Neurosurgery and Parkinson Disease
Past, Present, and Future of Deep Brain Stimulation

BY ATOM SARKAR, MD, PHD

Magnetic Resonance’s Impact on Diagnosis, Prognostication, and Therapeutic Approaches in Neuromuscular Disorders
BY KENNETH BENDER, PHARMD, MA

A Critical Evaluation of Disease-Modifying Strategies in Parkinson Disease
BY CHARBEL MOUSSA, MBBS, PHD; FERNANDO PAGAN, MD; AND YASAR TORRES-YAGHI, MD

Obstructive Sleep Apnea: Stopping the “Loud Killer”
BY WILLIAM H. NOAH, MD

Evaluating Spinal Muscular Atrophy in the Era of Telehealth
Cure Connections

CLINICAL VIEWPOINT
Income and Education: Predicting Telehealth Use in Parkinson Disease
WITH JAMES BECK, PHD
*Screening and monitoring should be performed before, during, and after treatment.

**INDICATION**
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.

**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**
- 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. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
Proven efficacy across key clinical and MRI endpoints

In the pivotal CLARITY, Phase III, randomized, placebo-controlled trial, MAVENCLAD demonstrated efficacy across the following endpoints:

**ARR (primary endpoint)**

<table>
<thead>
<tr>
<th>MAVENCLAD (n=433)</th>
<th>Placebo (n=437)</th>
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</thead>
<tbody>
<tr>
<td>0.14</td>
<td>0.33</td>
</tr>
<tr>
<td>58%</td>
<td>vs placebo</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
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**EDSS PROGRESSION**

<table>
<thead>
<tr>
<th>MAVENCLAD (n=433)</th>
<th>Placebo (n=437)</th>
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<tr>
<td>0.33</td>
<td>vs placebo</td>
</tr>
<tr>
<td>33%</td>
<td>P=0.05 (nominal)</td>
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</table>

**TI-Gd+**

<table>
<thead>
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<th>MAVENCLAD (n=433)</th>
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</thead>
<tbody>
<tr>
<td>0.67</td>
<td>vs placebo</td>
</tr>
<tr>
<td>0</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

**ACTIVE T2**

<table>
<thead>
<tr>
<th>MAVENCLAD (n=433)</th>
<th>Placebo (n=437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>vs placebo</td>
</tr>
<tr>
<td>0.67</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

MOST COMMON (>20%) ADVERSE REACTIONS IN CLARITY

<table>
<thead>
<tr>
<th>MAVENCLAD (n=440)</th>
<th>Placebo (n=435)</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>
</tbody>
</table>

Other adverse reactions reported in <10% of patients included nausea, back pain, arthralgia and arthritis, insomnia, bronchitis, hypertension, fever, and depression.

**WARNINGS AND PRECAUTIONS (CONTINUED)**

- **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 patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.

**See more efficacy, safety, and dosing information at MAVENCLAD.com/hcp**

ARR: annualized relapse rate; CLARITY: CLAdRibine Tablets treating multiple sclerosis orally; EDSS: Expanded Disability Status Scale; HR: hazard ratio; T1-Gd+: T1 gadolinium-enhanced.
IMPORTANT SAFETY INFORMATION (CONTINUED)

- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin 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 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 parenteral 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. Acute short-term therapy with corticosteroids can be administered.

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 Brief Summary of full Prescribing Information, including boxed WARNING on the following pages.

Visit MAVENCLAD.com/hcp to learn more about this short-course oral 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 malignancies 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 (5.1)]

**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. Malignations 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 [see Contraindications (4), Warnings and Precautions (5.1)]

**INDICATIONS AND USAGE**

MAVENCLAD is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting, primary progressive, and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who are unable to tolerate, 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.

**CONTRAINDICATIONS**

MAVENCLAD is contraindicated:

- in patients with current malignancy [see Warnings and Precautions (5.1)]
- in pregnant women and in women 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)]

**WARNINGS AND PRECAUTIONS**

**5.1 Malignancies**

Treatment with MAVENCLAD may increase the risk of malignancy. In controlled and extension clinical trials worldwide, malignancies occurred more frequently in MAVENCLAD-treated patients (19 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, cervical carcinoma 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 [2.1 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 17 events per 100 patient-years [0.91 events per 100 patient-years] calculated from the start of cladribine treatment in Year 3]. The risk of malignancy with reintitiation 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. [see Contraindications (4) and Warnings and Precautions (5.1)]

**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 to avoid pregnancy 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 5% 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 lymphocyte count. Obtain complete blood count (CBC) with differential and platelet count monthly during treatment with MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. [see Warnings and Precautions (5.5)]

**5.4 Infections**

MAVENCLAD can reduce the body’s immune defense and may increase the likelihood of infections. Infections occurred in 19% 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 coccidiodomycosis. 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.

In patients currently receiving immunosuppressive or immunosuppressive 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 1,976 (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 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.

**Herpes Virus Infections**

In 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 (2.6% vs. 1.2%). Serious herpes zoster infections occurred in 0.2% of MAVENCLAD-treated patients. Orientation 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 8 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 time when the patients were not experiencing this degree of lymphopenia. Administer anti-herpetic prophylaxis in patients with lymphocyte counts less than 200 cells per microliter.

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

**Progressive Multifocal Leukenoencephalopathy**

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. PML 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 cladribine, cases of PML with clinical indications, cases of PML have been reported in the postmarketing setting. Obtain a baseline (within 3 months) magnetic resonance imaging (MRI) before 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 6 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 (5.2)], decreases in other blood cell counts and hematological parameters have been reported with MAVENCLAD in 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 decreases in neutrophil counts (cell count below 1,000 cells per microliter) were observed in 3.8% of MAVENCLAD-treated patients compared to 2.8% of placebo patients. Decreases in hemoglobin levels, in general mild to moderate (hemoglobin
80 mg 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 at dosages similar to or higher than the approved MAVENCLAD dosage, serious cases of thrombocytopenia, neutropenia, and pancytopenia (one with documented bone marrow hypoplasia) requiring transfusion and granulocyte-colony stimulating factor treatment have been reported [see Warnings and Precautions (5.8) 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 5- to 10-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)]. 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, jaundice, 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 treatment (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, mucus membrane ulceration, throat swelling, vescio, 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 (5.3).
- 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

7. Drug Interactions With MAVENCLAD

7.1 Immunomodulatory, Immunosuppressive, or Myelosuppressive Drugs

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 (5.4)].

7.2 Interferon Beta

Concomitant use of MAVENCLAD with interferon beta did not change the exposure of cladribine to a clinically significant effect; however, lymphopenia risk may be increased [see Warnings and Precautions (5.3)].

7.3 Hematotoxic Drugs

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)].

7.4 Antiviral and Antiretroviral Drugs

7.5 Potent ENT, CNT, and BCRP Transporter Inhibitors

7.6 Potent BCRP and P-gp Transporter Inducers

7.7 Hormonal Contraceptives

Prevention or Management: Women using systematically 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 (5.3)].

Data

Animal Data
When cladribine was administered intravenously (0, 0.5, 1.5, or 3 mg/kg/day) to pregnant mice 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, 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, 0.5, 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) [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 8) [see Clinical Pharmacology (12.3)].

17. PATIENT COUNSELING INFORMATION

Advising 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, infections, 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.

MAVENCLAD® (cladribine) tablets, for oral use

Distributed by:

EMD SERONO, Inc.
One Technology Place
Rockland, MA 02370

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Neurology and Parkinson Disease: Past, Present, and Future of Deep Brain Stimulation

BY ATOM SARKAR, MD, PHD

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PEOPLE IN THE NEWS

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Raising Awareness and Improving Education

**EVEN FOR A CONDITION** as well-known as Parkinson disease (PD), the importance of raising awareness is critical. This is why awareness campaigns such as PD Awareness Month, celebrated annually in April, are essential to recognize. Increased attention can remind those who are already aware and can lead to the education of those who are otherwise naïve. In addition, the downstream effects of those efforts can improve the funding for the research and development of novel therapies.

Although the PD community has been fortunate to have an existing gold standard therapy in levodopa for decades, no treatment can serve as a single solution, so challenges remain. Additional therapeutic options provide the treating physicians and their patients new ways to approach PD management, which in turn improves clinical care.

For this reason, this month’s issue of *NeurologyLive®* has a special focus on PD care, with a range of content covering the field’s ongoing conversations and outlooks. This issue was put together with the insight and guidance of guest editor-in-chief Jill Giordano Farmer, DO, MPH, assistant professor of neurology, and director, Parkinson’s Disease & Movement Disorder Program, Global Neurosciences Institute, who notes the significance of stopping to take in the freshness of spring this month and to allow it to remind us of the bright future ahead.

The cover story on page 28, from Atom Sarkar, MD, PhD, takes an in-depth look at the gains that have been made in neurosurgery tactics for PD treatment and the impact that deep brain stimulation has had on patients. The field has come a long way since its inception, and these leaps in the past half century have positioned neurologists and neurosurgeons to make great advances in care strategies in the near future.

These gains in surgical approaches to PD must be paired with pharmacologic developments as well, a topic that Charbel Moussa, MBBS, PhD; Fernando Pagan, MD; and Yasar Torres-Yaghi, MD, assess in their feature story on page 51. The challenge of overcoming the efficacy of levodopa in this process of development has held up a number of disease-modifying therapies, and this trio evaluates the work that must be completed in biomarker identification and translational science to surpass this roadblock. One such study that is ongoing in advanced PD is explored on page 46.

In addition to PD, this issue also covers a number of other areas of interest, including a feature on page 48 that explores how magnetic resonance imaging and magnetic resonance spectroscopy has led to innovations in the diagnosis, prognosis, and therapeutic approach to neuromuscular diseases. As well, our coverage of the latest science and data in multiple sclerosis that were presented at the ACTRIMS Forum 2021, a clinical assessment of the potential of the interleukin-6 pathway in neuromyelitis optica spectrum disorder, and more are included in this month’s issue.

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 senior editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.

Mike Hennessy Sr
Chairman and Founder MJH Life Sciences™
FROM THE EDITOR

Stop to Smell the Tulips: Parkinson Disease Awareness Month

APRIL IS PARKINSON DISEASE (PD) AWARENESS MONTH, and I have always loved that it secured that spot on the calendar. The metaphor of spring and the symbol of the tulip are not lost on the clinicians who care for patients with PD and those who live with them. This April and this spring is even more symbolic as we come out of a year-long freezing episode that disrupted everyone involved in PD care. We know that coronavirus disease 2019 (COVID-19) has wreaked havoc on the PD community—uprooting routines, forcing isolation—and although having PD doesn’t increase the risk of contracting COVID-19, we know it increases the risk of a more significant clinical course. Results of a study of 358 people with PD showed those who had a higher COVID-19–related stressor load experienced more PD symptoms, and this effect was mediated by the degree of psychologic distress. Almost half (46.6%) of individuals with PD were less physically active since the pandemic began, and reduced physical activity correlated with worsened PD symptoms. Symptoms that worsened the most were rigidity, fatigue, tremor, pain, and concentration. Presence of neuropsychiatric symptoms (eg, anxiety and depression) before the pandemic, as well as cognitive dysfunction and several personality traits, predicted increased psychologic distress during the pandemic.1

It has been hard. But looking ahead, as spring is blossoming, we can also take a nice deep breath and look at the changes that, although born out of necessity, can now be enjoyed as a convenience. The virtual world has much to offer and going forward when it is not a requirement but an option, will afford much more access more readily and easily to specialists, to community resources, and to PD education. Telemedicine is changing the landscape of medicine. According to the Centers for Disease Control and Prevention’s data, the 154% increase in telehealth visits during the pandemic compared with the same period in 2019 is a direct correlate to telehealth policy changes and public health guidance.2 There is proposed legislation to continue these policies going forward. It is widely believed telehealth will continue to be an option for those that prefer it but getting back to face-to-face interactions in the office will also be refreshing. Patient education programs are now available on-demand from the convenience

GUEST EDITOR IN CHIEF

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Jill Giordano Farmer, DO, MPH is an assistant professor of neurology at Drexel University School of Medicine in Philadelphia, Pennsylvania and director of the Parkinson’s Disease & Movement Disorder Program at Global Neurosciences Institute (GNI) in New Jersey. She is board certified in neurology.

As the first movement disorder specialist with GNI, Farmer has developed a comprehensive movement disorder program to address medical management, surgical management, and rehabilitation strategies for patients with Parkinson disease and other movement disorders.

Farmer has developed clinics for botulinum toxin therapy to treat dystonia and spasticity, as well as deep brain stimulation to manage Parkinson disease, essential tremor, and dystonia. Farmer was also the first movement disorder specialist in New Jersey to use Duopa, the newest surgical intervention for Parkinson disease.

In 2019, Farmer was elected president of the Philadelphia Neurological Society and also coordinates the Delaware Valley Regional Movement Disorder Meeting.

Read more about the latest clinical news and treatment updates in Parkinson disease at NeurologyLive.com.
of wherever you want to be, but we are all looking forward to the community and comradery of doing these in person again soon. What is nice is that we will have the option of both, and options expand our experiences. As this month of awareness awakens our focus on the future and what is to come, again, the PD community does not disappoint. There are close to 3000 clinical trials investigating the treatment and pathology of PD currently. There is a shift of focus from treating the symptoms of the disease to figuring out how to actually alter the pathology to change the clinical course and modify it for the better through various established and novel mechanisms.

In this issue, we will look at 2 opportunities on the horizon. Deep brain stimulation (DBS) has been around since the 1970s, and currently about 150,000 people are implanted with a DBS device. In the past few years, the technology of DBS has entered a renaissance period. In this space, Medtronic has had to make room for Boston Scientific and Abbott device companies. This increased diversity has led to smaller rechargeable batteries, the utilization of different modes of stimulation through voltage or current, and the ability to precisely target the area of the brain with directional leads. In this issue’s cover story, Atom Sarkar, MD, PhD, director, functional neurosurgery, Global Neuroscience Institute, explores what is on the horizon not just through the hardware of the device but the software with sensing and reactive technology to adapt to changes in the brain that precede symptom return and modulate the stimulation accordingly.

The changes coming to the surgical interventions are matched by changes coming to the medical management. Smaller pumps that can deliver continuous infusion of carbidopa/levodopa just under the skin, without a procedure, are currently in phase 3 clinical trials. While the symptomatic improvement this can bestow on patients is exciting, it still lacks the ability to modify the disease course in some way. That is the next frontier in research and the focus of Charbel Moussa, MBBS, PhD; Fernando Pagan, MD; and Yasar Torres-Yaghi, MD, of Medstar Georgetown University Hospital, in their feature that considers the pipeline of disease-modifying therapies and the hope they hold.

While we are all experiencing fatigue—COVID-19 fatigue, caregiver fatigue, clinician fatigue—we are no strangers to it. As a community, patients with PD and those that care for them are resilient to fighting this fatigue, and the beauty of Parkinson Awareness Month is that it gives us a rejuvenating pause during the spring thaw, and reminds us to stop and smell the tulips, and with a deep breath of fresh air, keep moving forward.

REFERENCES
FDA Provides Feedback on NurOwn ALS Therapy, Requests More Data
By Marco Meglio
Following a review of the current clinical phase 3 (NCT03280056) data of BrainStorm Cell Therapeutics’s NurOwn (autologous mesenchymal stromal cells secreting neurotrophic factors) amyotrophic lateral sclerosis (ALS) therapy, the FDA concluded that the current level of data does not cross the threshold of substantial evidence to support a biologics license application (BLA), according to an announcement from the company.1

The FDA did advise that this recommendation does not preclude BrainStorm from proceeding with a BLA submission.

In November 2020, the company announced topline results from its phase 3 trial, demonstrating that treatment with NurOwn was generally well tolerated in a population of patients with rapidly progressing ALS. While showing a numerical improvement in the treated group compared with placebo across the primary and key secondary end points, the trial results did not reach statistical significance.2

“BrainStorm will first consult with principal investigators, ALS experts, expert statisticians, regulatory advisors, and ALS advocacy groups to assess the benefit/risk of a BLA submission before making a final decision,” Chaim Lebovits, chief executive officer, BrainStorm Cell Therapeutics, said in a statement.1

Using historical clinical trial data and NurOwn phase 2 data, investigators used improvement of 1.25 points per month in the post-treatment Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) slope as the primary efficacy end point, powered on assumed treatment response rates of 35% on NurOwn vs 15% on placebo.7

Following the conclusion of the trial, the primary end point was achieved in 34.7% of participants in the NurOwn group compared with 27.7% for placebo (P = .453), demonstrating that the NurOwn treatment about met the expected 35%, but the high placebo response exceeded placebo responses observed in contemporary ALS trials.

“Many of us with longstanding experience in ALS therapy development agree that there was evidence of benefit from NurOwn cell therapy and hope that there will be an opportunity for further assessment of this modality in ALS,” Robert Brown, DPhil, MD, director, Program in NeuroTherapeutics, University of Massachusetts Medical School, said in a statement.1

The secondary efficacy end point, measuring mean change in ALSFRS-R total score from baseline to week 28, was –5.52 with NurOwn compared with –5.88 for placebo, a difference of 0.36 (P = .693).

Of note, in a subgroup of patients with early disease based on ALSFRS-R baseline score, the treatment demonstrated a clinically meaningful response across the primary and key secondary end points and remained consistent with pretrial and data-derived assumptions. In this subgroup, 34.6% and 15.6% of responders met the primary end point definition on NurOwn and placebo, respectively (P = .288).

