How Big Data Can Drive Advancements in MS Research

Sonja W. Scholz, MD, PhD, on Advancing Genomics Against Complex, Polygenic Neurodegenerative Disorders

Sparing the Hippocampus in Epilepsy Surgery: Critical Decisions for Outcome Optimization
BY MARCIA MORITA-SHERMAN, MD, PHD, AND LARA JEHI, MD, MHCDS

Compounding Challenges: Conducting Clinical Trials in Alzheimer Disease

PACAP Pathway and Its Role in Migraine
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CLINICAL VIEWPOINT
Aducanumab and the Alzheimer Disease Treatment Landscape
WITH STEPHEN SALLOWAY, MD, MS

NEUROLOGYLIVE.COM
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 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:\( ^2 \):

- **ARR (primary endpoint)\( ^1 \)**
  - Relative reduction in ARR at 96 weeks
  - MAVENCLAD (n=433) vs placebo (n=437)
  - HR 0.67; P < 0.001

- **EDSS PROGRESSION\( ^3 \)**
  - Reduction in risk of 3-month confirmed EDSS progression
  - MAVENCLAD (n=433) vs placebo (n=437); HR 0.67; P < 0.001

- **T1-Gd\( ^+ \)**
  - Reduction in median number of T1-Gd+ lesions
  - MAVENCLAD (n=433) vs placebo (n=437); HR 0.33; P < 0.001

- **ACTIVE T2\( ^1 \)**
  - Reduction in median number of active T2 lesions
  - MAVENCLAD (n=433) vs placebo (n=437); HR 0.33; P < 0.001

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**MOST COMMON (>20%) ADVERSE REACTIONS IN CLARITY\( ^1 \)**

<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.

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**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.

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**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.

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Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed WARNING on the following pages.
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 parental cladribine used for treatment indications other than multiple sclerosis.

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

**Drug Interactions/Concomitant Medication:** Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. 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

**REFERENCES:**
MAVENCLAD® (cladribine) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: MALIGNANCIES AND RISK OF TERTIARY ANGIOTENOSIN

Malignancies

Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy or 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 is contraindicated in women who are or plan to become pregnant, 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 [see Contraindications (4), Warnings and Precautions (5.1)]

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

MAVENCLAD is contraindicated:

• in patients with current malignancy [see Warnings and Precautions (5.1)].
• in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. May cause fetal harm [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)].
• in patients infected with the human immunodeficiency virus (HIV) [see Warnings and Precautions (5.4)].
• in patients with active chronic infections [e.g., hepatitis or tuberculosis] [see Warnings and Precautions (5.4)].
• in patients with a history of hypersensitivity to cladribine [see Warnings and Precautions (5.6)].

5 WARNINGS AND PRECAUTIONS

5.1 Malignancies

Treatment with MAVENCLAD may increase the risk of malignancy. In controlled and extension clinical studies worldwide, malignancies occurred more frequently in MAVENCLAD-treated patients (10 events in 3,754 patient-years [0.27 events per 100 patient-years]), compared to placebo patients (3 events in 2,275 patient-years [0.13 events per 100 patient-years]). Malignancy cases in MAVENCLAD patients included metastatic pancreatic carcinoma, malignant melanoma (2 cases), ovarian cancer, compared to malignancy cases in placebo patients, all of which were curable by surgical resection (basal cell carcinoma, 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 (2.3)]. 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 (0.2 events per 100 patient-years) [0.9 events per 100 patient-years] calculated from the start of cladribine treatment in Year 3). The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

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

5.2 Risk of Teratogenicity

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

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

5.3 Lymphopenia

MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and progressively decreased with each additional treatment course. In patients treated with a cumulative dose of MAVENCLAD 3.5 mg per kg over 2 courses as monotherapy, 21% and 1% had nadir absolute lymphocyte counts less than 500 and less than 200 cells per microliter, respectively. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells per microliter; median time to recovery to at least 800 cells per microliter was approximately 28 weeks. Additive hematological adverse reactions may be expected if MAVENCLAD is administered prior to or concomitantly with other drugs that affect the hematological profile [see Drug Interactions (7.1)].

