, the medication was reintroduced into the market with very clear guidelines to regulate its use. The presence of anti-JCV antibodies, treatment duration longer than 24 months, and prior exposure to immunosuppressive therapy have been identified as significant risk factors for the development of PML with the use of natalizumab and are used for risk stratification. The anti-JCV antibody index has emerged as a biomarker that reliably predicts the risk of natalizumab-associated PML. Hence it is used in clinical practice to guide treatment selection and monitored periodically during natalizumab therapy to mitigate the risk of PML. However, its utility in assessing PML risk with other DMTs such as fumarates, sphingosine-1 phosphate receptor modulators, and anti-CD20 agents is limited, and routine monitoring with these DMTs is overall not recommended.

**Absolute lymphocyte count**

Certain DMTs have been associated with lymphopenia and the absolute lymphocyte count (ALC) serves as a safety biomarker during the use of these treatments. For instance, approximately 17% of patients treated with dimethyl fumarate (DMF) develop grade 2-3 lymphopenia. In PwMS treated with DMF, persistent lymphopenia has been found as a potential risk factor for PML. Therefore, ALC monitoring is necessary in patients receiving DMF to identify those at risk for complications. Other DMTs associated with lymphopenia include fingolimod and other sphingosine-1 phosphate receptor modulators, alemtuzumab, cladribine, and teriflunomide. With some DMTs, lymphopenia may be associated with complications, therefore the ALC is a reliable biomarker in risk stratification before and during therapy.

**CD19 lymphocyte count**

The CD19 lymphocyte count is a biomarker for treatment response in patients treated with B-lymphocyte depleting drugs such as ocrelizumab, rituximab, and ofatumumab, and this test can serve as a biomarker for individualized dosing strategies. Baseline CD19 count has been shown to predict B-lymphocyte repopulation in patients treated with ocrelizumab. Monitoring of the CD19 lymphocytes in these patients can aid in a more individualized dosing approach through determination of individual B-lymphocyte repopulation rates and detection of early repopulation.

**Neutralizing antibodies**

Natalizumab, interferon β, and rituximab therapies have been associated with neutralizing antibodies (Nabs) in a subset of patients treated with these medications. The incidence of persistent antinatalizumab antibody is reported to be about 6% and associated with suboptimal clinical response and persistent infusion reactions. Neutralizing antibodies against interferon β have also been recognized as a factor that leads to poor efficacy. Evaluating for Nabs in patients treated with these DMTs may be relevant, as this test serves as a biomarker for efficacy and safety.

**Closing Remarks**

Biomarkers have strong clinical significance and are relevant in the diagnosis, prognostication, treatment selection and response, and safety monitoring in MS management. It is critically important for clinicians to understand how to utilize the currently available biomarkers to enhance clinical care and optimize the long-term outcomes of PwMS. Further research is ongoing to discover and develop novel biomarkers in multiple sclerosis.
Explore MS Website

Managing the neuroinflammation of today may help slow the irreversible neurodegeneration of tomorrow.

Visit the MS website to explore early MS neuropathology, disease progression, and patient perspectives through interactive tools that span the spectrum of MS.

Truths and Myths of MS
Challenge your understanding of MS in this game that includes questions on the diagnosis, management, and some needs of patients with MS.

Disease Progression in MS
Explore this case example of RRMS illustrating how early neuroinflammation may progress to irreversible neurodegeneration and clinical disease progression over time.

Immunoglobulins in MS
View this PDF to learn about the role of immunoglobulins in patients with MS.

Mechanism of Disease in MS
Explore how autoreactive immune cells trigger early neuroinflammation in MS.

MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.