In January, BrainStorm announced that patients who completed the recently conducted phase 3 trial and met specific eligibility requirements can be admitted to the newly initiated Expanded Access Program (EAP). The company’s development of the EAP was in partnership with the FDA and will give patients less severely affected by ALS, as measured by the ALSFRS-R, highest priority to receive the treatment.3

“We learned a lot about the efficacy and safety of NurOwn in people with ALS in this well-conducted trial. We also learned some of the challenges with the use of ALSFRS-R at the lower end of the scale. Additional discussions with the community and sharing all the data in a peer-reviewed publication are critical next steps,” Merit Cudkowicz, MD, chief of neurology and director of the Sean M. Healey & AMG Center for ALS, Massachusetts General Hospital, said in a statement.1

New Agent Approved for Those With DMD Amenable to Exon 45 Skipping
By Matt Hoffman
The FDA has approved casimersen (Amondys 45; Sarepta Therapeutics) for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed mutation amenable to exon 45 skipping.4

The ESSENCE trial (NCT02500381; also known as Study 4045-301)—a placebo-controlled confirmatory trial to support the Sarepta product’s approval—is ongoing and expected to conclude in 2024. As part of its accelerated approval pathway, casimersen’s continued approval is contingent on the demonstration of a clinical benefit in confirmatory trials. Notably, the antisense oligonucleotide therapy has met the full statutory standards for safety and effectiveness and is, therefore, not considered investigational or experimental.

“This is an important day for Sarepta and, far more importantly, for the patients who we serve. After years of scientific commitment, investment, and development, the approval of Amondys 45, Sarepta’s third approved RNA therapy, offers treatment to the 8% of the DMD community who have a confirmed exon 45 amenable mutation,” said Doug Ingram, president and chief executive officer of Sarepta, in a statement. “Along with our other approved RNA therapies, we can now offer treatment options for nearly 30% of Duchenne patients in the United States. And our commitment to bring therapies to the greatest percentage of the DMD community as soon as possible continues.”

Kidney toxicity, including potentially fatal glomerulonephritis, has been observed after the administration of some antisense oligonucleotides, but such toxicity has not been observed in clinical studies of casimersen to date. It is advised that kidney function should be monitored in patients receiving the drug.

In the clinical trial of casimersen, the most common adverse events observed in at least 20% of patients treated, and at least 5% more frequently than in the placebo group, were upper respiratory tract infections (casimersen: 65%; placebo: 55%), cough (casimersen: 33%; placebo: 26%), fever (casimersen: 33%; placebo: 23%), headache (casimersen: 32%; placebo: 19%), joint pain (casimersen: 21%; placebo: 10%), and pain in mouth and throat (casimersen: 21%; placebo: 7%).

For a full list of references, see the article on NeurologyLive.com.
“Decades of research and commitment have fueled and now accelerate our progress toward new treatments for Duchenne,” said Marissa Penrod, founder, Team Joseph, and a parent of a teenager with DMD. “The extraordinary diligence and persistence of the Duchenne community—patients and families, clinicians and researchers—have led us to today’s approval, where we now have exon-skipping treatments for almost a third of those with Duchenne.”

The agent is part of Sarepta’s phosphorodiamidate morpholino oligomer platform. The company noted in its announcement that the indication was based on the observed statistically significant increase in dystrophin production in skeletal muscle in clinical study of the therapy.

Sarepta made its new drug application (NDA) filing in June 2020 and requested a priority review, which was granted by the FDA. The NDA included data from the casimersen arm of the ESSENCE study, which is a global, randomized, double-blind, placebo-controlled phase 3 study evaluating the efficacy and safety of casimersen in patients amenable to skipping exon 45.

An interim analysis from ESSENCE, announced in March 2019, implied that treatment was associated with a statistically significant increase in dystrophin production, as measured by western blot in patients who received casimersen compared with baseline and placebo. The study is ongoing and remains blinded to collect additional efficacy and safety data.

In ESSENCE, patients amenable to exon 45 skipping were randomized to receive a once-weekly intravenous infusion of casimersen dosed at 30 mg/kg (n = 27) or placebo (n = 16) for 96 weeks. The interim analysis was performed on data from 2 biopsies of the bicep muscle, one at baseline and one on treatment at week 48. Key findings from the interim analysis showed mean dystrophin protein increased to 1.736% of normal compared with a mean baseline of 0.925% of normal (P <.001) in the casimersen arm. Additionally, there was a statistically significant difference in the mean change from baseline to week 48 in dystrophin protein between the casimersen-treated arm and the placebo arm (P = .009).

As well, there was a statistically significant positive correlation between exon 45 skipping and dystrophin production (Spearman rank correlation = 0.635; P <.001). In March 2019, 22 patients receiving casimersen were tested for increased exon-skipping mRNA using reverse transcription-polymerase chain reaction, and all 22 of them displayed an increase in skipping exon 45 (P <.001) above baseline levels, representing a 100% response rate.

The FDA’s decision was based on results from the company’s latest randomized controlled clinical trial, which were presented publicly at the American Heart Association’s virtual International Stroke Conference, March 17-19, 2021.

The AI-powered therapy is based on biological insights retrieved from brainwaves, using proprietary machine learning algorithms that translate into a frequency-tuned low-intensity electromagnetic field (ELF-EMF). It is delivered through a cloud-connected wearable device, the noninvasive BQ System, and is designed for scalable and portable treatment with the flexibility to be accessed at home.

Excited with the FDA’s decision, Yotam Drechsler, chief executive officer and cofounder, BrainQ, wrote in a statement, “Stroke is a debilitating condition with limited recovery options, creating a huge unmet need in the United States. COVID-19 has only made things worse by limiting patients’ access to treatment facilities. FDA breakthrough designation is an important milestone in our mission to reduce disability for these patients and treat them in the comfort of their homes.”

Not only does the designation allow for an expedited process for developmental plans and premarket clearance, but it gives BrainQ access to the new Medicare Coverage of Innovative Technology (MCIT) pathway. The MCIT role will provide national Medicare coverage as early as the same day as the FDA’s market authorization for a breakthrough device, with coverage lasting for 4 years. This coverage pathway offers beneficiaries nationwide predictable access to new, breakthrough devices to help improve their health outcomes.

“FDA breakthrough device designation provides hope for the millions of stroke survivors who will be eligible for BrainQ’s therapy,” said Eilon D. Kirson, MD, PhD, a member of BrainQ’s board of directors and previously the chief scientific officer of Novocure, in a statement. “More than half of stroke patients in the United States are covered by Medicare. Breakthrough designation holds the potential to provide immediate access to BrainQ’s therapy for the majority of stroke patients in desperate need of improvement in function and mobility in the coming future.”

The novelty of BrainQ’s investigational treatment lies in the data-driven method it deploys to inform the ELF-EMF frequency parameters. In choosing these parameters, the company’s aim is to select frequencies that characterize motor-related neural networks in the central nervous system and that are related to the disability a patient experiences following stroke or other neurological trauma.
Tumor Necrosis Factor Signaling Inhibition Fails to Prevent or Delay Parkinson Disease

By Marco Meglio

Results from a study published in Neurology provide Class II evidence that tumor necrosis factor receptor 1 (TNF-TNFR1) signaling inhibition is not associated with the risk or age at onset of Parkinson disease (PD).

Lead author Xioying Kang, MPH, BSc, of the Department of Medical Epidemiology and Biostatistics at Stockholm’s Karolinska Institut, and colleagues found that TNF-TNFR1 signaling inhibition was not estimated to affect PD risk (odds ratio [OR] per 10% lower circulating C-reactive protein [CRP], 0.99; 95% CI, 0.91–1.08) or age at onset (0.13 years later onset; 95% CI, –0.66 to 0.92). To the authors’ knowledge, this was the first Mendelian randomization (MR) study to address whether exposure to TNF inhibitors affect PD.

“[The field of] human genetics provides valuable guidance for therapeutic programs because the chances of successful drug development are substantially improved when genetic evidence links a drug’s target to an indication for therapeutic use,” Kang et al wrote. “Hence, our findings should be considered as part of discourse on the repurposing potential of TNF inhibitors for PD prevention and treatment, particularly if/when selective inhibitors of TNF-TNFR1 signaling become available.”

A total of 23 single nucleotide polymorphisms (SNPs) in the vicinity of the gene TNFRSF1a, which encodes TNFR1, the principal effector of proinflammatory signaling following TNF agonism, were present in CRP data derived from genome-wide association studies from the International Parkinson’s Disease Genomics Consortium and 23andMe, Inc (n = 204,402). The effects of TNF-TNFR1 inhibition were estimated for PD risk (cases, n = 37,688; controls, n = 981,372) and age at PD onset (n = 28,568).

Investigators found, however, that genetically induced inhibition of TNF-TNFR1 signaling was predicted to reduce the risk of Crohn disease (OR, 0.75; 95% CI, 0.65–0.86) and of ulcerative colitis (OR, 0.84; 95% CI, 0.74–0.97), but to increase the risk of multiple sclerosis (MS; OR, 1.57; 95% CI, 1.36–1.81). These results were expected, the authors noted.

In secondary analyses, the more liberal linkage disequilibrium (LD) clumping yielded 4 correlated SNPs associated with CRP at false discovery rate-corrected (P < .05), 1 of which was not associated with either white blood cell count (P = .07) or mean platelet volume (P = .95) and was therefore removed. The other 3 variants were associated with all 3 inflammatory markers for secondary MR models.

Using adapted inverse variance weighting methodology to account for correlations among genetic variants, MR estimates based on the 3 SNPs remained consistent with the main results that neither PD risk nor age at onset were predicted to be affected by TNF-TNFR1 blockade.

Kang and colleagues also found that there were no associations of the genotypes of implicated functional variant (rs1800693) with PD risk (OR, 1.00 per TNF-inhibiting allele; 95% CI, 0.98–1.02) or age at onset (0.05 years of increase per TNF-inhibiting allele; 95% CI, –0.13 to 0.24), despite strong associations of this SNP with other inflammatory traits.

Intensive Arm Motor Therapy Improves mRS Scores in Poststroke Patients

By Victoria Johnson

Data from a recent study published in Neurology suggest that intensive arm motor therapy can improve modified Rankin scale (mRS) scores in poststroke patients, although specific motor impairments may be better rehabilitation therapy targets than others.

In their study of 77 patients, the researchers found that the patients’ median mRS score decreased from 3 (interquartile range [IQR], 2–3) to 2 (IQR, 2–3) at 30 days post therapy (P < .0001). The proportion of patients with mRS scores less than or equal to 2 increased from 46.8% at baseline to 66.2% at 30 days post therapy (P = .015). Altogether, mRS score decreased in 24 (31.2%) patients. Patients with a treatment-related mRS score improvement, compared with those without, had similar overall motor gains in Fugl-Meyer motor scale (FM) score (P = .63).

First author Steven C. Cramer, MD, of Ronald Reagan UCLA Medical Center’s Department of Neurology, and colleagues wrote, “We examined results from a trial of intensive rehabilitation therapy targeting the arm that reported body structure/function gains (FM score), here hypothesizing that intensive rehabilitation therapy also improves activities limitations (mRS scores). To further probe this issue, mRS gains were explored in relation to improvements in body structure/function, both at the summary level (change in total FM score) and at the level of specific motor impairments.”

Cramer and colleagues analyzed data from 77 patients at 160 days (SD, 48) poststroke at baseline (mean [SD] age, 62.0 [13.1] years; 29.9% [n = 23] women). By race, the included patients were White (n = 50; 64.9%), Black (n = 18; 23.4%), and Asian (n = 8; 10.4%). Ischemic and intracerebral stroke had been experienced by 66 (85.7%) and 11 (14.3%) patients, respectively. The mean (SD) baseline FM score was 40.6 (8.3) points and increased by 7.5 (5.8) points at 30 days post therapy (P < .0001).

Median mRS score decreased from 3 (IQR, 2–3) at baseline to 2 (IQR, 2–3; range, 1–4) at 30 days post therapy (P < .0001). mRS changes were driven by 5 patients who each experienced a 2-point drop and 19 with a 1-point drop each; however, 50 patients (64.9%) experienced no change and 3 patients (3.9%) each experienced a 1-point increase.

Cramer and colleagues also found that nonsignificant proportions (P = .07) of patients in the telerehabilitation group (17 of 43; 39.5%) and the in-clinic therapy group (7 of 34; 20.6%) had mRS score decreases. mRS score decreases were also similar (P = .73) between patients with ischemic stroke (n = 20; 30.3%) and intracerebral hemorrhage (n = 4; 36.4%).
The researchers found that patients who had an mRS score decrease (n = 24; mRS, 3 [IQR, 3-3.75]) had higher baseline mRS scores than those who did not (n = 53; mRS, 2 [IQR, 2-3]; P = .0002). The likelihood of mRS score decrease was unrelated to the number of days post stroke at study entry (odds ratio [OR], 1.49; 95% CI, 0.3-7.3; P = .62).

The in-clinic an telerehab groups did not differ in the number of study-provided treatment sessions (P = .70) or number of hours at any rehabilitation therapy outside of study procedures (P = .92). The 2 groups also did not differ in the change in the total FM motor score over the same period (P = .63). Change in total FM score was not related to change in mRS score (P = .25) or to the likelihood of a mRS score decrease (P = .70).

Cramer and colleagues found differences in specific motor impairments that improved in patients with mRS improvements vs without. They examined the 4 specific motor impairments with the highest OR of mRS improvement logistic regression analysis and found that together they did predict likelihood of improvement (P = .034). These motor impairments were (1) flexing all fingers at the metacarpophalangeal and interphalangeal joints, (2) full shoulder girdle elevation, (3) no reflex hyperactivity in the arm, and (4) circumcision of the wrist through full range of motion in a smooth manner.

“These findings emphasize the importance of understanding the relationship between changes in activities limitations and loss of body structure/function after stroke. This would be aided by including both types of measures in acute stroke trials and in stroke recovery trials, as has been recommended,” Cramer and colleagues concluded. “Such knowledge would foster a more cohesive system for understanding the benefit of stroke therapeutics, from acute to recovery targets.”

REFERENCE

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Common Migraine Interventions Are Ineffective in Reducing Disease Burden
By Victoria Johnson

Data from a recent study suggest that prior to 2018, when novel calcitonin gene-related peptide (CGRP) antagonists were introduced, preventive treatments for migraine did not greatly reduce its burden on patients.

The majority (70.1%) of patients studied between March 2016 and October 2017 had not used preventive treatments despite having an mean of 9.6 (SD, 5.0) headache days per month. Patients who did use preventive treatments reported a lack of efficacy, leading to poor adherence.

Senior author Richard B. Lipton, MD, director of the Montefiore Headache Center, and colleagues wrote that “high discontinuation rates suggest that the preventive medications being offered during the period of the study did not meet the treatment needs of patients. In addition, the decisions by about half of patients to alter their prescribed treatment plan without consulting their provider can pose substantial health risks...These findings suggest the need for more effective and better tolerated preventive treatment options.”

Lipton and colleagues enrolled 234 patients with episodic (EM) or chronic migraine (CM) who were initiating or changing preventive treatment at 28 US primary care or neurology clinics as part of the real-world, 6-month observational, noninterventional, ATTAIN study (Assessment of Tolerability and Effectiveness in migrAINe Patients using Preventive Treatment).

Of the patients enrolled, 118 had EM (50.4%) and 116 had CM (49.6%). The patients had a mean (SD) age of 41 (12) years at enrollment and 22 (11) years at diagnosis. The majority of patients were women (n = 204; 87.2%) and White (n = 178; 76.1%).

Lipton and colleagues found that 70.1% (n = 164) of patients were treatment naïve, meaning they had not used preventive migraine treatment in the last 5 years, despite having a mean (SD) of 9.6 (5.0) headache days per month. Treatment-experienced patients (n = 70) had a mean 12.4 (7.0) headache days per month.

Patients most commonly used nonsteroidal anti-inflammatory agents as acute medications at baseline (n = 124; 53.0%), followed by acetaminophen-based products (n = 112; 47.9%) and triptans (n = 105; 44.9%). Topiramate was the most common preventive treatment (n = 100; 42.7%), followed by tricyclic antidepressants (n = 39; 16.7%), beta blockers (n = 26; 11.1%), and onabotulinumtoxinA (n = 24; 10.3%).

A majority of patients had a severe Migraine Disability Assessment score, including 110 (67.1%) treatment-naïve and 54 (77.1%) treatment-experienced patients. Similarly, Headache Impact Test scores indicating severe impairment were seen in 145 (88.4%) treatment-naïve and 62 (88.6%) treatment-experienced patients.

Lipton and colleagues also surveyed patients with the Work Productivity and Activity Impairment questionnaire and found that an mean of 53.3% productivity loss was reported by employed patients.

During the study period, 116 patients (49.6%) modified their treatments, either discontinuing preventive treatment (n = 88 modifications; 28.2%) or modifying their pattern of use (n = 224 modifications; 71.8%), often without consulting their doctors.

Avoiding adverse events (AEs) was the primary reason for modification, with 52 patients (59.1%) discontinuing, 37 (41.6%) decreasing frequency or dose, and 29 (33.7%) skipping doses due to AEs. Because of perceived lack of efficacy, 20 patients (22.7%) discontinued, 15 (16.9%) decreased frequency or dose, and 18 (20.9%) skipped doses.

“Recent regulatory approvals for CGRP biologics, a new class of migraine preventive drugs, provide an additional treatment option with favorable efficacy and [AE] profile with substantially lower discontinuation rates in clinical trials compared with other available oral preventive therapies. The rapidity of onset and favorable tolerability of CGRP biologics are attributes that promise to address the considerable limitations of previously available oral preventive options for migraine,” Lipton and colleagues concluded.