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

Obtain complete blood count (CBC) with differential and platelet count before initiation of each treatment course of MAVENCLAD and at least 4 to 6 weeks after starting MAVENCLAD, 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-hyperglobulin to patients with lymphocyte counts less than 200 cells per microliter.

Patients with lymphocyte counts below 500 cells per microliter who would 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.

Herpes Virus Infections

In controlled clinical studies, 6% of MAVENCLAD-treated patients developed a herpes virus 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 would 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 Leukenoecephalopathy

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

No case of PML has been reported in clinical studies of cladribine in patients with multiple sclerosis. In patients treated with cladribine for lymphoid 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 (5.3)], decreases in other blood cells 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 severe 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
8.0 g per dl to < LLN, were observed in 26% of MAVENCLAD-treated patients, compared to 19% of placebo patients. Decreases in platelet counts were generally mild (cell count 75,000 cells per microliter to < LLN) and were observed in 11% of MAVENCLAD-treated patients, compared to 4% of placebo patients. In clinical studies at dosages similar to or higher than the approved MAVENCLAD dosage, serious cases of thrombocytopenia, neutropenia, and pancytopenia (some with documented bone marrow hypoplasia) requiring transfusion and granulocyte-colony stimulating factor treatment have been reported (see Warnings and Precautions (5.4) 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-MST 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 advisable.

5.7 Liver Injury

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

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to the first and second treatment course (see Dosage and Administration [2.1]). 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 and/or dark urine), promptly measure serum transaminases and total bilirubin to interrupt or discontinue treatment with MAVENCLAD, as appropriate.

5.8 Hypersensitivity

In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD (e.g., dermatitis, pruritus) occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. One patient had a serious hypersensitivity reaction with rash, mucous membrane ulceration, throat swelling, vertigo, diplopia, and headache after the first dose of MAVENCLAD. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine (see Contraindications [4]).

5.9 Cardiac Failure

In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately 1 week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis. Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., breathlessness, 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])

6.1 Clinical Trials Experience

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>MAVENCLAD (N=460) %</th>
<th>Placebo (N=435) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td>5</td>
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<td>Insomnia</td>
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<td>Bronchitis</td>
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<tr>
<td>Hypertension</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

**Hyperkalemia**

In clinical studies, 11% of MAVENCLAD patients had hyperkalemia adverse reactions, compared to 7% of placebo patients (see Warnings and Precautions [5.4]).

**Alopecia**

Alopecia occurred in 3% of MAVENCLAD-treated patients compared to 1% of placebo patients.

**Myelodysplastic Syndrome**

Cases of myelodysplastic syndrome have been reported in patients that had received parenteral cladribine at a higher dosage than that approved for MAVENCLAD. These cases occurred several years after treatment.

**Hepatitis**

Hepatitis occurs in patients who have received parenteral cladribine and is typically reversible. In some cases, hepatitis was severe and required hospitalization.

**Neutropenia**

Neutropenia occurs in patients who have received parenteral cladribine and is typically reversible. In some cases, neutropenia was severe and required hospitalization.

**Anemia**

Anemia occurs in patients who have received parenteral cladribine and is typically reversible. In some cases, anemia was severe and required hospitalization.

6.4 Drug Interactions

**Drug Interactions With MAVENCLAD (continued)**

**7.2 Interferon Beta**

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

**Prevention or Management**

Concomitant use is not recommended.

**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]).

**Prevention or Management**

Monitor hematological parameters.

**7.4 Antiviral and Antiretroviral Drugs**

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

**Prevention or Management**

Avoid concomitant use.

**7.5 Potent ENT, CNT, and BCRP Transporter Inhibitors**

Cladribine is a substrate of breast cancer resistance protein (BCRP), equilibrative nucleoside (ENT1), and concentrative nucleotide (CNT) transport proteins. The bioavailability, intracellular distribution, and renal elimination of cladribine may be altered by potent ENT1, CNT3, and BCRP transporter inhibitors.