REFERENCE

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MIND MOMENTS SPOTLIGHT
Multimedia highlights from our coverage of neurologic disorders

TOP TWEETS

National Headache Foundation @NHF
Check out Jill Dehlin, RN, talking about the Burden of Migraine on @neurology_live @jdehlin #NHF

Rutgers Institute for Health @rutgersifh
IFH Director @XinQiDong spoke with @neurology_live for a new segment of #NeuroVoices about his work on a recently published National Academies report looking at care interventions for people with dementia and their caregivers #IFHResearch #IFHCommunity

Clene Nanomedicine @CleneNano
Our Chief Medical Officer Robert Glanzman discussed our recently presented blinded interim data on CNM-Au8 from the VISIONARY-MS and REPAIR-MS #ClinicalTrials. To learn more, check out a clip from the interview on @neurology_live here:

Northwestern Department of Neurology @NMNeurology
Join Phyllis Zee, MD, PhD (@PhylZee) and Alon Avidan, MD, MPH as they discuss Excessive Daytime Sleepiness on episode one of “Treating Narcolepsy and Excessive Daytime Sleepiness.” via @neurology_live

OHSU Brain Institute @OHSUBrain
A recent study found that a quick and simple postural sway test may be an important tool in identifying patients with mild to moderate #multiple-sclerosis (#MS) at risk of falling via @neurology_live

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EVALUATING DEMENTIA INTERVENTIONS, AREAS OF IMPROVEMENT
XinQi Dong, MD, MPH, director of the Institute for Health, Health Care Policy, and Aging Research at Rutgers University, discussed his recent findings on assessing evidence for dementia care interventions.

VIEW VIDEO neurologylive.com/dementia-intervention

THE VARIABILITY OF CEREBRAL PALSY CARE
Bhooma Aravamuthan, MD, DPhil, assistant professor of pediatric neurology at the Washington University in St Louis, spoke to the insights gleaned from a recent survey she and colleagues conducted.

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COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA
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DATA FROM A RETROSPECTIVE ANALYSIS of a cohort of individuals with neurologic dysfunction suggest that central nervous system (CNS) demyelination persists in prolonged follow-up, despite tumor necrosis factor alpha inhibitor (TNFαi) treatment discontinuation.1

The study’s findings were presented virtually at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2021, February 25-27, by Spencer K. Hutto, MD, clinical fellow in advanced general and autoimmune neurology, Massachusetts General Hospital, and colleagues.

“TNFαi have a recognized association with [CNS] demyelination since the lenerecept trial for the treatment of multiple sclerosis (MS). It remains unclear if the relationship is causal or related to unmasking of an underlying risk,” Hutto and coauthors wrote.

The agents are often used to treat rheumatologic diseases such as rheumatoid arthritis.

The group analyzed data from 21 patients evaluated for neurologic dysfunction during TNFαi use from the Mass General Brigham Research Patient Data registry from January 1998 to August 2020. Patients with a previous CNS inflammatory disorder were not included.

The patients included had a mean age of 44 years (range, 16-68) at first demyelinating event. Most patients were women (n = 20; 95%); 90% (n = 19) were White while 5% (n = 1) were Black and 5% (n = 1) were Hispanic/Latinx. The patients had a median rheumatologic illness duration of 102 months and a mean TNFαi use of 11 months. TNFαis used were adalimumab (n = 10; 48%), etanercept (n = 6; 28%), and infliximab (n = 5; 24%).

More than half of the patients (n = 12; 57%) had new neurologic disease activity over time. Clinical relapse was experienced by 48% (n = 10), with a median of 41 months (range, 12-80) to first relapse. MRI lesion accrual was experienced by 47% (n = 10), with a median of 28 months (range, 3-139) to new lesion or lesions.

TNFαi were discontinued at the onset of demyelinating events in 86% (n = 18) of patients, and 69% (n = 14) were treated acutely with steroids. Ultimately, 42% (n = 9) of patients used MS disease-modifying therapies (DMTs). Hutto and colleagues found that participants in the study had risk factors for MS including obesity (n = 3; 16%), tobacco use (n = 11; 52%), vitamin D deficiency (n = 11; 50%), and family history of autoimmune disease (systemic, n = 15; 71%; CNS demyelination, n = 4; 17%).

Hutto and colleagues also found that retrospectively, 19% (n = 4) of patients had remote transient neurologic dysfunction, and 10% (n = 2) had prior MRI scans consistent with radiologically isolated syndrome. MRI surveillance was continued for a median of 26 months (range, 0-147), with 52% (n = 11) of patients surveilled for more than 2 years. Mean follow-up duration was 28 months (range, 0-71).

Cerebrospinal fluid pleocytosis was present in 22% (n = 5), elevated protein in 33% (n = 7), and oligoclonal bands in 43% (n = 9). The authors found that tests for antibodies against myelin oligodendrocyte glycoprotein in 10% (n = 2) of patients and against aquaporin in 38% (n = 8) of patients were all negative.

All told, 22% (n = 5) of patients made a complete recovery, while 67% (n = 14) made a partial recovery, 5% (n = 1) had no recovery, and 5% (n = 1) experienced disease progression. One death (5%) occurred, unrelated to demyelination. The median modified Rankin score (mRS) at last follow-up was 1 (range, 0-6), with 79% (n = 17)
of patients achieving an mRS score less than 2. Ultimately, 50% (n = 11) of patients were diagnosed with MS, 40% (n = 8) with TNF-α-induced demyelination, and 10% (n = 2) with “possibly either” diagnosis. Revised 2017 McDonald criteria were met by 65% (n = 14) of patients at onset and by 75% (n = 16) by last follow-up.

Hutto and colleagues analyzed subgroups and found that 75% (n = 16) of patients who rechallenged or continued on TNFα relapsed. Of those starting a DMT after the index event, 50% (n = 11) had evidence of continued disease activity, with 33% (n = 7) experiencing clinical relapses and 50% (n = 11) having accrual on MRI. More than half (n = 12; 56%) of patients off medications from onset, either by discontinuing TNFαi or not starting DMTs, had subsequent evidence of continued disease activity, with 44% (n = 9) experiencing relapses and 44% (n = 9) having MRI lesions.

“In patients with CNS demyelination while on TNFα, continued evidence of disease activity was common despite TNFα discontinuation over a period of prolonged follow-up,” Hutto and colleagues concluded.

REFERENCE
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). Delays 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.
FOR PATIENTS WITH FIRST SIGNS OF PROGRESSION IN RMS AND ACTIVE SPMS†

STAY AHEAD OF PROGRESSION WITH MAYZENT®
(siponimod)

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 S1P 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.8†‡

"Patients in EXPAND had a mean EDSS score of 5.4."8
"From a preplanned interim analysis of an open-label extension study."8
"6-month CDP, ARR, and SDMT were exploratory end points and assessments of efficacy measurements, respectively, in the EXPAND extension study."8

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

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,
• 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 unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization.

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

Bradycardia 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 Ia or Class III anti-arrhythmic drugs

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

**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-photoctherapy 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 (S1P) receptor modulator. Such events have not been reported for patients treated with MAYZENT in clinical trials. If patients develop any unexpected neurological or psychiatric symptoms, a prompt evaluation should be considered. If PRES is suspected, MAYZENT should be discontinued.

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

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

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

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

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

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

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


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East Hanover, New Jersey 07936-1080 ©2021 Novartis 2/21 MZT-1400690
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 or not MAYZENT should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus
Patients with a history of uveitis and patients with 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 myocardial infarction, 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 I second degree AV-block or higher grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [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 similar 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 require 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 I 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- and second-degree (Mobitz type I) AV block, or a history of myocardial infarction or heart failure, if not contraindicated, ECG testing and first-dose monitoring is recommended [see Dosage and Administration (2.1, 2.4) in the full prescribing information and Contraindications (4)].

Treatments
- Initiation of MAYZENT treatment should be delayed in patients with severe active infection unless patient has a functioning pacemaker [see Warnings and Precautions (5.3)].
- 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.
MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy if a serious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased cardiovascular risk, cases of cutaneous malignancies has also been reported in association with another S1P modulator.

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 inbradine and digoxin). Concomitant use of these drugs during MAYZENT initiation may be associated with severe bradycardia and heart block.

Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, 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)].

• 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 and Drug Interactions (7.2)].

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.

5.6 Cutaneous Malignancies
Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). In Study 1, the incidence of BCC was 0.1% in MAYZENT-treated patients. 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 for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer; exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-phototherapy is not recommended in patients taking MAYZENT.

5.7 Increased Blood Pressure
In Study 1, MAYZENT-treated patients had an average increase over placebo of approximately 3 mmHg in systolic pressure and 1.2 mmHg in diastolic pressure, which was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Hypertension was reported as an adverse reaction in 12.5% of MAYZENT-treated patients and in 9.2% of patients receiving placebo. Blood pressure should be monitored during treatment with MAYZENT and managed appropriately.

5.8 Fetal Risk
Based on animal studies, MAYZENT may cause fetal harm [see Use in Specific Populations (8.1)]. Because it takes approximately 10 days to eliminate MAYZENT from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT treatment.

5.9 Posterior Reversible Encephalopathy Syndrome
Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an S1P receptor modulator. Such events have not been reported for MAYZENT-treated patients in the development program. However, should a MAYZENT-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, MAYZENT should be discontinued.

5.10 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies
When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating MAYZENT.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended [see Drug Interactions (7.1)].

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

5.12 Immune System Effects After Stopping Mayzent
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 [see Clinical Pharmacology (12.2) in the full prescribing information]. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 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 to 4 weeks after the last dose of MAYZENT [see Drug Interactions (7.1)].

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

- Infections [see Warnings and Precautions (5.1)]
- Macular Edema [see Warnings and Precautions (5.2)]
- Bradyarrhythmia and Atrioventricular Conduction Delays [see Warnings and Precautions (5.3)]
- Respiratory Effects [see Warnings and Precautions (5.4)]
- Liver Injury [see Warnings and Precautions (5.5)]
- Cutaneous Malignancies [see Warnings and Precautions (5.6)]
- Increased Blood Pressure [see Warnings and Precautions (5.7)]
- Fetal Risk [see Warnings and Precautions (5.8)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.9)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies [see Warnings and Precautions (5.10)]
- Severe Increase in Disability After Stopping Mayzent [see Warnings and Precautions (5.11)]
- Immune System Effects After Stopping Mayzent [see Warnings and Precautions (5.12)]

6.1 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 (16) 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 59.0% 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 increase.

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.
Periodic skin examination is recommended for all patients, particularly those with risk factors for noma, have also been reported in patients treated with MAYZENT and in patients treated with icant liver injury is confirmed. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated and 1.4% of MAYZENT-treated patients, respectively, compared to 1.5% and 0.5% of patients (ALT/AST/GGT) elevations.

Terms were combined as follows: headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.

Hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.

alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.

edema peripheral, joint swelling, fluid retention, swelling face.

bradycardia, sinus bradycardia, heart rate decreased.

pain in extremity

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), asthma, and pulmonary function test decreased [see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)].

Seizure 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.

Respiratory Effects

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.

Malignancies

Malignancies such as basal cell carcinoma, squamous cell carcinoma, malignant melanoma, and seminoma were reported in MAYZENT-treated patients in Study 1 (in the core or extension parts).

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 (5.7)].

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.

MAYZENT 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 la (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 bradycardia. 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 be not 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-zem), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) [see Warnings and Precautions (5.3) 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 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 recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluconazole) 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 moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (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, etravirine) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 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. Based 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 recommended dose of 2 mg/day.

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

Data

Animal Data

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 (skeletal and visceral) were increased at the lowest dose tested, the only 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 2 mg/day.

When siponimod (0, 0.1, 1, or 0.75 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryolphythality and increased incidences of fetal skeletal variations were observed 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 development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m2 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 (Th-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.

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DATA FROM A RECENT STUDY SUGGEST that infusion-related adverse events (AEs) with natalizumab (Tysabri; Biogen) appear to be rare and generally mild, and they occur only during the first few infusions in patients with relapsing-remitting multiple sclerosis (RRMS).

Findings from the study were presented virtually at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2021, February 25-27, by Yujie Wang, MD, University of Washington Medical Center, and colleagues.

“Natalizumab is an approved treatment for [RRMS] since 2006. Although infusion reactions are usually mild, occur typically within the first 6 months of treatment and clinically relevant infusion reactions are extraordinarily rare, there is a mandatory 1-hour postinfusion monitoring after each dose, independent of treatment duration. This has posed concerns of unnecessarily increasing SARS-CoV-2 exposure risks for patients and staff,” Wang and colleagues wrote.

Wang et al conducted a retrospective cohort study of 333 patients with RRMS receiving natalizumab at the University of Washington’s MS center infusion suite from July 2012 to September 2020. They investigated the frequency, severity, nature, and timing of infusion reactions that occurred during infusion and 1-hour postinfusion monitoring. They also analyzed patient data, such as details of natalizumab treatment and presence of anti-natalizumab antibody in serum.

The patients had a mean (SD) age of 41 (12) years and 87 (26%) were men. Altogether, the patients underwent 9862 infusions of natalizumab. The mean number of infusions was 27 per patient (range, 1-174).

A total of 33 infusion-related AEs (0.34% of infusions) were recorded in 26 patients (7.8%). The majority of AEs occurred during infusion (77%) rather during than the 1-hour postinfusion monitoring, and 92% of AEs occurred within the first 6 months of treatments.

Wang and colleagues found that all reported AEs were categorized as being of mild severity. Common AEs included itching, gastrointestinal symptoms, headache, and flushing. These symptoms were either self-limited or easily managed with standard clinical protocols. No patients required emergency care or hospitalization. Anti-natalizumab antibody presence was assessed in 4 cases but was absent in all. No patients discontinued natalizumab infusion treatment.

“In this systematic review of almost 10,000 natalizumab infusions, all infusion-related AEs were mild, and no clinically relevant safety concerns were associated with natalizumab infusions. This highlights a potential opportunity to improve and streamline the infusion and postinfusion monitoring process. Anticipated benefits may include reducing SARS-CoV-2 exposure risks for patients and staff, reducing patients’ treatment burden, increasing efficiency, as well as improving access to care without neglecting patient safety,” Wang and colleagues concluded.

REFERENCE
Increasing Prevalence of Early DMT Prescription in Radiologically Isolated Syndrome

By Victoria Johnson

RESULTS OF A RECENT STUDY indicate that disease-modifying therapy (DMT) treatment in patients with radiologically isolated syndrome (RIS) has been increasing in prevalence, compared with previously reported data.

The results were presented virtually at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2021, February 25-27, 2021, by neurologist Ilena George, MD, of Massachusetts General Hospital, and colleagues. George et al investigated the prevalence of DMT initiation, choice of DMT, and provider rationale for prescribing a DMT.

“RIS can be considered a presymptomatic or early form of multiple sclerosis (MS). Since the condition remains rare, the number of cohorts demonstrating the long-term outcomes in RIS are few. There is equipoise on treating RIS, when to initiate treatment, and with which DMTs,” George and colleagues wrote.

The researchers analyzed data from patients with evidence of demyelinating disease or diagnosis of RIS from the Mass General Brigham Research Patient Data registry seen between May 2005 and September 2020. Patients with a solitary demyelinating lesion and serum autoantibodies were excluded. Altogether, the researchers looked at 89 patients, 11 of whom were then excluded due to conversion from RIS to clinically isolated syndrome (CIS) or MS prior to initiation of DMTs. Patients who were followed for at least 2 years were additionally included in a long-term outcome assessment.

George and colleagues analyzed 49 patients with RIS who had a mean age of 41.0 years at diagnosis; 38 (77.6%) were women. Of the patients, 20 (40.8%) were treated with a DMT and 1 was treated with mycophenolate mofetil for uveitis.

The DMT-treated group had a mean age of 37.6 years at diagnosis, younger than the mean age of 44.1 years in the untreated group (P = .03). More than 2 Barkhof criteria were met in 36 patients (73.5%). Across all DMTs, the median treatment duration was 2.67 years. One patient (5%) with RIS treated with DMTs developed CIS during the observation period while on the DMT.

Physicians reported their rationales for prescribing DMTs, the most common of which was MRI change over time including newly gadolinium-enhancing lesions, reported by doctors in 13 cases (65%). Other reasons included clinical suspicion for a high risk of conversion to MS, reported in 6 cases (30%), and/or a high burden of central nervous system demyelinating disease on MRI, reported in 4 cases (20%).

“It is a bit of an open question whether disease activity by itself—meaning MRI change over time—should be enough to prompt an initiation of a DMT,” George told NeurologyLive® in an interview.

First-line DMTs included dimethyl fumarate (n = 7), glatiramer acetate (n = 5), teriflunomide (n = 4), ocrelizumab (n = 2), and fingolimod (n = 1). Second-line agents were initiated in 7 patients with RIS, 5 for DMT tolerability and 2 for MRI activity.

“There is increasing interest in treating the earliest phases of MS, including RIS. In this cohort, [more than] 40% were treated, mainly with low-to-moderate efficacy DMT and primarily after new lesion activity on imaging. Patients had a higher degree of DMT initiation for RIS than previously reported in the literature,” George and colleagues concluded.

REFERENCE

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PREScribing DMT IN RADIOLOGICALLY ISOLATED SYNDROME

Ilena George, MD, a neurologist at Massachusetts General Hospital, discussed the rationales for prescribing disease-modifying therapy in patients with radiologically isolated syndrome.

View video: neurologylive.com/dmt-ris or scan here

Scan the QR code with your smartphone camera or visit NeurologyLive.com for more coverage of the ACTRIMS Forum 2021.
Remote Technology Improves Adherence Rates in Relapsing MS

By Marco Meglio

A REMINDER SYSTEM using electronic “smart” pill-bottle caps paired with remote smartphone app technology produced greater rates of adherence for people with multiple sclerosis (PwMS). The results nonetheless suggested that developing strategies to improve adherence to oral disease-modifying therapies (DMTs) remains a need within MS care.

The results of the study were presented virtually at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2021, February 25-27, by Dylan Rice, BS, clinical research coordinator of Massachusetts General Hospital. Rice and colleagues collected data on 85 PwMS who were randomized 1:1 to remote smartphone app- and bottle-based adherence tracking, either alone (monitoring-only arm) or with medication reminders (reminders arm).

Overall, the mean perfect adherence over the 90-day study period for all participants was 65.0% (SD, 21.2%; range, 14.2%-98.9%). Mean perfect adherence was significantly higher in the reminders arm (68.0%) compared with the monitoring-only arm (61.4%; P = .006). Notably, there was no difference observed in perfect adherence by once- vs twice-daily dosing.

“Because participants had the app, where they could look at a log of the medications they were taking over this 90-day study period, we found that a lot of participants reported it was extremely useful in being able to look back at that record and see if they’ve taken their pill already,” Rice told NeurologyLive®.

Of 5959 total scheduled doses in the monitoring-only arm, 4.0% were taken early, 61.4% on time, 5.6% late, 4.7% in excess, and 24.4% not at all. Of 7135 doses in the reminders arm, 3.4% were taken early, 68.0% on time, 3.7% late, 12.2% in excess, and 12.8% not at all.

All participants completed baseline health history surveys, such as the Montreal Cognitive Assessment and Symbol Digit Modalities Test, and were followed for 90 days. Perfect adherence was defined as the proportion of doses a participant took within 3 hours of the scheduled time.

“Because participants had the app, where they could look at a log of the medications they were taking over this 90-day study period, we found that a lot of participants reported it was extremely useful in being able to look back at that record and see if they’ve taken their pill already.” — DYLAN RICE, BS

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The electronic smart caps were designed by Pillsy, and they have a multitude of features to track patient medication adherence. Pillsy’s capabilities allow the dose to be marked as taken when the user opens the bottle; the phone app does not need to be accessed. Data are stored on the device and syncs opportunistically, even when the app is not opened on the smartphone.

“Because participants had the app, where they could look at a log of the medications they were taking over this 90-day study period, we found that a lot of participants reported it was extremely useful in being able to look back at that record and see if they’ve taken their pill already.” — DYLAN RICE, BS

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References

FOR AS LONG AS HUMANS have coalesced as communities, beginning nearly 10,000 years ago in the Neolithic period, there has been a fascination with the skull and brain. From here emerged the rudiments of neurosurgery. In regions ranging from the Ensisheim in Alsace, France, to the Peruvian Altiplano, we know trepanation was practiced. In trepanation, a hole is scraped or drilled into the human skull, and it is the oldest documented surgical procedure performed by man. While we can only speculate about the millennia-old reasons for such “procedures”—spanning from the mystical to spiritual and ritual—they must be favored over any current-day notion of medicinal. Nevertheless, such experiences of the shaman and healers of lore should not be discounted, because some of our current neurosurgical practices, in particular the practice of minimal-access surgery, harken back to their legacy of transcervical access.

In general, neurosurgical interventions can be considered corrections of structural deformities. For instance, **FIGURE 1** depicts a disc herniation impinging on a nerve root. Here, a right-sided C6/7 disc herniation causes a right C7 radiculopathy, with associated pain and triceps weakness. Since an adequate trial of conservative care failed, our solution was to remove the pathology. In this instance, an anterior cervical discectomy was performed to remove the C6/7 disc, and in the process decompress the afflicted C7 root. An arthroplasty was performed, with immediate relief in symptoms and restoration of normal structural alignments.

In some instances, the structural anomaly is far more serious, such as in the **FIGURE 2** example of a patient with Klippel-Feil syndrome. The osseous dyssegmentation spinal anomalies resulted in an ominous situation in which the dens of C2 was being drawn into the foramen magnum, causing a symptomatic pithing of medulla. The solution here was to decompress the suboccipital bone, while stabilizing the occipital-cervical alignment with a titanium plate-screw-rod as well as bone fusion construct. In doing so, the occipital-cervical junction was repositioned back toward a nonpathologic, native axial alignment. Our neurosurgical intervention, which relieved the pressure that had been present at the cervicomedullary junction, was critical in maintaining neurological integrity and averting quadriparesis.

Even tumors can be considered a structural problem for a neurosurgeon to combat. The images in **FIGURE 3** (left panels) demonstrate a temporal-parietal-occipital mass that is impinging on the posterior aspect of the left lateral ventricle. This patient did not even appreciate their visual deficit until it was demonstrated on physical exam; it had instead been the loss of the ability to read that had prompted admission. While the patient could spell and recite letters, the ability to process letters into words had been affected. Two weeks following surgery (right panel), their ability to recognize simple 3- and 4-letter words was starting to return.

In contrast to structural problems such as those illustrated above, the movement disorders that afflict some patients are distinctly different. In an individual with essential tremor, Parkinson disease...
been just over 200 years since James Parkinson, published his 1817 monograph, An Essay on the Shaking Palsy. Devotees of James Parkinson will appreciate that only 6 index cases were described, and of these, 3 patients were evaluated from casual observation, or in Parkinson’s own words, “...next noticed was casually met with in the street...” While Parkinson’s keen sense of observation allowed him to identify some of the cardinal features of the then-designated “shaking palsy/paralysis agitans”—tremor, rigidity, and postural instability—it was Jean-Martin Charcot’s meticulous analysis that added the fourth cardinal feature: bradykinesia. It was also Charcot who suggested that such individuals should be designated as patients with Parkinson disease. James Parkinson was a man of many talents, both medical and nonmedical. Like his father, John, he was an apothecary. His nonmedical interests included geology and paleontology as well as political activism. What is perhaps often forgotten with the passage of time is that Parkinson was a surgeon, and his affiliation as a member of the Royal College of Surgeons is prominently evident on his landmark publication. However, Parkinson was most certainly not a neurosurgeon, because, historic trephination notwithstanding, neurosurgery as an emerging field wouldn’t occur for nearly 70 years, when the neurologist Sir William Gowers, MD, collaborated with the pioneering neurosurgeon Sir Victor Horsley, MD. As such, Parkinson’s advocacy was for solutions that were in keeping with the times: bloodletting and blistering. While the methods were antiquated, his belief that such maneuvers would relieve inflammatory pressure away from the medulla, while incorrect, was prescient at least in suggesting subcortical pathology.

Approximately 10 million individuals globally carry the diagnosis of PD. The disease is neurodegenerative and is second only to Alzheimer disease with regard to neurodegenerative prevalence. The hallmark pathology of PD occurs in the ventral midbrain. Specifically, it is the selective loss of dopaminergic neurons in the pars compacta of the substantia nigra. The mechanism of deterioration is not entirely clear, aside from its association with selective neuronal loss and the prevalence of aggregates of the intrinsically unstructured, otherwise soluble protein, alpha-synuclein. Ninety percent of PD is idiopathic. Although its cause is unknown, certain risk factors are recognized:

- **Age:** Infrequently, PD can affect young adults. The frequency for individuals aged over 60 years is estimated to be 1%, increasing to 5% in individuals aged over 85 years.
- **Heredity:** Having close relatives with PD increases one’s chances of developing the disease, although the genetic understanding of PD is murky at best.
- **Sex:** Men are 1.5 times more likely to develop PD than women.
- **Environmental:** Exposure to such toxins as herbicides and pesticides may slightly increase the risk of developing PD.

Patients lose autonomy as the disease progresses, which is incalculable in terms of personal loss. Economically, the estimated annual cost to the health care system in the United States alone is more than $50 billion.

Movement disorders, in general, fascinated neurosurgeons from the start, perhaps because their associated debilitation was so obvious. Conditions such as hemiballism, Huntington chorea, and PD offered opportunities to create therapeutic ameliorations surgically by disrupting the motor pathways. All points of contact were explored, from the cortex to the internal capsule, from the basal ganglia to the cerebral pyramids, and even the spinal cord.

As early as 1890, Horsley resected the motor cortex, and while this operation was performed with some frequency in the 1920s, over the ensuing 20 years, it became clear that such an approach to treating movement disorders was risky and ineffective; it frequently left the patient far worse off. For instance, in patients with PD, while the immediate postoperative period saw a disappearance of the tremor due to motor paresis, the tremor would relapse, with the extrapyramidal rigidity being substituted for pyramidal spasticity. Even more disappointing was with progression of disease. Patients with PD who had undergone such cortical extirpations were left with a paretic limb contralateral to their surgery, and a tremulous or rigid limb heralded the march of neurodegeneration in their other extremity.

Marching caudally, hope remained that subcortical surgery focused on the pyramidal tracts might hold promise over the unpromising cortical interventions. In the late 1940s, E. Jefferson Browder, MD, advocated for the frontal transventricular approach. His surgery involved resecting the caudate nucleus as a means to trace the anterior limb of the internal capsule fibers back toward the genu to induce a subcortical paresis. Unsurprisingly, the outcomes here were no better than those of the cortical resections, with the added downside that ventricular entry increased risks and complications. Additionally, behavioral changes from the destruction of the internal capsule’s anterior limb left patients neuropsychiatrically altered.

Around the same time as Browder, also in the quest to find a subcortical pyramidal tract target suitable for destruction, A. Earl Walker, MD, proposed sectioning the pyramidal tracts at the level of the mesencephalon. Such a surgery was subtemporal, thereby avoiding the complications that were then associated with intraventricular surgery. Pedunculotomy was a technical feat and had its proponents, but compromising the pyramidal tracts, whether...
supratentorially or infratentorially, was typically unsuccessful and left the patient worse off than they began.

Extending most caudally, surgical approaches reached the spinal cord. Fundamentally, efforts here were coupled with low success and high complication rates and are effectively a remnant of the past, despite the fact that pioneers such as Tracy J. Putnam, MD, investigated spinal pyridotomy.

Turning to the concept of surgery upon the basal ganglia and its extrapyramidal motor system, we note that one of the founding fathers of neurosurgery, the preeminent American surgeon Walter Dandy, MD, had posited in the 1920s that the ventral striatum was critical for consciousness and therefore not to be touched during neurosurgery. Colleagues dutifully followed his lead. However, in 1939, Russell Meyers, MD, serendipitously cared for a conscious patient with a horrendous open-skull fracture injury that lay bare for observation a bilaterally injured ventral striata. After this encounter, Meyers hypothesized that he might improve functional outcomes for patients with PD by operating “safely” and selectively on their extrapyramidal system without compromising their consciousness. While there was much to be admired in this bold innovation, the high morbidity and mortality of such a transventricular approach to the basal ganglia rapidly fell out of favor.

In 1952, serendipity again arose in allowing Irving Cooper, MD, to surmise that a lesion to the globus pallidus/thalamus might be the key toward quelling the extrapyramidal symptoms of PD. During a pedunculotomy operation Cooper was performing on a patient with postencephalitic parkinsonism, a ferocious bleed forced him to ligate what was later determined to be the anterior choroidal artery. What must have undoubtably felt like an intraoperative calamity turned out to be a surprising postoperative success, as the patient’s tremor and rigidity were quelled without hemiparesis. However, as was true of many other innovative operations in the history of functional surgery, early enthusiasm was quashed by complications that included unacceptably high morbidity and mortality.

What was immediately clear, though, from Meyers’ and Cooper’s independent observations of extirpative and vascularly occlusive surgeries, respectively, was that the future of PD surgery lay in innovative selective ablation of basal ganglia nuclei that could be achieved with minimal morbidity. Also, another point worth emphasizing was that movement disorder surgical investigations, starting with those of Horsley and modified by global pioneers, were able to address only “hemi-parkinsonism.” In other words, although PD manifests bilaterally as it progresses, these pioneers believed that in any surgery to try to ameliorate symptoms of PD, which would result in paresis of 1 side of the body, in turn, limiting the ability to address symptoms on both sides.

Still, while the definitive surgical therapies emerging from the 1890–1960 period had significant limitations, those surgeons and their teams have to be applauded. It is easy to forget how few resources, relatively, were available at the time. There was certainly little in the way of modern imaging or intraoperative navigation, and for sure, visualization of the operative field was not accompanied by magnification or even illumination. As such, taken in context, the notion of these collective investigations is just simply remarkable.

At this point, it would be logical to transition to a discussion of stereotactic and modern functional/neuromodulation procedures. We stop here, though, to introduce the work of one physician/scientist—Oleh Hornykiewicz, MD—who is fundamental to any discussion of PD treatment. In July 1961, Hornykiewicz, in collaboration with the neurologist Walther Birkmayer, MD, (head of the neurological ward of Vienna’s largest home for the aged, Wien-Lainz), effectively established the medical and pharmacological practice of transmitter-based therapeutics so widely used today. The dopamine miracle is what happened that day when intravenous levodopa was infused into a patient with PD. In Hornykiewicz’s own recollections, the results were spectacular. Consequently, and not surprisingly, interest in surgery to treat PD quickly waned.

Human stereotactic surgery found its inception in Philadelphia, which is also the birthplace of many American institutions and ideas. The neurology-neurosurgeon collaboration of Ernest A. Spiegel, MD, and Henry T. Wycis, MD, at Temple University heralded the first human stereotactic procedure in 1947. Their device was called the “stereoencephalon,” and their first patient had Huntington chorea. The genius of this approach was that for the first time, internal cerebral landmarks, such as the air outline of the ventricular system, as well as other in situ markers, such as the calcified pineal gland, correlated to a brain atlas that had been developed by the Temple team. This allowed deep intracranial structures to be approached with relative accuracy and safety.

The field of stereotactic surgery for the next 40 years would refine itself utilizing 2 principles—progressive minimalism and high-fidelity targeting—which would allow for increasingly finely tuned “lesionectomies.” Lesionectomies were performed in a variety of ways that were sufficient to impart irreversible cellular or tissue injury; they included caustic measures as well as those utilizing thermal/energy means via extreme temperatures, either hyperthermia or hypothermia. The important point to note here is that these therapies were still destructive/ablative. These lesions are irreversible, fixed, and unmodifiable.

The first half of the 1980s saw a change away from the emphasis on lesionectomies, and the age of functional and neurorestorative surgery was ushered in. Neurosurgeon/physicist Alim-Louis Benabid, MD, PhD, was performing stereotactic operations for movement disorders at the Université Joseph Fourier in Grenoble, France. A unilateral lesion to the ventral intermediate nucleus of thalamus was a reliable way of treating “hemi-parkinsonism.” As Benabid has described, “At the time, the treatment for PD was [levodopa], and that had side effects, and neurosurgery had complications.”  

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The anatomy of the thalamus is somatotopic, and surgeons use this information to physiologically define critical vital areas to avoid, allowing them to impart lesions while minimizing adverse effects. The motor thalamus is anterior, and the sensory thalamus posterior; the face is represented more medially, while the legs are more lateral in both motor and sensory somatotopy. The internal capsule is lateral and carries the pyramidal motor fibers. Prior to creating a precise thermally ablative lesion in the thalamus, testing with microelectrode stimulation ensued. Using physiologic neuronal firing frequencies ranging from 20 Hz to 50 Hz, the thalamus and adjacent structures could be mapped. Ideally, stimulation would identify a spot just anterior to the somatosensory thalamus, but safely enough medial to the internal capsule, which would be targeted for ablation. By his own admission, curiosity prompted Benabid to stimulate at low frequencies—starting at 1 Hz, and then going up to the maximal stimulation frequency of the electrical pulse generator, 100 Hz, which remarkably stopped the tremor! Much like the “Eureka!” moment that must have flooded Hornykiewicz and Birkmayer more than a quarter century earlier, Benabid realized that high-frequency stimulation, rather than ablation, might be the solution, and this ushered in our present era of neurorestorative, neuromodulatory, nonablative surgery. The beauty here is that the “currency” of the brain is electricity, and deep brain stimulation (DBS) elegantly offers a solution using electricity as a therapeutic, prompting some to call this manner of intervention “electroceutical” treatment.

The impact of Benabid’s work and of his realization, as well as its clinical implementation, must not be underestimated. Prior to Benabid’s insight, procedures for PD or any other movement disorder were necessarily unilateral. Even with carefully deployed thalamic ablations, a bilateral procedure carried a risk for dysarthria as high as nearly 30%. The absolute benefit of PD DBS neuromodulation is that bilateral nuclei can be targeted, to afford relief for not just “hemisymptoms” but rather full body control. Additionally, unlike ablative interventions, DBS is dynamic—very important, since PD is not static. While the disease will invariably progress, the ability to program DBS therapy to modify its parameters—current/voltage, pulse width, and frequency—can often combat disease progression, thereby keeping disabling symptoms at bay.

Typically, bilateral electrode placements that lead to an impulse generator battery are placed in the subclavicular region. The battery may be either rechargeable or nonrechargeable and it can be wirelessly programmed or interrogated. Barring any compromise of intracranial electrodes, they are a permanent fixture; the impulse generator battery will require periodic surgical exchange, depending upon the battery’s demands. All components are subcutaneous and effectively hidden from view. In FIGURE 4, the montage shows bilateral globus pallidus internal (GPi) implants in one of our patients with PD. The arrows in the brain CT scan show bilateral electrode tips; the skull films give an overall appreciation of the electrodes in relationship to the cranial anatomy, highlighting the deep nature of these implants and the absolute need for precise submillimetric stereotactic accuracy. In this particular patient, 2 impulse generators were placed subclavically, and the leads can be seen coursing down each side of the neck, terminating into right and left batteries.

Perhaps the single most important factor in predicting DBS success for patients with PD is patient selection. Herein lies the importance of assembling a multidisciplinary team. Ever since Horsley and Gowers, neurosurgeons and neurologists have been inextricably linked. Today, in addition to the requisite support staff, a multidisciplinary movement disorder team requires a neuropsychologist, a movement disorder neurologist, and a stereotactic/functional neurosurgeon. In addition to patient selection, target selection is also key. In patients with PD, either the subthalamic nucleus (STN) or the GPi must be selected as the target, and the choice is typically based on multidisciplinary input from neuropsychologists, neurologists, and neurosurgeons. For instance, concern for postsurgical cognitive impairment would favor implanting the GPI, but a desire to taper medications secondary to adverse effects might favor an STN implant.