**Prevention or Management**

Avoid co-administration of potent ENT1, CNT3, or BCRP transporter inhibitors (e.g., ritonavir, elotrombopag, curcumin, cyclosporine, diltiazem, nelfinavir, nirmatrelvir, ocrelizumab, pasireotide, or rasviral) during the 4- to 5-day MAVENCLAD treatment cycles. If this is not possible, consider selection of alternative concomitant drugs with no or minimal ENT1, CNT3, or BCRP transporter inhibiting properties. If this is not possible, dose reduction of the minimum mandatory dose of drugs containing these compounds, separation in the timing of administration, and careful patient monitoring is recommended.

**7.6 Potent BCRP and P-gp Transporter Inducers**

Possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered.

**Prevention or Management**

Consider a possible decrease in cladribine efficacy if potent BCRP or P-gp (e.g., ritonavir, cobicistat, or fosamprenavir) are used during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course.

**7.7 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.
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 embryotoxic when administered to pregnant mice and produced malformations in mice and rabbits [see Data]. The observed developmental effects are consistent with the effects of cladribine on DNA [see Contraindications (4) and Warnings and Precautions (5.2)].

Data

Animal Data

When cladribine was administered intravenously (0.0, 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, 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, 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 systematically acting hormonal contraceptives. Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course. Women who become pregnant during MAVENCLAD therapy should discontinue treatment [see Warnings and Precautions (5.2) and Drug Interactions (7.7)].

Males

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Patients With Renal Impairment

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

8.7 Patients With Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown [see Clinical Pharmacology (12.3)]. No dosage adjustment is recommended in patients with mild hepatic impairment. MAVENCLAD is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score greater than 8) [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

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

Inform patients of the possible risk of malignancies, teratogenicity, lymphopenia, and other hematologic toxicity, 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.

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How Big Data Can Drive Advancements in MS Research

BY NICOLA DAVIES, PHD

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How Pharmaceutical Innovation Is Saving the World

IN MARCH 2020, the United States was in the early stages of the coronavirus disease 2019 (COVID-19) pandemic. We shut down the entire country and ground the economy to a halt to slow the spread of the virus. Think back to March and how much uncertainty we were living under.

Nine months later, the FDA approved 2 COVID-19 vaccines under emergency authorization. Before New Year’s Day, millions of Americans had received the vaccine, including frontline physicians and health care providers and nursing home patients, our most vulnerable citizens. Nine months. Take a moment to let that sink in.

The mainstream media has crafted a narrative about the COVID-19 pandemic that's almost entirely negative. For the purpose of ratings, they have described the US response to the pandemic as blundering from 1 mistake to the next. This narrative is false.

There is a way to tell the story of the past 9 months. It is a story of heroism, innovation, and precise science, performed under unbelievable pressure. It is the story of physicians, like Jennifer Frontera, MD, neurointensivist, NYU Langone, and David Langer, MD, chair of neurosurgery, Lenox Hill Hospital, answering the call and stepping into converted hospital settings, such as the Javits Center, to care for patients. It’s the story of medical organizations, like the Consortium of Multiple Sclerosis Centers, building resources and tools to help physicians stay up to date on the best care practices during such a difficult time.

Let’s not mince words: The US and the world must appreciate the role of the pharmaceutical industry—the investigators, physicians and business leaders—who are rescuing the world from COVID-19. It’s the medical breakthrough of our lifetime.

Since the discovery of COVID-19, here is some of what scientists have accomplished: They identified a novel virus; unlocked and sequenced its genetic code; created new therapies to save lives; and developed multiple safe and effective vaccines using messenger RNA technology, a technology hopefully applicable to future vaccine development. Margaret Liu, MD, a biomedical scientist and member of the MJH Life Sciences™ COVID Coalition, called it a breakthrough for mRNA vaccines. The United States has 2 vaccines approved for emergency use, 1 from Pfizer/BioNTech and another from Moderna. In addition, there are 64 vaccines undergoing clinical trials at the moment, including 20 in phase 3 trials. In the US and throughout the world, the pharmaceutical industry has answered the call and invested heavily in this effort.