It has been 50 years since Hornykiewicz and Birkmayer experienced the dopamine miracle, and it is certainly reasonable to muse what the next 50 years will bring. For neurosurgeons and neurologists alike, it is perhaps best to reflect back not on the successes but some of the major shortcomings regarding our current treatment paradigm for PD. Of the 4 cardinal features that define PD, postural instability is least likely to improve with this paradigm. In addition,
since the first implant in Grenoble, approximately 200,000 patients century both directly and indirectly developing DBS. In the 34 years much more thoroughly than it has been. Curious neurosurgeons, exists for patients with epilepsy, in a device colloquially referred to as a preset parameters are met. Such a closed-loop therapeutic already deliver therapy, but act in the manner of a true brain-machine inter “off” of a light switch. The DBS of the future, however, will incorporate loop,” which means that therapy is always on, much like the “on” and “off” of a light switch. The DBS of the future, however, will incorporate artificial intelligence and deep learning to record, sense, screen and process local field potentials. In other words, the device will not only deliver therapy, but act in the manner of a true brain-machine interface, imparting stimulation in an episodic “closed-loop” manner when preset parameters are met. Such a closed-loop therapeutic already exists for patients with epilepsy, in a device colloquially referred to as a brain pacemaker.

Finally, DBS therapy as a treatment for PD needs to be embraced much more thoroughly than it has been. Curious neurosurgeons, neurologists, and scientists have collectively spent more than a century both directly and indirectly developing DBS. In the 34 years since the first implant in Grenoble, approximately 200,000 patients have been implanted globally, inclusive of all neuromodulatory applications. To compare that with another neurosurgical technique, there were about 300,000 thoracolumbar fusion operations just in the United States alone in 2020.

Part of that gaping disparity represents the prevalence of spine disease vs PD, but an even bigger part lies in apprehension on the part of the patients and even their care providers in considering DBS. Innovations in neurobiology, science, technology, engineering, and public awareness will shape the future of DBS in ways that we might not even be able to imagine right now. All the work will have been for naught, though, if DBS continues to enjoy simply a niche status. Surgical care for PD is safe and effective, period. It should no longer be treated as a consideration of last resort, but as a treatment option discussed early in the disease course with the patient and their family.

REFERENCES

More Expert Perspectives on Parkinson Disease on NEOUROLOGYLIVE.COM

Daniel E. Kremens, MD, JD, and Rajeev Kumar, MD, review 2 recently approved oral therapies for Parkinson disease OFF episodes—istradefylline and opicapone oral capsules—and share their insight on the data from their respective clinical trial programs, and what the treatments offer to clinicians treating this patient population.

View video: neurologylive.com/off-episodes or scan here

Rajeev Kumar, MD, and Daniel E. Kremens, MD, JD, discuss the intricacies of treating OFF episodes in Parkinson disease during the COVID-19 pandemic, including overcoming the initial challenges that come with the use of telemedicine, and offer their advice for community neurologists who are seeing these patients during the COVID-19 era.

View video: neurologylive.com/pd-covid or scan here
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Interleukin-6 Receptors in the Treatment of Neuromyelitis Optica Spectrum Disorder

By Jennifer S. Sun, PhD

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD), also known as Devic disease, is a rare, debilitating autoimmune disorder of the central nervous system that preferentially damages the optic nerves and spinal cord.1-4 Women and people of African or Asian descent are disproportionately affected.4 A single episode of attack may be enough to result in disabilities such as total blindness, muscle damage, and paralysis.1,5,6

Most patients with NMOSD will subsequently experience severe relapses that can cause permanent neurological damage and, in some cases without treatment, death.4,5 Distinct from relapsing-remitting multiple sclerosis (MS),4,5,7 NMOSD is mediated by the humoral immune system; consequently, NMOSD does not respond to standard treatments for MS, which is primarily a cell-mediated autoimmune disorder, by comparison.4,7 Emerging therapies targeting specific molecules related to NMOSD pathogenicity are needed for patients who are refractory to standard treatments for NMOSD, which includes high-dose corticosteroids, apheresis therapies, and off-label use of immunotherapies for relapse prevention.5,7

NMOSD is associated with elevated levels of the pleiotropic cytokine interleukin-6 (IL-6).4,8 IL-6 signaling through both membrane-bound (classic signaling) and soluble forms of the IL-6 receptor (IL-6R; trans-signaling) regulates inflammatory immune responses (FIGURE).2,5,8,9 Dysregulation of IL-6 expression or signaling contributes to NMOSD pathogenesis.5,10 The resulting inflammatory feedback loop triggers secretion of astrocyte-damaging anti–aquaporin-4 immunoglobulin G (AQP4-IgG) autoantibodies.1,5,7

IL-6R is thus a key therapeutic target for NMOSD.1 Anti–IL-6R monoclonal antibodies (mAbs), such as the investigational tocilizumab (Actemra; Genentech) and satralizumab (Enspryng; Chugai and Roche), are effective in blocking IL-6 signaling, inhibiting AQP4 autoantibody production, and mitigating pain and general fatigue in patients.3,4,8,9 Moreover, these anti–IL-6R therapeutics reduce the severity of NMOSD and even prevent relapses in patients who cannot tolerate standard immunosuppression therapy.5,7

Tocilizumab was most recently approved by the FDA in 2017 for T-cell–induced cytokine release syndrome after its original 201 approval.8,9,11 In the open-label, multicenter, randomized, phase 2 TANGO trial (NCT03350633)12,13 that included 118 patients with NMOSD, intravenous tocilizumab administered at 8 mg/kg every 4 weeks was associated with reduced risk of relapse and improvement in the relative risk of 24-week confirmed disability progression, by 78%, in patients with refractory NMOSD compared to those treated with azathioprine.8,9,12

Satralizumab also is a humanized mAb targeting IL-6R administered subcutaneously. It was bioengineered from tocilizumab via novel recycling antibody technology, which prolongs its availability in the circulation.3,4 It was approved in 2020 for the treatment of AQP4-IgG–positive NMOSD in adults (and adolescents in Canada),3,8 after results of the multinational, randomized, double-blind, placebo-controlled phase 3 SAkuraStar (NCT02073279)14,15 and SAkuraSky (NCT02028884)2,16 clinical trials demonstrated its efficacy in patients seropositive for AQP4-IgG. The primary end point in both studies was the time to first relapse, defined as new or worsening objective neurologic symptoms, as determined by independent review committees.2,15

In SAkuraStar, 95 patients with NMOSD who were AQP4-IgG-seropositive, aged 18 to 74 years, were randomly assigned (2:1) to...
monotherapy with a dose of 120 mg satralizumab or placebo at weeks 0, 2, and 4, followed by a dose of 120 mg every 4 weeks thereafter.\textsuperscript{8,9,15} Patients experiencing clinical relapse in the prior 30 days were excluded, though patients included were required to have had a relapse in the prior year.\textsuperscript{8} Concomitant immunosuppressant use was prohibited. A total of 76\% and 72\% of patients on satralizumab were relapse free at weeks 48 and 96, compared with 61.9\% and 51.2\%, respectively, with placebo. The hazard ratio (HR) of satralizumab to placebo in patients who were AQP4-IgG seropositive (n = 64) for clinically defined relapse was 0.26 (95\% CI, 0.11-0.63).

In SAkuraSky, satralizumab (n = 42) or placebo (n = 41) was added to baseline immunosuppressant therapy for 83 patients aged 12 to 74 years.\textsuperscript{2,8} Patients treated with any drug targeting the IL-6 pathway were excluded. In contrast to SAkuraStar, patients were required to have experienced at least 2 relapses in the prior 2 years, with at least 1 in the previous year. Patients were randomly assigned to satralizumab or placebo (1:1) with a dose of 120 mg at weeks 0, 2, and 4, followed by a dose of 120 mg every 4 weeks thereafter. A total of 89\% and 78\% of satralizumab-treated patients were relapse free at 48 and 96 weeks, compared with 66\% and 59\%, respectively, with placebo. In the subgroup of patients who were AQP4-IgG seropositive (n = 55), 11\% of satralizumab-treated patients had a protocol-defined relapse, compared with 43\% of those receiving placebo (HR, 0.21; 95\% CI, 0.06-0.75). Meanwhile, relapse in the AQP4-IgG-seronegative subgroup was not statistically different between patients receiving satralizumab and placebo.

The results of these pivotal studies indicated that satralizumab decreased risk of relapse and was well tolerated when administered with or without accompanying immunosuppressant therapy, making satralizumab an attractive treatment option for patients with NMOSD.\textsuperscript{2,3,5} The pharmacokinetics of satralizumab are not affected by patient age, sex, or race.\textsuperscript{3} Serious adverse effects (AEs) were reported in SAkuraStar and SAkuraSky, with both placebo and satralizumab groups having similar rates.\textsuperscript{2,3,5} The most common AEs with satralizumab in both studies included headache, arthralgia, and injection-related reactions.\textsuperscript{3}

For patients with refractory NMOSD, clinical improvement will depend on the development of therapeutics that can target different key players in NMOSD pathologic autoimmunity. The primary goal of this treatment, whether administered as monotherapy or in combination with other agents, is to prevent relapse and reduce the severity of attacks. Larger and longer trials should be undertaken to clarify optimal dosing regimens, efficacy, durability, and safety of satralizumab for long-term use. As AQP4-IgG-seropositive patients are encouraged to maintain therapy for years after an attack, less invasive and more effective drugs like satralizumab could be the key to these patients functioning much more independently. \( \blacksquare \)

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

Contraindication:

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.

WARNINGS AND PRECAUTIONS

The precise mechanism by which KESIMPTA exerts its therapeutic effects is unknown.

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.


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)†‡
• Profound reduction in mean number of Gd+ T1 lesions per scan of up to 98% (P<0.001)†
• Superior reduction in mean number of new or enlarging T2 lesions per year of up to 85% (P<0.001)†
• Significant risk reduction in 3-month CDP of 34% (P=0.002) and 6-month CDP of 32% (P=0.01)‡

PRECISION

• A targeted and precisely delivered B-cell therapy‡

Safety

• Favorable safety profile similar to teriflunomide as demonstrated in 2 pivotal trials†

FLEXIBILITY

• The first once-monthly (20 mg), SC, B-cell therapy administered at home or anywhere§

Learn more at KesimptaHCP.com
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.

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KESIMPTA® (ofatumumab) injection, for subcutaneous use

**INDICATIONS AND USAGE**

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.

**CONTRAINDICATIONS**

KESIMPTA is contraindicated in patients with:

- Active HBV infection [see Warnings and Precautions (5.1)].

**WARNINGS AND PRECAUTIONS**

### 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 infection 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 immunosuppressive 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 (HBV)**

**Reaction**

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 (HBsAg) and Hepatitis B Core Antibody (HBcAb) 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 [HBcAb+] or are carriers of HBV [HBsAg+], 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 immunization guidelines at least 4 weeks prior to initiation of KESIMPTA for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines. KESIMPTA may interfere with the effectiveness of 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 [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 6% 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 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 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 Reactions</th>
<th>KESIMPTA 20 mg</th>
<th>Teriflunomide 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 946</td>
<td>N = 938</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, tracheitis.

**Injection-Related Reactions and Injection-Site Reactions**

The incidence of injection-related reactions (systemic) was highest with the first injection (14.4 %), decreasing with subsequent injections (4.4 % with second, less than 2 % with third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) patients treated with KESIMPTA reported serious injection-related reactions. There were no life-threatening injection-related reactions. Most frequently reported symptoms (2% or greater) included fever, headache, myalgia, chills, and fatigue.

In addition to systemic injection-related reactions, local reactions at the administration site were very common. Local injection-site reactions were all mild to moderate in severity. The most frequently reported symptoms (2% or greater) included erythema, pain, itching, and swelling [see Warnings and Precautions (5.2)].
Laboratory Abnormalities

Immunoglobulins

In Study 1 and Study 2, a decrease in the mean level of IgM was observed in KESIMPTA-treated patients but was not associated with an increased risk of infections [see Warnings and Precautions (5.3)]. In 14.3% of patients in Study 1 and Study 2, treatment with KESIMPTA resulted in a decrease in a serum IgM that reached a value below 0.34 g/dL. KESIMPTA was associated with a decrease of 4.3% in mean IgG levels after 48 weeks of treatment and an increase of 2.2% after 96 weeks.

6.2 Immunogenicity

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 fetuses at both doses when assessed on gestation day 100. Plasma exposure (Cave) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (Cave) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.

Intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys throughout pregnancy resulted in no adverse effects on the development of the offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the high dose. The deaths at the high dose were considered secondary to B-cell depletion. Plasma exposure (Cave) in dams at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose.

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.

Data

Animal Data

Intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestations days 20 to 50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was observed in fetuses at both doses when assessed on gestation day 100. Plasma exposure (Cave) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (Cave) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.

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Additional Notes

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Evaluating Spinal Muscular Atrophy in the Era of Telehealth

Two experts in spinal muscular atrophy (SMA) care, Diana Castro, MD, and Garey H. Noritz, MD, offer tips and demonstrations for screening and diagnosing SMA via telehealth, and they outline resources provided by Cure SMA for families and clinicians who suspect, or have a patient with a diagnosis of, SMA.

By Matt Hoffman

TELEMEDICINE AND TELEHEALTH have gained much traction in clinical care over the last decade, and with the coronavirus disease 2019 (COVID-19) pandemic pushing many physicians and patients away from their centers and into the virtual model, it has never been more incorporated into regular care. For neurologists and neuromuscular specialists, however, this has led to some challenges due to the inability to conduct physical exams—a crucial part of the clinical routine.

Despite the challenges, the neuromuscular disease community has adjusted rapidly, and that shift was discussed by a pair of experts in the care of spinal muscular atrophy (SMA) in a recent segment of the NeurologyLive® Cure Connections® series, “Cure SMA: Evaluation of SMA in the Era of Telehealth.” The conversation featured insights from Diana Castro, MD, pediatric neurologist, Children’s Health; assistant professor, UT Southwestern Medical Center; center director, Cure SMA Care Center; and co-director, Muscular Dystrophy Association Clinic–Dallas; as well as pediatrician Garey H. Noritz, MD, division chief, Complex Health Care Program, Nationwide Children’s Hospital; and professor of pediatrics, The Ohio State University.

The duo dove into the experience at their respective centers, with topics of discussion ranging from the state of screening for SMA to the ins and outs of the telehealth visit with affected children and their parents, and beyond.

Newborn Screening for SMA

In Texas, where Castro practices, newborn screening for SMA has not yet arrived, although Cure SMA, a patient advocacy group, continues to push for it nationwide. Like many pediatric neurologists treating SMA, Castro is in favor of this screening, particularly because of its success in patient identification. She noted that screening can catch 95% of the infants with SMA, in part because of the homozygous deletion of the SMN1 gene in 95% of cases of the disease. However, that remaining 5% may have a point mutation that can be caught only by sequencing the gene itself.

Castro noted that it has become important to her to ensure that the gene is fully sequenced and that the SMN2 copy number is included in the screening.

“I have cases where the patient has the deletion in one allele and a mutation in the other allele, or they may have mutations in both

FEATURED

Diana Castro, MD
Assistant Professor of Pediatrics, Neurology, and Neurotherapeutics, UT Southwestern Medical Center
Co-Director, Muscular Dystrophy Association Clinic, Dallas

Garey H. Noritz, MD
Division Chief, Complex Health Care Program, Nationwide Children’s Hospital
Professor of Pediatrics, The Ohio State University
alleles,” Castro explained. “Those patients are not going to be captured by the newborn screening. As a neurologist, if you still have that concern, you can send the [SMNI gene sequence analysis] right away. The test will check for SMNI deletion and sequencing, and it also will give you the SMN2 copy number.”

Additionally, carrier testing is available and has become a tool utilized by obstetricians and gynecologists across the United States to test mothers prior to pregnancy, or in its early stages; when positives are detected, the fathers are tested as well. In these instances, Castro said, amniocentesis can be performed but is often forgone due to its risks to the pregnancy. The screening for SMA, though, can be done the day the baby is born.

“What we do in those cases is prenatal counseling, and we give the test kit to the mother to take to the hospital when she delivers the baby. The testing can be done the same day,” Castro said. “We have so many opportunities to get this diagnosis [but] we have to be informed of what’s going on. Many neurologists don’t know how many options we have for treatment, and I think it’s important to stay up to date on all the knowledge.”

**Signs and Symptoms of SMA**

Physicians like Castro who don't have the advantage of newborn screening must rely instead on the eyes, ears, and hands of pediatricians like Noritz—as well as family doctors, physical therapists, and families—to recognize potential signs of SMA.

Pediatricians are most often exposed to infants with SMA types 1, 2, and 3 (type 4 has adult-onset symptoms). Castro discussed the key signs to watch for in patients with each of these types.

Type 1 patients often appear with what Castro described as a “disconnect” between the face and the body. “Usually, these kids are beautiful. They are extremely alert. They look around. They seem to understand everything, even better than other children do,” she explained. Upon examining the body, though, “it’s almost like [it] is not connecting well with their face.”

Other key signs include low muscle tone, limited mobility, and absent reflexes. Additionally, individuals with SMA type 1 present with weak cry, difficulty swallowing during feedings, failure to thrive, and difficulty lifting extremities against gravity. From there, signs like breathing abnormalities can appear.

For SMA type 2, the referral point is often the inability to stand and walk. Many of these patients, Castro explained, can only sit. This often sparks parental concern and the journey to her office. On the other hand, patients with SMA type 3 are often able to stand and walk, but issues of falls and fatigue begin when children are aged 8 to 10 years or so. Type 3, for Castro, is the most difficult to diagnose due to the length of time it takes to appear.

“Pediatricians, I’m sure it’s sometimes hard for you to get reflexes checked, but I think it’s key,” she explained. “In the setting of a kid who has low tone and cannot stand up, that’s a patient with SMA who should be referred to us.”