The next step of the process—distribution of the vaccine—will be as challenging as the development phase, if not more so. But again, the pharmaceutical industry is rising to the occasion. Factories worldwide are working on overdrive to produce hundreds of millions of vaccine doses. Just more than a month after the Pfizer vaccine was approved, more than 48 million doses of vaccine have been distributed throughout the country, and more than 21 million individuals have received their first dose, according to CDC data. Many patients are already receiving their second dose.

Although 15 million doses in the early phases are impressive, some expected 20 million doses. But that is moving the goal line, as 6 months ago many observers didn’t think a vaccine would be available until 2021.

Members of our COVID Coalition told us that the holidays slowed the rollout considerably. Nancy Messonnier, MD, a physician with the National Center for Immunization and Respiratory Diseases at the CDC, expected this rapid increase in administered vaccines during the first few weeks of 2021.

Every day, more people will be vaccinated. After health care workers and our most vulnerable citizens, other frontline workers will be next. Teachers will be vaccinated so our children can return to school. And soon, all Americans will be able to receive the vaccine at their doctor’s office or at a CVS or Walgreens.

Remember, we accomplished this in 9 months, with the help, dedication, and expertise of our pharmaceutical industry heroes. Next time you turn on the TV and see negativity, turn it off and imagine instead where we will be in 9 months.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder
2020 Epilepsy Review: Much to Be Excited About

THE EPILEPSY THERAPEUTICS SPACE was one of the few bright spots of 2020, with many pharmacologic options emerging for patients. Over the past 10 years, some therapies offered marginal improvements in efficacy and adverse effect profile compared with earlier generations of antiseizure medications (ASMs). The mold was broken in 2020 with a paradigm shift in what clinicians consider effective therapies, and agents that offer a significant improvement in quality of life.

In 2020, ASMs to treat focal seizure in adults as well as seizures in Dravet syndrome received FDA approval. Cenobamate (Xcopri) is a novel tetrazole alkyl carbamate derivative thought to work on both sodium and gamma aminobutyric acid channels. In phase 2 study results, adults with focal epilepsy had median seizure reductions of 55.6%, 38.7% had a 75% or greater seizure reduction, and 28.3% were seizure free in a post hoc analysis of the maintenance phase. In a dose-comparison study of cenobamate by Krauss and colleagues, median seizure reduction of 400 mg/D was 55%, and in the maintenance phase of the modified intent-to-treat cohort, the same dosing resulted in 65% seizure reduction. Although it is not possible to directly compare these rates of seizure freedom and reduction with pivotal trials of other ASMs, these rates are higher than those shown in the meta-analysis and pooled analysis of lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, zonisamide, pregabalin, lacosamide, eslicarbazepine, perampanel and brivaracetam. If real-world experience is similar to the results of these pivotal trials, cenobamate may represent a new threshold for ASM efficacy in the treatment of focal epilepsy.

Similar paradigm changes may be afoot in the treatment of Dravet syndrome. In 2017, a North American consensus panel recommended valproic acid or clobazam as first-line therapies, with stiripentol, topiramate, or
FROM THE EDITOR

keto-diet as second-line treatments. Also in 2017, cannabidiol (Epidiolex) was FDA approved after demonstrating a median seizure frequency reduction of 43%. Fenfluramine (Fintepla), FDA approved in 2020 as well, demonstrated median seizure frequency reduction of 75% in its pivotal trial. As in the case of cenobamate, head-to-head comparisons of Dravet-specific therapies such as stiripentol, fenfluramine, and cannabidiol cannot be made. However, such impressive seizure reductions seen with both cenobamate and fenfluramine beg the question: Should we consider redefining what is considered a “significant” seizure reduction?

The abortive therapy space in epilepsy had languished with a paucity of therapies until 2019. The most recent FDA approval prior to then occurred in 1997 with rectal diazepam (Diasat), designed to allow caregivers to give an emergency-use medication to abort acute repetitive seizures. At the end of 2019, clinicians were given permission to prescribe FDA-approved nasal midazolam (Nayzilam) for patients 12 years and older. Its ease of use and clear dosing guidelines make it a valuable option for teenagers and adults. In 2020, nasal diazepam (Valtoce) also became available to US prescribers for patients 6 years and older; its advantages include dosing flexibility and long shelf life. Both of these nasal therapies met a previously unmet need for children and adults with epilepsy: an agent that can be quickly administered with greater social acceptability.

The focuses of epilepsy studies currently underway range from tantalizing first-in-class medications, new uses of older therapies, and even gene therapy, giving hope for more exciting developments in the coming year, even as we can reflect on the advances that emerged in 2020 in both prophylactic and abortive treatments for epilepsy.

Here’s to 2021….

References

Vol. 4 | No. 1 | February 2021
FDA OKs Shorter Ocrelizumab Infusion in MS

The FDA has approved a shorter 2-hour infusion time for ocrelizumab (Ocrevus; Genentech), dosed twice yearly for patients with relapsing-remitting multiple sclerosis (RRMS) or primary progressive MS (PPMS) who have not experienced any prior serious infusion reactions (IRs).1

The basis for the approval was from the randomized, double-blind ENSEMBLE PLUS study, a prospective substudy to the open-label, single-arm, phase 3b ENSEMBLE (NCT03085810) trial. Results showed similar frequency and severity of IRs for a 2-hour ocrelizumab infusion time compared with the previously approved 3.5-hour time in patients with RRMS.

“More than 170,000 people with MS have been treated with Ocrevus—the only approved B-cell therapy with a twice-yearly dosing schedule—and it is the most prescribed MS medicine in the United States,” Levi Garraway, MD, PhD, chief medical officer of Roche and head of its Global Product Development division, said in a statement.

Patients included in the study received the first dose using the approved dosing schedule (two 300-mg intravenous [IV] infusions separated by 2 weeks) and the second or later doses (600-mg IV infusion) through the shortened administration time.

The primary end point of the study was the proportion of patients with IRs following the first randomized 600-mg infusion, with frequency and severity assessed during infusion and 24 hours after. Investigators found that the frequency of IRs was comparable between those who received the 2-hour infusion (24.6%) and those who received the 3.5-hour infusion (23.1%).

More than 98% of the IRs were resolved within both groups without complication, and IRs were mild or moderate. There were no discontinuations due to an IR and no new safety signals observed.

“We constantly strive to improve the experience that patients and their physicians have with our medicines, and we believe people with relapsing and primary progressive MS will find the shorter 2-hour Ocrevus infusion time to be more convenient,” Garraway added.

The FDA accepted the supplemental biologics license application for the shorter-infusion ocrelizumab in April.2 Ocrelizumab, the first-of-its-kind treatment of PPMS, was approved in 2017.

In January 2020, the FDA updated the drug’s label with new safety information, including additions to possible infusion-related reactions, information regarding the need for immunizations, revisions to pregnancy risk summary, and updates to the patient counseling section.3

In February 2020, at the Americas Committee for Treatment and Research in Multiple Sclerosis Forum, data were presented from an assessment of the open-label OPERA 1 (NCT01247324) and OPERA 2 (NCT01412333) studies, which showed that those with relapsing MS who initiated ocrelizumab treatment earlier reported better rates of 24-week confirmed disability progression and relapse compared with those who received initial interferon treatment.4

In November 2020, results from the ongoing, long-term, open-label extension of the phase 3 ORATORIO study (NCT01194570) demonstrated that earlier and continuous treatment with ocrelizumab provided sustained benefits on measures of disease progression in patients with PPMS compared with patients switching from placebo.5