**Telehealth During COVID-19**

For Noritz, the biggest challenge in the last year has been the access to resources for families. Many communities nationwide were shut down out of necessity, leaving patients and their families to figure out the shift to telehealth on their own. As he put it, “If there’s anything we’ve learned [in 2020], it’s that you have to be flexible and ready to change on a moment’s notice.”

Castro pointed to the Child Neurology Foundation’s telehealth tip sheet, which has served to help families navigate the telemedicine system. She also outlined her clinic as an example of how the system may work for some families. For her patients, schedulers will reach out to the families to inform them about the program and how to connect to it, which is followed by reminders and access to the platform’s app.

“Obviously, we encounter other issues through the visit. Sometimes it gets disconnected and things like that. We tell them to be at home for the televisit, not driving, and to also have the patient with them rather than being by themselves,” Castro said. “But all of us—not only the families, but all of us—are learning. We have to learn these different options for virtual care.”

**Resources for Physicians and Families**

In addition to the Child Neurology Foundation’s tip sheet, Castro and Noritz suggested several other SMA resources to help physicians and families, including Cure SMA and their standard-of-care guidelines.

Noritz noted that a general pediatrician’s chances of coming across a baby with SMA are not extraordinarily high, but they are present.

For Castro, Cure SMA stands as the best resource to offer, not only to the families of infants, but for the physicians in need of information. One of its key programs is the recently launched SMArt Moves program, which offers tools to help physicians in the diagnostic process. The website offers videos of key findings and suggests what physicians should be looking for to try to get the patient diagnosed. Additionally, the Cure SMA website offers the standard-of-care guidelines for reference, most recently updated in 2018.

“[Cure SMA is] a really good resource because even as pediatricians, we try to be the center of care, but we need you to be the center of care with us. We need to work together to make sure the patient is getting all the care they need. They need pulmonology, gastroenterology, orthopedics, and rehab. They need all of these specialties, and these guidelines talk about this, so it’s a really good resource to have,” Castro said.

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This activity was financially supported by the Cure SMA Industry Collaboration. At the time financial support was provided, members of the Collaboration included Genentech/Roche Pharmaceuticals, Novartis Gene Therapies, Biogen, Cytokinetics, and Scholar Rock.
Income and Education: Predicting Telehealth Use in Parkinson Disease

By Matt Hoffman

RECENTLY, THE PARKINSON’S FOUNDATION, in collaboration with the Movement Disorders Division of the Department of Neurology at Columbia University Vagelos College of Physicians and Surgeons and the New York-Presbyterian/Columbia University Irving Medical Center, conducted a survey that revealed disparities in telehealth use among people with Parkinson disease (PD) based on income and education levels.

As a whole, telehealth use for the 1342 surveyed patients increased from 9.7% prior to the coronavirus disease 2019 (COVID-19) pandemic to 63.5% during it. Household income greater than $100,000 per year was associated with the highest usage of telehealth (odds ratio [OR], 1.54; 95% CI, 1.06-1.76); high usage was also strongly linked to postsecondary education (OR, 2.05; 95% CI, 1.16-3.62) and telehealth use prior to the pandemic (OR, 2.27; 95% CI, 1.34-3.85). The survey also revealed that more telehealth appointments were for doctor’s appointments (n = 777; 91.2%) rather than physical (n = 142; 16.7%), occupational, speech, or mental health therapies (n = 162; 19%). Although approximately half (n = 617; 46%) of all respondents reported that they would prefer to continue using telehealth always or sometimes after the pandemic ends, respondents who used telehealth for mental health services were less likely to prefer using it after the pandemic (OR, 0.31; 95% CI, 0.1-0.76), leading investigators to suggest that these services should be improved.

NeurologyLive® reached out to James Beck, PhD, chief scientific officer of the Parkinson’s Foundation and an adjunct associate professor in the Department of Neuroscience and Physiology, New York University School of Medicine, to learn more about the challenges that patients with PD face during the COVID-19 pandemic. He discussed how friends and family can help assist patients with PD in scheduling and attending telemedicine appointments.

Q: Can you describe some unique challenges patients with PD have had to face during the pandemic?
One challenge is the fact that even though they are not more susceptible to developing COVID-19, they have a harder time recovering from COVID-19. PD symptoms include difficulty in swallowing and other issues, and just mobility as a whole, [and those] seem to make recovery a bit difficult. They’ve also had some challenges regarding their access to health care providers, access to their medications that they normally need to take, and even [access to] exercise programs—which are incredibly useful for improving overall symptoms. Also, COVID-19 allowed what is a very isolating disease to become more isolating, because of the social distancing restrictions.

Q: This study found a relationship between more telehealth visits and higher household income. How can that income gap be bridged?
That’s a really good question. In completing this study, we were among the first [researchers] to really get a measure of the use of telemedicine, both prior to COVID-19 and during the time of COVID-19, for people with PD. We saw a large increase in overall utilization of telehealth, but as you point out, there is apparent disparity between household income and usage of telemedicine.

Something we need to do as an organization—and we are working to do so—is increase knowledge about telemedicine and to provide support online to encourage people to utilize friends and family members to help them with telemedicine. Many people who live with PD are elderly. These are people with an average age of diagnosis in their mid-60s. A lot of these individuals may be more technically challenged than others, so having
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someone available—a care partner, a loved one, another family member, a friend—to help them with their telemedicine visit will be really important.

As we’ve progressed during the course of the pandemic, I imagine more people are utilizing telemedicine than we anticipated. We ran this survey in the very early days of the pandemic, in spring 2020. I suspect the data have changed significantly since that initial survey.

**Q:** Have you observed a discrepancy between the care a patient requires and actual care appointments being made?

It’s hard to say whether they’re not getting the care they need. I certainly hope they are getting the care they need. I think part of the problem has to do with the pragmatic, practical aspects of the different allied health professions and the services they provide. Speech therapy and occupational therapy, as well as physical therapy, often may need one-on-one, face-to-face engagements to really be most effective. That said, I know the field has incredibly talented providers and they’re thinking about ways in which to adapt a traditional face-to-face approach to the telemedicine approach.

I do know that sometimes reimbursement for these procedures via telemedicine is not always straightforward. It’s not something that’s supported by all third-party payers. So, to the extent that we are able to, as a nation, instill this goal of providing equal payment, whether someone has been seen in person vs via telemedicine, will be really important. Headway is definitely being made with the medical appointments, but I think we have some progress to be made with these allied health appointments as well. Insurance basically doesn’t pick up the tab at the same rate, and that can make it difficult both for providers as well as for the patients who utilize the services.

**Q:** Those using telehealth for mental health services were less likely to want to continue to use telehealth post pandemic. Why do you think that is?

That’s a really good question. I don’t have an answer, and it’s worth following up on that in a subsequent survey of our population, which we have planned. I think what it could be is that, again, this disease can be socially isolating, and that is now impacted with the isolation from COVID-19 and not being able to have that rapport with a mental health professional. That kind of social support that could be there—in-person support—could be an aspect that may be missing.

Certainly, one reason why many people with PD said they preferred telehealth, or would be willing to participate in it moving forward, is just the sheer convenience of it. People with PD have problems with movement: It is a movement disorder. What we’re typically asking from a person with PD, someone who has difficulty moving, is to go to a major medical center or someplace in a city where access is not necessarily the easiest, and, [to boot,] it can be difficult to drive to. As a result, it can take hours to complete an appointment that you or I might be able to accomplish in much less time. So that sheer convenience—being able to have the telemedicine visit inside one’s home at a time that’s a bit more convenient for them—will be great. As telemedicine becomes really standardized across different platforms, I think it’ll be easier for everyone moving forward as well.

**Q:** What is the importance of social contact for patients with PD? Do you think physicians should try and monitor this more?

It’s difficult to prescribe or monitor social interactions. What I think social interactions do is help broaden one’s environment. They can do many things to increase the affective nature of a person to increase their mood and increase other aspects of their life, maybe even reducing apathy. That can be brought about by social interaction. To the extent providers should be monitoring social interaction, it’s probably best to be asking whether providers can be monitoring the mental health of their patients, perhaps even doing short screens to determine whether their patients are suffering from depression, or aspects of depression or anxiety.

People with PD suffer a tremendously high level of depression compared with the general population. It seems to be organic to PD, and yet it’s eminently treatable. We have discovered is that it may not be screened at the level that would be we would like. Many people come into their clinic visits with a list of problems, and mental health is usually not a top priority. Clinicians are in a tough situation, because they have a limited amount of time and really want to address the concerns that [they can see] right in front of them. These concerns may be either highlighted by observing their patient or have been raised by their patient to address, and so they often don’t have that time or the luxury to really be able to query further ways to be able to help their patients in these particular situations.

**Something we need to do as an organization—and we are working to do so—is increase knowledge about telemedicine and to provide support online to encourage people to utilize friends and family members to help them with telemedicine.**

— JAMES BECK, PHD
Q. Did any other notable findings emerge from the survey that you’d like to discuss? Did any surprise you?

Certainly the telemedicine utilization was really interesting, and how that increased. The disparities were not terribly surprising, but I think [they] just provide a fine point on what we can do as an organization and as a society to really ensure that people have equal access to care.

Something we have seen anecdotally, through some other studies that we’re engaged with that involve telemedicine, is that the research aspect of telemedicine has been really great at providing an opportunity to offer an egalitarian approach to clinical research. Part and parcel of clinical care, as we’ve discussed in this COVID-19 survey, is the clinical research access that many people with PD, and many people living with diseases in general, would appreciate. We have seen that even though we may have limited physical sites that are able to have in-person recruitment, the minute we open it up to telemedicine, we’ve been able to see a large increase in interest and in the ability of people with PD throughout the country to be able to participate. I think it could be really important to think about that, and how it can be facilitated.

Another thing we’ve seen is that people with PD, as I mentioned, have this sense of isolation and depression and anxiety. To help combat that, the foundation has created a PD health-at-home series. This is a weekly series, several days a week, providing programming to people with PD around mental health, around exercise, as well as detailed educational support for the issues that are current and are important for persons with PD. This general wellness programming is available in English and in Spanish, trying to reach the broadest communities possible, and we’ve found these things have been really helpful in combating many of the complications our community has faced in dealing with the COVID-19 pandemic.

Q. What other projects are the Parkinson’s Foundation working on?

One of the most important endeavors we have underway is our large PD GENEration study, designed to offer genetic testing and counseling to 15,000 people with PD. Our goal is to improve the care of people with PD by offering genetic testing, and we think it’s going to improve care by not only empowering people to learn more about their disease, and whether they have a genetic form of PD—recognizing that it’s only about 10% to 15% of people who will have a genetic mutation leading to their PD. We’re on the cusp of a precision medicine initiative within the PD field. Several large pharma companies have targeted therapies to individuals who may have a certain genetic mutation, but we’re not ready yet. Our goal is to be able to screen as many people with PD as possible so that they potentially could participate in these upcoming clinical trials, which could lead to better care for these individuals, ultimately, if any of these experimental therapies become approved by the FDA.

Right now, for a person with PD, if you do offer genetic testing and identify a genetic form of PD, it doesn’t yet inform clinical practice. We do our genetic testing in partnership with the clinicians so that they can be aware of their own patients within their practice who might have a genetic form of PD. Neurologists are smart individuals. They’re constantly looking to make connections and are very observant, so the more people we’re able to make aware of genetics and PD and clinical outcomes, I think the better off we’ll be as a community to make new discoveries that we hadn’t appreciated before about clinical outcomes, being able to, again, empower people with PD. The third thing, of course, is the pragmatic goal of trying to speed up clinical trials for targeted therapies for people with PD.

REFERENCE


For more direct access to expert insight into Parkinson disease, go to the NeurologyLive® “Movement Disorders” Clinical Focus page.
Subcutaneous Levodopa/Carbidopa Delivery Provides Potential Breakthrough in Parkinson Disease

By Marco Meglio

FOR YEARS, the combination of carbidopa and levodopa has been the standard of care for symptom management in patients with Parkinson disease (PD). As PD progresses, patients may experience fluctuations hour to hour from an ON state to an OFF state, during which they are slower, stiffer, and have more difficulty moving, leading to the need for treatments to make these fluctuations less drastic.

In January 2015, AbbVie received FDA approval for Duopa, the first and, to date, only treatment providing 16 continuous hours of carbidopa and levodopa together to help control motor fluctuations in advanced PD. The enteral suspension is administered using a small, portable infusion pump that delivers carbidopa and levodopa directly into the small intestine through a tube placed during an outpatient procedure.1

Now, AbbVie has announced that it will be conducting a new phase 3 study (NCT04380142), called M15-736, which will measure the efficacy, safety, and tolerability of continuous subcutaneous infusion of ABBV-951, its investigational soluble formulation of carbidopa and levodopa prodrugs, in patients with advanced PD (TABLE).

The 12-week study will have 2 treatment arms, one of which will receive ABBV-951 as a continuous subcutaneous infusion via external pump plus oral placebo capsules. In the second arm, participants will receive placebo solution as a continuous subcutaneous infusion plus oral capsules containing carbidopa/levodopa.2 The company expects the trial, which is currently recruiting, to enroll approximately 130 participants from 80 sites internationally. By providing continuous nonstop care, ABBV-951’s subcutaneous infusion/pump mechanism could represent a potentially landscape-altering treatment option, according to David Standaert, MD, PhD, chair of the Department of Neurology at the University of Alabama at Birmingham and a consultant for AbbVie. The new mechanism has several advantages over the percutaneous endoscopic transgastric jejunostomy (PEG-J) tube through which Duopa is administered, he says.

“The big difference from a patient perspective is that the drug can be delivered by a small subcutaneous needle that’s a continuous way of delivering levodopa. The need for levodopa comes out of what happens in advanced PD, where patients develop wearing off of their medications,” he told NeurologyLive®. “About 50% of patients at 5 years will experience wearing off, and there are ways to treat wearing off with oral medications, but many times we get to the point where you cannot control the wearing off anymore.” Standaert, who is also among the investigators for the phase 3 study, asserts that the size of ABBV-951 is another of its advantages.

Although patients with PD have benefited greatly from Duopa, issues with tube clogging and breakage can occur, and endoscopy is required when a tube needs replacement. If the ABBV-951 mechanism proves successful, it could be implemented in-office, with no need for the necessary gastroenterologist involvement and potential complications that come with a PEG-J tube.

Patients included in the study will be evaluated on change in ON time hours without troublesome dyskinesia from baseline up to week 12. Other key secondary outcome measures include changes in OFF time, score on the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale, sleep symptoms, and quality of life. Adult participants with advanced PD who complete the M15-736 study will be enrolled into an open-label extension (NCT04750226), in which researchers will assess adverse events (AEs) and changes in disease activity accompanying 96 weeks of treatment with ABBV-951.

Prior to the use of the Duopa pump, “many of these patients weren’t able to travel or go anywhere,” explained Standaert. “[After getting] the Duopa pump, they [can] travel, go out, be counted on, work—and they’re not fearful of wearing off. If the same can be achieved with a much simpler hardware setup, that would have a very impressive impact,” he emphasized.

According to Standaert, several ongoing phase 2b studies are looking at longer durations of the ABBV-951 therapy, but they have not reached an end point nor have any results been published. Results from a phase 1b study published in early 2020 demonstrated that ABBV-951 was well tolerated when delivered via continuous subcutaneous infusion. Among a cohort of 21 patients included in the safety analysis, AEs occurred in 19 patients (90.5%); 2 serious AEs (cellulitis and abdominal abscess) were reported in 1 patient who prematurely discontinued the study.3 Researchers found no clinically significant changes in laboratory, electrocardiography (ECG), or vital sign parameters. Exploratory efficacy results showed decreased OFF time compared with baseline during the 28-day study period and supported future investigations of ABBV-951.

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

TABLE. M15-736 Study Design

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<th>Eligibility criteria</th>
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<td>• Diagnosis of idiopathic Parkinson disease that is levodopa responsive</td>
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<td>• Aged ≥30 years</td>
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<td>• Must be taking a minimum of 400 mg/day of levodopa equivalents and have recognizable OFF and ON states</td>
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<th>Randomization</th>
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<td>• 11 ABBV-951 and placebo for oral LD/CD, or placebo for ABBV-951 and oral LD/CD</td>
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<th>Primary and secondary end points</th>
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<tr>
<td>• Change in ON time without troublesome dyskinesia</td>
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<td>• Change in OFF time</td>
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<td>• Change in motor experiences of daily living, using MDS-UPDRS</td>
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By Marco Meglio

CLINICAL TRIAL FOCUS MOVEMENT DISORDERS

Potential Breakthrough in Parkinson Disease

Subcutaneous Levodopa/Carbidopa Delivery Provides

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Discover the History of Monoclonal Antibodies, the Pathophysiology of CGRP in Migraine, and a Therapeutic Option for Migraine Prevention

Join expert faculty in this educational iPub® to learn more about migraine pathophysiology and a therapeutic option for migraine prevention.

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In this iPub®, Drs. Jessica Ailani and Andrew Charles will:

- Provide an overview of migraine pathophysiology, the history and design considerations of therapeutic monoclonal antibodies, and the basis for targeting calcitonin gene-related peptide (CGRP) for the treatment of migraine
- Present the results from clinical trials demonstrating the efficacy and safety of a monoclonal antibody in the preventive treatment of migraine
- Review current recommendations for migraine prevention and examine characteristics for patient selection

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Magnetic Resonance’s Impact on Diagnosis, Prognostication, and Therapeutic Approaches in Neuromuscular Disorders

Advances in MRI and MRS techniques and protocols enhance diagnosis of neuromuscular disorders and provide prognostic and intervention efficacy biomarkers

By Kenneth Bender, PharmD, MA

IN ADDITION TO FACILITATING DIAGNOSIS, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are increasingly used in neuromuscular disorders to detect and predict deterioration and to evaluate efficacy of disease-modifying interventions.