The proportion of patients with significantly lower Expanded Disability Status Scale (EDSS) scores was higher in those receiving continuous ocrelizumab (64.8%) than in those switching to ocrelizumab (51.7%), a difference of 13.1% (95% CI, 4.9%-21.8%; P = .0018) after the full follow-up. Similar results were seen on 9-hole peg test (30.6% vs 43.1%; difference, 12.5% [95% CI, 4.1%-20.9%]; P = .0035), timed 25-foot walk (63.2% vs 70.7%; difference, 7.5% [95% CI, –0.3% to 15.2%]; P = .058), and composite progression (73.2% vs 83.3%; difference, 10.1% [95% CI, 3.6%-16.6%]; P = .0023). Additionally, time to require a wheelchair (EDSS ≥7) was observed in 11.5% of those who received continuous ocrelizumab treatment compared with 18.9% of those who switched, for a difference of 7.4% (95% CI, 0.8%-13.9%; P = .0274).

Novel Platform Trial Adds Promising ALS Agent

Seelos Therapeutics announced that its phase 2b/3 study of SLS-005 (trehalose) has been selected by the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital to be included in the HEALEY ALS Platform Trial, the first platform trial for the treatment of amyotrophic lateral sclerosis (ALS).1

The investigational new drug (IND) application for the platform trial was approved by the FDA in January 2020, ultimately granting a “may proceed” to 3 of the 5 drugs selected by the Therapy Evaluation Committee: CNM-Au8 (Clene Nanomedicine), verdiperstat (Biohaven Pharmaceuticals), and zuliprcipan (Ra Pharmaceuticals).2

The selected investigational agents are all first-in-class biotherapeutic innovations that were developed to treat neurodegenerative disorders, although not necessarily targeting ALS. Now, SLS-005 joins that list.

“We are excited to work with Seelos and look forward to studying SLS-005 in an accelerated format through the HEALEY ALS Platform Trial,” Merit Cudkowicz, MD, director, Sean M. Healey & AMG Center for ALS, and chief of the department of neurology, Massachusetts General Hospital, and principal investigator of the trial, said in a statement.1 “The design team will work closely with Seelos on their regimen-specific protocol as well as completing required steps with the central ethics review board and the FDA.”

SLS-005 is a low-molecular-weight disaccharide that crosses the blood-brain barrier, stabilizes proteins, and activates autophagy. That occurs through the activation of the Transcription Factor EB, a key factor in lysosomal and autophagy gene expression. In November 2020, the FDA granted an orphan drug designation to SLS-005 for the treatment of ALS.

Seelos’ phase 2b/3 trial will enroll 160 patients with either familial or sporadic ALS. Patients will be randomized 3:1 to either SLS-005 or placebo and evaluated on change from baseline on the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale score after 24 weeks.3

Secondary end points of the study will also be measured at 24 weeks, including change from baseline in slow vital capacity, muscle
strength, and quality-of-life measures, as well as additional signs of disease progression.

“The inclusion of the registrational phase 2b/3 study of SLS-005 in this first-ever platform trial is the result of extensive work identifying trehalose as a potential treatment to study in ALS,” Raj Mehra, PhD, chairman and chief executive officer, Seelos, said in a statement. “The Healey Center’s recognition of this potential therapy is a major validation, and being part of this platform trial should help to expedite the trial by helping to provide greater access to patients.”

The agent was also previously granted orphan drug designations for Sanfilippo syndrome, spinocerebellar ataxia type 3, and oculopharyngeal muscular dystrophy.

The Healey Center received approximately 30 applications from 10 countries from its initial request for proposals. Ultimately, the Healey Center Therapy Evaluation Committee selected 5 therapies, with SLS-005 marking the sixth.