Developments and innovative applications of the technologies are revealing disease progression before it manifests in functional testing. These technologies are also providing quantifiable biomarker endpoints for clinical trials that are challenged to detect efficacy of interventions for rare, slowly progressing conditions in small cohorts of likely phenotypic variability.

“Now, an MR scanner is no longer viewed as a simple camera. [It’s seen] as an advanced scientific and clinical tool that not only takes ‘pictures,’ but also, via recently developed methodologies, can report on disease evolution, lean muscle tissue volume, fraction of muscle replaced by fat, metabolism, inflammation, and contractility of muscle,” wrote Julia Dahlqvist, MD, and colleagues in their recent review published in the *Annals of Neurology.*

Dahlqvist is a member of the Department of Neurology, Copenhagen Neuromuscular Center, of Denmark’s Copenhagen University.

In the review, Dahlqvist and colleagues point to Duchenne muscular dystrophy (DMD) as one of the conditions that is more accurately and usefully characterized with the advancing MRI technology. They note studies that have correlated muscle histology and MRI changes, and they point out advances that have been made since the initial visual grading systems were introduced for semiquantification of fat infiltration in muscle.

“Visual grading systems are satisfactory for cross-sectional characterization of disease severity, but not to monitor subtle changes over time as needed in clinical trials,” Dahlqvist and colleagues wrote.

The Dixon imaging technique, utilizing multiecho-chemical-shift encoded water-fat imaging, is now the most frequently used method to quantify fat deposition in muscular dystrophy. In contrast to semiquantitative scoring, the Dixon technique provides the fat fraction as a continuous variable. This allows for greater sensitivity in detecting small differences in fat infiltration, according to another review by Doris Leung, MD, PhD, of the Center for Genetic Muscle Disorders, Hugo W. Moser Institute at Kennedy Krieger Institute, and the Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland.

Others rely on proton spectroscopy to measure increases in fat fraction, especially in younger patients in the early stages of the disease. Dixon imaging is advantageous in providing spatial resolution, acknowledged Krista Vandenborne, PhD, PT, of the Department of Physical Therapy, University of Florida in Gainesville, “but MRS is, in our view, a more sensitive and robust method for quantifying fat fraction,” she commented to *NeurologyLive*.
Muscle edema or inflammation often precedes fat replacement in many muscular dystrophies, according to Dahlgqvist and colleagues. They note the utility of both relaxation time (T₂) mapping and of sensitive, fat-saturated sequences—most often, short tau inversion recovery (STIR) to visualize muscle edema—and find T₂ relaxation time mapping superior to STIR in quantifying the level of edema.

In addition to progressive replacement of muscle by fat, often accompanied by and preceded by edema, Dahlgqvist and colleagues note that fibrosis commonly occurs in connective tissue, resulting in the muscle stiffness characteristic of many neuromuscular conditions, especially muscular dystrophies. They find potential for assessing muscle fibrosis in other technologies that include MR elastography, magnetization transfer, and sodium imaging (MRI imaging conducted with nonproton nuclei, such as ²³Na).

### Determining MR Biomarkers for DMD

The ImagingDMD study investigated the potential of MRI and MRS to be used in lower and upper extremity muscles to reveal biomarker end points for clinical trials of therapeutics for DMD. Vandenborne and colleagues characterized longitudinal progression of lower extremity muscle MRI/MRS biomarkers, examined their relationship with functioning over time, and ascertained their validity for predicting clinically meaningful sentinel events.

“Although a body of literature exists that establishes quantitative MR measures as high-quality biomarkers for DMD, a high burden of proof is required to establish MR biomarkers as secondary end points or surrogate outcomes,” Vandenborne and colleagues indicated.

The largest MR natural history study in DMD to date, the ImagingDMD study includes data collected over 10 years and more than 100 participants completing at least 4 years of data collection. “The ImagingDMD study’s long duration has been important for 2 reasons,” Vandenborne explained to *NeurologyLive*. “First, it has allowed us to evaluate the predictive value of MR biomarkers—measuring early MR markers of disease involvement, then prospectively monitoring each individual’s functional ability to quantify changes over time.” Vandenborne said. “Second, it has allowed us to capture the natural history of DMD and evaluate patterns within and [among] individuals over a wide range of ages and disease severities.”

The investigators monitored 160 participants with DMD at 3 study sites. The initial inclusion criteria required participants to be able to walk at least 100 meters and climb up 4 stair steps, but the criteria later expanded to include nonambulatory individuals. At the baseline visit, participants underwent an MRI and MRS examination of the lower leg and thigh, followed by clinical assessments of ambulatory function. Participants returned annually for follow-up MR and functional and medical history data collection, for up to 7 years.

“The disease trajectory can vary considerably [among] individuals and muscles, independent of genetic mutation or corticosteroid treatment,” Vandenborne commented. “Recognizing this variability is critically important in designing clinical trials, matching study arms, and ensuring that a study is properly powered.”

Vandenborne and colleagues reported that vastus lateralis fat fraction (FF) measured by MRS, vastus lateralis MRI T₂, and biceps femoris long head MRI T₂ biomarkers were the fastest progressing biomarkers over time in this primarily ambulatory cohort. Over the study period, biomarker values tended toward a nonlinear, sigmoidal trajectory.

The investigators found that the lower extremity biomarkers predicted functional performance over the subsequent 12 and 24 months; additionally, the magnitude of change in an MRI/MRS biomarker over time was related to magnitude of change in function.

“The longitudinal study has allowed us to establish that the current FF in the leg muscles is highly predictive of future functional changes,” Vandenborne said. “We can predict, based on someone’s MR data, the likelihood that they will maintain their walking ability over the coming year or years.”

### The Utility of Sodium MRI

With availability of high-field MRI systems, sodium MRI is increasingly being utilized for studies of muscle dystrophies such as DMD as well as muscular channelopathies. In a recent review, Marc-André Weber, MD, MSc, of the Institute of Diagnostic and Interventional Radiology, Pediatric Radiology and Neuroradiology, at University Medical Center Rostock, in Germany, and colleagues found that ²³Na MRI has demonstrated “a muscular Na⁺ overload” in DMD.

“This permanent Na⁺ overload in all DMD patients may be osmotically relevant and may play a role in the development of the muscle edema that was present and persisted in all studied DMD patients,” Weber and colleagues posit.

The prevailing theory of muscle edema in DMD, according to Weber et al, is that it represents the initial inflammatory stage of the ongoing muscle degeneration. They note that increased Na⁺ concentrations can be present even without apparent fatty degenerative changes or increased T₂ relaxation times. The possibility that increased sodium concentrations are relevant to pathogenesis has prompted studies examining effects of diuretic drugs in cell models of DMD and in exploratory human trials.

“This demonstrates that ²³Na MRI can be a very sensitive technique for the analysis of muscular diseases,” Weber and colleagues conclude.

### Artificial Intelligence and ML Quicken MRI

The capacity to reveal minute distinctions across innumerable tissue slice images represents both the value of MRI technology and the challenge of correct assessment and interpretation. The application of algorithms and of machine learning, however, promises more efficient and rapid elucidation of clinically significant findings.

In a recent proof-of-concept study, an active contour-evolution algorithm was successfully employed to enable semiautomated quantification of muscle MRI results. It was “reliable and time-efficient.”
in determination of muscle volumes of neuromuscular patients,” the investigators related. In this study, Madlaine Müller, of the Department of Neurology at University Hospital Aachen in Germany, and colleagues described the results they achieved when performing 3D semiautomated segmentation of standardized muscle MRI datasets to analyze whole-muscle volumes of thighs and lower legs in 65 patients with established neuromuscular diagnoses (from molecular genetics, histological examination, and/or clinical tests).

The investigators reported similar determination of muscle volume for all subjects—patients with either neuropathy or myopathy, and controls—whether measured by semiautomatic algorithm assist or by manual segmentation (semiautomated: 2613 cm³; manual: 2594 cm³). There was, however, significant time efficiency with the semiautomated approach across patient groups (29.7 ±2.7 vs 399.3 ±9.2) minutes per patient; P < .0001.

**Recognizing this variability [in disease] is critically important in designing clinical trials, matching study arms, and ensuring a study is properly powered.**

— KRISTA VANDENBORNE, PHD, PT

In addition to demonstrating the efficiency in ascertaining muscle volume, the investigators are working on a protocol for semiautomated segmentation of the FF. Müller et al posit, however, that their work in improving efficiency in measuring remaining muscle volume could help detect disease progression in long-term studies “more accurately, or even before the fat fraction shows any significant differences.”

**Machine Learning Models and MRI**

While algorithms that improve efficiencies in building MRI datasets will help speed results, technology that boosts proper interpretation of these data could improve the relevance of the data to diagnosis and patient care. Machine learning (ML) platforms are being developed to enhance the utility of MRI in untangling complex, and often overlapping, patterns to differentiate among neuromuscular disorders.

In the genomics realm, next-generation sequencing has increased diagnostic efficiency in neuromuscular disorders, but it has limitations. These could be alleviated at least in part by enhanced MRI-aided diagnostics, according to Jordi Díaz-Manera, MD, PhD, of the Neuromuscular Disorders Unit, Neurology Department, Hospital de Santa Creu i de Sant Pau, Barcelona, Spain, and colleagues.

“The candidate gene sometimes does not fit with the phenotype, potential disease-causing variants in more than 1 gene can be found, or variants of unknown effect can be identified,” Díaz-Manera and colleagues point out. “In all these situations, clinical data and results of complementary tests continue to be of great value to make sense of the results obtained.”

Díaz-Manera and colleagues sought to develop ML-enhanced MRI as an informatic tool to help the diagnostic process for neuromuscular disorders. They used a “random forest” methodology to analyze the data and to find a model that would best distinguish among the different disorders. “Random forest is a [ML] tool capable of fitting large datasets and performing both classification and regression tasks,” Díaz-Manera and colleagues explain.

The ML program was trained on almost 1000 MRI datasets from the lower limbs of patients with 10 different diseases, against previously confirmed diagnoses. Two thousand different models were generated, and the best performed with 95.7% accuracy with an overall sensitivity of 92.1% and specificity of 99.4%.

The investigators then tested the ML diagnostics program on scans from 20 new, undiagnosed patients, against the diagnoses rendered by 4 neuromuscular MRI experts who had also not previously encountered them. The model outperformed each of the 4 experts.

“The results were impressive,” declared Jasper Morrow, MBChB, PhD, of the Department of Neuromuscular Diseases, Queen Square UCL Institute of Neurology, London, England, and Maria Sormani, PhD, of the Department of Health Sciences, University of Genoa, and IRCCS Ospedale Policlinico, San Martino, both in Italy, in commentary accompanying the published study.7

“This is an exciting proof-of-concept study applying ML to pattern assessment of lower-limb muscle MRI involvement in muscular dystrophies,” Morrow and Sormani wrote.

**The Future of MRI and MRS**

Vandenborne foresees continued acceleration of technological capabilities. Citing the 10-year ImagingDMD study as a pivotal example, she anticipates that the advances will yield increasing returns to patients and practitioners. The ImagingDMD team is particularly focused on helping transition-sensitive MR biomarkers into clinical trials, with the goal of accelerating therapeutic development.

“At this point, an MR Imaging Biomarker Steering Committee, consisting of industry stakeholders, private foundations, and other DMD community representatives, [is] helping us prepare a fit-for-purpose application to [submit to] both the FDA and the European Medicines Agency,” Vandenborne explained.

She continued that the 10-year ImagingDMD data will serve as the backbone for this initiative. They will be the foundation for creating an MR biomarker clinical trial simulation tool that could offer its users a way to simulate hypothetical drug effects on disease progression characteristics for particular subpopulations of patients with DMD. Additionally, Vandenborne said, it will help with investigators’ selection of clinical trial design characteristics.

“This tool will be open and made publicly available in order to facilitate easy access, broad use, and high impact,” Vandenborne said.
A Critical Evaluation of Disease-Modifying Strategies in Parkinson Disease

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A NUMBER OF DISEASE-MODIFYING THERAPIES have been investigated in Parkinson disease (PD), and they all encountered a common roadblock: overcoming the efficacy of levodopa. Major obstacles are evident in the inability to translate preclinical data into therapies and in the failure to identify reliable biomarkers. Novel approaches like immunotherapies, gene therapies, and tyrosine kinase inhibition provide alternate methods for the development of disease modification in PD.

The Valley of Death: From Preclinical Mechanisms to Clinical Effect

Previous PD research efforts focused on motor function and symptoms, although PD includes complexities beyond these. The Neuroprotective Exploratory Trials in PD (NET-PD) program intended to accelerate therapeutic evaluation in PD trials. Preclinical animal data provided strong justification for clinical investigation into more than 80 compounds. The incentives for initiation of NET-PD were the relatively good drug safety profiles. These drugs were studied in concurrent clinical trials, but ultimately, they led to collective failure. Several shortcomings have since been noted that strongly dispute the supposed rigor of NET-PD studies, including lack of biomarkers that could be reliably measured in animals and the noninclusion of patients with PD to prove target engagement and drug effects. Pharmacological diligence and drug dose selection were absent—most NET-PD studies tested a single-dose level—suggesting that potential clinical or biomarker effects were missed. Some studies progressed to phase 3, such as SURE-PD3 and STEADY-PD III, but these late-stage studies showed no effect on the primary motor outcome. Collectively, these studies were predominately early-stage, lacked a specific biomarker, did not employ satisfactory dose selection strategies, and, overall, focused on motor outcomes over a short period of time (<12 months) in levodopa-treated PD patients. The accelerated NET-PD studies were a “rushed effort” that omitted adequate pharmacological scrutiny and aimed to show the efficacy of neuroprotective agents on motor symptoms compared with levodopa.

The Conundrum: Biomarkers and Clinical Effects

PD involves motor and nonmotor symptoms, loss of dopaminergic neurons, and accumulation of misfolded alpha-synuclein (αS) oligomers. Research in PD is lagging that of other
neurodegenerative diseases, like Alzheimer disease (AD), owing to the availability in those other diseases of dopaminergic and other symptomatic therapies. In idiopathic PD, a biomarker system to evaluate investigational disease-modifying drug effects is absent. Conversely, in AD, novel drug candidates rely on the amyloid/tau/neurodegeneration system that may collectively represent pathological changes in the AD brain.9

PD is a progressive, multisymptomatic disease that requires increasingly more medications as the disease worsens. The primary limitation in phase 2 and 3 PD trials is emphasis on a short-term motor outcome in patients who are already medicated. Another common limitation of disease modification in PD trials is lack of treatment-specific target engagement and related biomarkers. PD treatment is unlikely to be similar to that of, say, hypertension (eg, a readout of the mean arterial pressure indicates immediate drug response), but an effective PD treatment would create a prolonged biological process that should halt or reverse neuropathology. Therefore, both earlier intervention in biomarker-confirmed PD and longer treatment in drug-naïve patients are needed to demonstrate motor and nonmotor benefit. Alternatively, medically optimized patients must be treated significantly longer compared with predicted placebo and/or standard of care (eg, levodopa, dopamine agents, etc) to observe the effects of long-term therapies that modify multiple pathologies integral to the “brain motor system,” including dopamine loss, oligomeric αS, and hyperphosphorylated tau (p-tau). As in AD, measurement of these biomarkers together as a “mix” may help to evaluate the efficacy of disease-modifying drugs.

The diagnostic error at the onset of motor symptoms is often significant; PD can be confused with other alpha-synucleinopathies such as Lewy body dementia (LBD) and primary tauopathies. Studying motor symptoms without biomarker confirmation is detrimental to clinical trials that exclusively focus on motor effects. The limitations of motor assessments and of scales like the Unified Parkinson’s Disease Rating Scale (UPDRS) must be recognized.10 For instance, the UPDRS should be performed together with developing technologies like wearable devices that could provide objective measures.

In addition to motor assessment, biomarkers should be used as measures of underlying biology for subtyping.11 For example, targeting leucine-rich repeat kinase 2–associated PD12 and glucocerebrosidase (GBA)-associated PD13 are efforts in the right direction within genetically defined conditions. αS gene duplication, multiplication, and mutations are causal genetic factors in familial PD.14 The cerebrospinal fluid (CSF) levels of αS oligomers increase in PD, while total αS decreases, compared with age-matched controls.15-17 These data provide an important distinction between normal, natively unfolded αS (referred to as total levels), which has an essential housekeeping function, and misfolded oligomers, which may form toxic fibrils and induce Lewy body pathology. The toxicity of αS is due to the transitional oligomers that are the building blocks of fibrils,18 and these transitional oligomers are measurable in the CSF of those with PD. Furthermore, p-tau leads to motor and nonmotor symptoms that may overlap with those of PD, and p-tau should be considered to be integral to a PD biomarker mix that represents the anatomical and molecular basis of motor and nonmotor symptoms in PD.

### Studying Dopamine Metabolism as a Biomarker

In animal models, the accumulation of αS aggregates impairs dopamine transmission, but eliminating these aggregates enhances dopamine release and utilization in the nigrostriatum.19 Reducing αS oligomers results in improved dopaminergic neuron activity in PD patients20; therefore, simultaneous measurement of oligomeric αS and dopamine is an index of functional activity of dopamine neurons. Total and oligomeric αS as well as 2 dopamine metabolites—homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC)—are robustly measured in the CSF of patients with PD.21 The brain contributes 10% to 15% of the plasma levels of HVA21; most of the circulating levels of HVA come from intestinal metabolism of dopamine, while DOPAC is a principal metabolite of brain dopamine and is transported from the brain to the plasma for excretion.22 Therefore, dopamine utilization and metabolism should be measured via concurrent CSF and plasma levels of HVA and DOPAC to indicate drug disease-modifying effects.

### Tyrosine Kinase Inhibition

In 2014, a seminal report showed the effects of a oncologic agent called nilotinib (Tasigna; Novartis) as a potential treatment in PD.23 Nilotinib lowers αS, including oligomers; reduces p-tau, via autophagy; and improves dopamine metabolism. A phase 1 study in late-stage (Hoehn &Yahr stages 4-5) levodopa-unresponsive PD and LBD patients demonstrated the feasibility of nilotinib.23 Nilotinib potently targets discoidin domain receptor (DDR)-1 at IC50 of 1 nM and much less potently inhibits Abelson (c-Abl) at 20 nM. It is FDA approved for chronic myelogenous leukemia.24 Phase 2 studies investigated the effects of nilotinib in medically optimized patients with moderately severe PD for 6 months,25 12 months,26 and 27 months.27 These phase 2 studies were underpowered for clinical outcomes, but they all met their primary objectives, demonstrating that nilotinib is safe. However, significant differences existed among these studies. Pagan et al showed that CSF nilotinib concentration is adequate to inhibit DDR1, but not c-Abl, and nilotinib treatment stabilized total αS, partially reduced oligomeric αS and lowered p-tau in a dose-dependent manner.20 Simuni et al, however, did not explore nilotinib effects on these biomarkers.26 Methodologically, Simuni et al performed one-time collection of CSF and serum, after 2 hours, that led to underestimation of drug availability.26 In 2019, Pagan et al staggered CSF collection at 1-4 hours, 30 minutes after blood draw, to obtain population-based pharmacokinetics.20,26 Monoamine oxidase B (MAO-B) inhibitors were allowed (>30%) in the study by Simuni et al,25 thus altering the level of dopamine metabolism, whereas the studies by Pagan et al excluded MAO-B inhibitors.20 Simuni et al28 did not control for levodopa in medically optimized patients28 and did not detect changes in dopamine metabolism.
metabolites. In contrast, data from animal studies,23 human phase 1 studies,24 phase 2 studies in PD, and phase 2 studies in levodopa-naïve patients with AD consistently demonstrated dose-dependent increases in dopamine after nilotinib treatment.20,21 This discrepancy could also be due to concurrent measurement of 17 metabolites that reduce the optimization of specific dopamine metabolites in serum and CSF by Simuni et al,24 whereas Pagan et al25,26 and Turner et al27 measured only 2 dopamine metabolites in plasma and CSF.

It is imperative to mention that the placebo and nilotinib groups did not decline using UPDRS at 6 months and 12 months, indicating that all patients were medically optimized. However, treatment of 27 months with nilotinib suggested that 300 mg is beneficial for motor, cognitive, and behavioral symptoms in medically optimized patients.27 These long-term effects are consistent with disease modification showing evidence of increased autophagy flux in animal models and CSF microRNA levels in PD and LBD patients.24,29

In addition to nilotinib, which will be investigated in phase 3 studies (KeifeRx), 2 c-Abl inhibitors are currently in phase 2 clinical trials, including K0706 in early PD (Sun Pharmaceuticals) and LBD (at Georgetown University) and bosutinib (Bosulif; Pfizer) in LBD (also at Georgetown University).

### Immune and Gene Therapies and Other Strategies

Several other strategies are in the pipeline for PD (TABLE).31 Deferiprone (Ferriprox; Chiesi) is FDA approved to treat some thalassemia syndromes as an iron chelation agent and is currently in phase 2/3 assessment for PD (at University Hospital, in Lille, France).32 The effects of glucagon-like peptide analogue (exenatide) on mitochondrial function (at Karolinska Institut, in Solna, Sweden) and a muscarinic and sigma-1 receptor agonist (ANAVEX atide) on mitochondrial function (at Karolinska Institut, in Solna, Sweden) are being investigated in phase 2/3 studies.

**TABLE.** Select Therapies in Phase 3 Trials in Parkinson Disease31

<table>
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<tr>
<th>Agent</th>
<th>Sponsor</th>
<th>Status</th>
<th>Estimated enrollment</th>
<th>NCT identifier</th>
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<td>AbbVie</td>
<td>Recruiting</td>
<td>240 participants</td>
<td>NCT03781167</td>
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<td>AbbVie</td>
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<td>Sunovion</td>
<td>Recruiting</td>
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Targeting αS with the monoclonal antibody (mAb) BIIB054 (Biogen) did not meet its primary objectives. The mAb PRX002/Ro7046015 (Prothena/Roche) and the glucocerebrosidase inhibitor GZ402671/SAR02671 (Sanofi), which prevents αS accumulation, are currently in phase 2.

A number of phase 1 studies using anti-αS mAbs, like MEDI1341 (AstraZeneca/Takeda), ABBV-0805 (AbbVie), LU AF82422 (Lundbeck), PD01 AFFITOPE (AFFiRiS), and NPT200-11/UCB0599 (Neurophere/UCB) are being studied to prevent αS aggregation. mAbs may have significant hurdles entering the cytoplasm and ligating αS en route to degradation. This strategy has yet to prove its success in human clinical trials.

Several gene therapies are also being explored in PD, including phase 2 studies using adeno-associated virus (AAVs) to increase GBA in the subthalamic nucleus (GAD-AAV; MeiraGTx), single implant into the putamen to increase aromatic L-amino acid decarboxylase (AADC) levels (AADC-AAV2/VY/AADC02; Voyager/Neurocrine), and bilateral putamen injection of AADC using a lentivirus (ProSavin, OXB-101; Oxford BioMedica/Sio Gene Therapies). Another anti-GBA agent that employs AAV is PR001 (Prevail Therapeutics). These gene therapies are still in early development, and while scientifically plausible, they face many challenges regarding stability of viral vectors; gene-of-interest expression and reversibility; adverse effects; and single vs multiple injections or surgeries.

Many agents show promise in having disease-modifying effects in PD, but in order to prove their viability, a specific target engagement and related biomarkers must be studied with the correctly termed clinical outcomes. Each agent may require unique criteria.
THIS YEAR, THE THIRD WEEK OF MARCH was Sleep Awareness Week, culminating on Friday, March 19, 2021, with World Sleep Day. The purpose of these designations is to promote better sleep and increase awareness of different sleep disorders: More than 90 exist. The most dangerous of these is obstructive sleep apnea (OSA), which, when untreated, results in mortality in up to 40% of cases within 12 to 15 years.1,2

Based on hazard ratios, OSA may present an even greater cardiovascular mortality risk than hypertension (HTN),1,3 which is known as the “silent killer” because it often goes unnoticed until it has wreaked havoc on the cardiovascular system. If HTN is the “silent killer,” then OSA is the “loud killer”—loud because most patients with OSA snore, and up to 87% of those who snore have OSA.4

With the knowledge we have today, snoring should no longer be a laughing matter. Snoring is the sound of a partially obstructed airway and the sound of someone struggling to breathe in their sleep. It is the sound of someone likely to be sleepy or fatigued the next day. It is the sound of someone more prone to depression, anxiety, and cognitive issues. It is the sound of future HTN, type 2 diabetes (T2DM), and cardiovascular disease (CVD).

The “Loud Killer” and the “Silent Killer,” T2DM, and CVD
OSA has a significant association with hypertension. In response to the partially obstructed airway, the body’s “fight or flight” reaction (sympathetic activation) is triggered, and the subsequent norepinephrine release momentarily relieves the obstruction (snoring). We at the Sleep Centers of Middle Tennessee (SCMT) created the acronym “S-Nore-R,” for sleep-norepinephrine-release, to emphasize the connection between norepinephrine release and snoring.

With OSA, S-Nore-R can occur hundreds of times each night, and since norepinephrine raises blood pressure, it becomes clear why continuous positive airway pressure (CPAP)—the primary treatment for OSA—improves HTN.5 Between 60% and 83% of patients with HTN have OSA.6,7 As far back as 2003, the Joint National Committee on Hypertension recommended that all patients with HTN who snore be tested for OSA.8

The “loud killer” is also likely a significant cause of T2DM. Up to 86% of patients with T2DM have OSA.9 S-Nore-R raises blood sugar, and thus insulin levels, which likely contributes to the development of insulin resistance and T2DM. Just 2 weeks of CPAP can improve insulin resistance, and CPAP use has been shown to lower glycated hemoglobin levels.10,11 Patients with T2DM need to be tested for OSA regardless of whether or not they snore. These patients should not miss the potential benefits of improving their blood sugar control.
without adding further medication. The International Diabetes Federation Task Force began recommending in 2008 that patients with T2DM be screened for OSA, but despite the recommendations, only 5% of patients with T2DM are being treated for OSA.

The main reason for underdiagnosis is the lack of OSA awareness among many health care providers. Whereas treatments for HTN and elevated cholesterol have been around for more than 60 years, there was, until recently, little to no emphasis on sleep in the curricula of medical training programs. Also, no pharmaceutical companies are behind the scenes pushing OSA awareness in medical practices.

Improving Awareness
A single week in March is devoted to OSA awareness, while HTN, T2DM, high cholesterol, and CVD each have their own awareness months. That may change in a few years when the first medications to treat OSA are released. It can be expected that pharmaceutical companies will then try to put OSA in the forefront of consumers’ and clinicians’ mind. Unfortunately, the agents in current trials are just for milder cases and specific subtypes of OSA. Plus, CPAP has more than 30 years of outcome data, and even if the medications are found to be safe, it will take years to complete similar studies for them. For the foreseeable future, CPAP will remain the safest, most effective, least expensive, and most supported treatment in the literature.

The term “obstructive sleep apnea,” we can also speculate, may be keeping many patients from treatment. It’s misleading, particularly the word “apnea.” An apnea is a complete obstruction to airflow, but most obstructions that cause S-Nore-R are partial obstructions to airflow; these are usually responsible for snoring noises. Many patients diagnosed with OSA do not actually have apnea. Conversely, the term “obstructive sleep apnea” results in many providers thinking that a patient has to “stop breathing” or “hold their breath” in their sleep to have a reason to undergo testing. The providers simply do not realize that snoring alone is enough reason to refer a patient for sleep testing.

The term “obstructive sleep apnea” was coined by Christian Guilleminault, MD, in 1976 when early sleep studies measured only apneas. In 1988, Gould et al first showed that partial obstructions—which are far more common—had the same sequelae as apneas. However, the term was never changed. Our group has begun experimenting with a modernized name and understanding for OSA (including S-Nore-R) that, so far, is helping more patients understand their sleep problems and adhere to treatment.

For many patients, obstacles still remain. Sometimes, OSA testing can be inconvenient and expensive, and it can take weeks to months to begin treatment. Also, CPAP is still wrongly perceived by many as akin to gas mask–like devices left over from World War I. Most importantly, the great value that CPAP can add to one’s life is not well understood. However, we have found that, with effort, these obstacles can definitely be overcome.

Despite Loudness, Snoring Is Mostly Ignored
While screenings for HTN, high cholesterol, and T2DM are standard in general medical practice, testing for OSA is uncommon, and as many as 90% of cases are undiagnosed. The main reason for underdiagnosis is the lack of OSA awareness among many health care providers. Whereas treatments for HTN and elevated cholesterol have been around for more than 60 years, there...
diagnose and treat OSA inexpensively, quickly (within days), and without the patient even having to leave their home. The program is called OSAinHome and is already accepting patients from 7 southeastern states. After a phone interview at no charge, appropriate patients are shipped a high-tech but simple-to-use sleep testing device to wear in their homes. The device uploads to the cloud in the morning, which is followed by a televisit with a sleep medicine provider. For patients who need CPAP, the device is then shipped directly to their homes. Inside the device is a cellular modem so that we can care for them remotely. Instruction provision and education can all be done virtually.

For most patients, we have made diagnosing and treating OSA as fast as ordering a lipid profile and starting a statin. Over 5 years, the costs of testing for and treating OSA are similar to, or even less than, testing for and treating elevated cholesterol with statins.27-29 The exception would be if you had your sleep test in a hospital-owned sleep facility.

Historically, CPAP usage among those who have been prescribed the devices has been poor,30-32 with as few as 25% to 35% of patients continuing its use at 1 year. In January 2021, our group published data regarding 4100 patients showing that those who were provided CPAP by SCMT (an integrated sleep practice) were 50% more likely to wear their CPAP long term than if CPAP was provided by a medical equipment company.33 The results of the study, which was a joint effort by Middle Tennessee State University, Vanderbilt University, and SCMT, showed that 89% of patients were still using CPAP at 3 months, but only 66% at 1 year. The study computations were done when remote patient monitoring had been in use for only 3 months. Today, SCMT monitors each CPAP patient for 7 months, and more than 85% of those prescribed CPAP are still using their devices at 1 year. Achieving these results requires great integrated effort and focus by the whole staff. However, now, SCMT patients are more likely to use CPAP than to take their cholesterol medication, mainly because cholesterol medications do not make you feel great in the morning as the correct use of CPAP does.

Remove the Loud Killer From Your Practice
Not just during Sleep Awareness Week, but every week, give attention to removing the “loud killer” from your practice. Just as you check every patient’s blood pressure, ask every patient if they snore—and remember, half of snorers deny it, so ask them if their bedpartner says they snore. Additionally, ask them what it would be worth to feel 50% to 100% better every day and to have more days to live. As of 2019, 37% of adults in the United States have OSA,35 and the prevalence is likely higher in your waiting room. The “loud killer” must be stopped.

William H. Noah, MD, has been practicing sleep medicine for more than 25 years. He is the senior medical director for Sleep Centers of Middle Tennessee and OSAinHome. He also chairs the Middle Tennessee State University Sleep Research Consortium.

For a full list of references, see the article on NeurologyLive.com.
**Washington University, St Jude Awarded NIH Grant**
The National Institute of Neurological Disorders and Stroke, a component of the National Institutes of Health (NIH), awarded scientists from Washington University in St Louis and St Jude Children’s Research Hospital a 5-year, $3.1-million grant for research relating to amyotrophic lateral sclerosis (ALS). Rohit Pappu, PhD, Edwin H. Murty Professor of Engineering in the Department of Biomedical Engineering, McKelvey School of Engineering, Washington University, and Tanja Mittag, PhD, associate member, St Jude Department of Structural Biology, received the funds to study RNA-binding proteins that are mutated in patients with familial forms of ALS. The goal of the study will be to uncover the mechanisms underlying the formation of solid inclusions of these RNA-binding proteins, as well as to allow future identification of new therapeutics for ALS and other neurodegenerative disorders.

**First-of-its-Kind Black Alzheimer Brain Study Launched**
The University of North Texas Health Science Center (HSC) at Fort Worth has launched the first Black Alzheimer’s (ALZ) Brain Study, which will aim to find answers regarding why Alzheimer disease disproportionately impacts Black families. HSC invested $7 million into the new study and plans to coordinate it as part of its historic Health and Aging Brain Study. The Black ALZ Brain Study will leverage state-of-the-art imaging and robotics to analyze brain protein markers, without requiring injections nor the administration of prescription drugs. Media personality Sybil Wilkes, as well as community, civic, and faith-based leaders, have joined the effort to help increase awareness and encourage Black residents in the Dallas–Fort Worth region to join the study. In a statement, Wilkes said, “My life’s mission is to super-serve our people and effect positive change. I’m grateful for the opportunity to help bring attention to this important study and encourage others to join.”

**ADDF Names Christopher Johnson Co-Chair of Board of Overseers**
The Alzheimer’s Drug Discovery Foundation (ADDF), a leading nonprofit organization dedicated to rapidly accelerating the discovery of drugs to prevent, treat, and cure Alzheimer disease (AD), appointed Christopher Johnson, chief executive officer of Rackson Restaurants, as co-chair of the ADDF’s Board of Overseers. Johnson’s connection to AD is through his father, Ron Johnson, the former New York Giants running back who was given a diagnosis of early-onset AD in 2008 and died in 2018. Christopher Johnson has been a longtime advocate of the ADDF and has raised more than $130,000 for the organization as part of their marathon-running team. During his first year on the board, Johnson was honored with the Charles Evans Award, which is presented to individuals whose contributions significantly advance the field. In a statement, Johnson said, “It’s an honor to be given the opportunity to co-chair the board of such a forward-thinking organization.”

**Former FDA Commissioner Stephen Hahn, MD, Joins Blackfynn Board of Directors**
Blackfynn, a company that uses clinical data, data modeling, and analytics to drive drug development, has announced that Stephen Hahn, MD, will join its Board of Directors. Hahn recently served as the commissioner of the FDA, where he led the development of new regulatory paradigms that ultimately allowed the expedited development, review, and approval of the first vaccines for coronavirus disease 2019. By training, he is also a radiation and medical oncologist who has held senior leadership positions at University of Texas MD Anderson Cancer Center and the University of Pennsylvania. Blackfynn focuses on optimizing clinical-stage assets for the near-term benefit of patients with Parkinson disease and other neurodegenerative disorders. Hahn said in a statement, “Blackfynn’s platform and tools have the potential to drive new regulatory paradigms, and I am excited to be at the leading edge of this new approach.”

**MLB Marks Lou Gehrig Day to Raise Awareness of ALS**
On the 80th anniversary of Lou Gehrig’s death, Major League Baseball (MLB) will mark June 2 as Lou Gehrig Day to honor the legacy of the Hall-of-Fame first baseman whose career was cut short by amyotrophic lateral sclerosis (ALS). Gehrig died at age 37, less than 2 years after the famous speech in which he told a crowd of 60,000 fans at Yankee Stadium that, despite his illness, “Today, I consider myself the luckiest man on the face of the earth.” Specially designed red patches and wristbands will be worn on June 2 by all MLB players, and individual teams will mark the day in their home ballparks. MLB will use the occasion to raise money for and awareness of the battle against ALS, and to pay homage to ALS advocacy groups, one of which—the LG4Day committee—turned an off-the-cuff text into a unifying cause for baseball. (Gehrig wore number 4 for the Yankees.)

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Fred is a person living with Parkinson’s disease (PD). And, while he is diagnosed with PD, it does not define him, and he does not let it stand in the way of the many things that he likes to do.

Fred’s story, and thousands of others like his, are what shape the Supernus Pharmaceuticals resolve to bring innovative therapies to the PD community.

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