CNM-Au8, which was among the originally listed drugs, is an orally administered, concentrated, aqueous suspension of pure faceted nanocrystalline gold that acts catalytically to support various intracellular biological reactions. The orally administered verdiperstat is an irreversible inhibitor of the enzyme myeloperoxidase (MPO), which is associated with increased oxidative stress and inflammation levels in the brain and spinal cord, according to Irfan Qureshi, MD, vice president, neurology, Biohaven Pharmaceuticals, who spoke with NeurologyLive® in February 2020.

Qureshi added, “The presence of large numbers of activated microglia is one of the hallmarks of neurodegeneration in ALS. MPO is a powerful pro-oxidant enzyme that is present in activated immune cells, including microglia. Inhibiting MPO is anticipated to ameliorate these pathological mechanisms, which are strongly implicated in the onset and progression of ALS.”

Zilucoplan is a macrocyclic peptide that binds to complement C5 to inhibit its cleavage into C5a and C5b in activation pathways, which have been linked with inflammation that can contribute to chronic central nervous system diseases.

Sabrina Paganoni, MD, PhD, assistant professor of physical medicine and rehabilitation, Harvard Medical School, and coprincipal investigator of the platform trial, told NeurologyLive in February 2020 that the research team will work to incorporate IC14, pridopine, and several other therapies that were not included in the IND. For a full list of references, see the article on NeurologyLive.com.

New Neurotoxin Approved for Pediatric Chronic Sialorrhea

Merz Therapeutics announced that its investigational agent incobotulinumtoxinA won FDA approval for the treatment of patients 2 years and older with chronic sialorrhea after review of its supplemental biologics license application (sBLA).1

Marketed as Xeomin, the treatment becomes the first and only FDA-approved neuromodulator with this indication, after previously being granted a priority review designation upon sBLA filing acceptance by the FDA.

The basis of this approval comes from a phase 3, prospective, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of incobotulinumtoxinA in 255 children and adolescents aged 2 to 17 years. Results showed that the treatment significantly reduced unstimulated salivary flow rate, a primary end point, compared with placebo at week 4 among patients aged 6 to 17 years, and it sustained efficacy over 64 weeks.

The study’s second primary end point, Global Impression of Change Scale (GICS) score, was also significantly improved and sustained over 64 weeks with the treatment compared with placebo.

“The current standard of care for sialorrhea is pharmacological management with anticholinergics such as glycopyrrolate or a scopolamine patch,” said Heakyung Kim, MD, the A. David Gurewitsch Professor of Rehabilitation and Regenerative Medicine and professor of pediatrics, Columbia University Medical Center, in an interview with NeurologyLive®.

“However, these medications could cause significant [adverse] effects (AEs) such as urinary retention, increased mucus plugging, and blurry vision. Therefore, botulinum toxin injection, including Xeomin, which he will be given locally, decreases the risk of systemic AEs.”

Improvements in chronic sialorrhea increased with each injection cycle of the treatment compared with baseline. Patients aged between 2 and 5 years, all of whom received incobotulinumtoxinA and not placebo, had comparable GICS scores.

There were no observations of clinical resistance or secondary treatment failure due to neutralizing antibodies. This finding supports the importance of the treatment’s unique purification process through XTRACT technology, according to Merz.

The safety findings were similar to those of previous adult and pediatric studies and in line with the known safety profile. Bronchitis, headache, and nausea/vomiting were among the most common AEs affecting 1% or more of patients aged 6 to 17 years. In children aged 2 to 5 years, nasopharyngitis was the most common AE.

“Pediatric patients living with chronic sialorrhea have suffered with this debilitating condition without a viable long-acting treatment option,” Kevin O’Brien, president of North America, Merz Therapeutics, said in a statement. “Merz Therapeutics is proud to offer Xeomin, the first and only FDA-approved neurotoxin treatment that is uniquely purified to provide safe and effective treatment for this condition.”

Notably, incobotulinumtoxinA has a number of serious potential AEs that may be life-threatening. These include problems swallowing, speaking, or breathing, which may result in death for those who deal with these issues to begin with. Additionally, the treatment may cause the spread of toxin effects, including to areas of the body away from the injection site, leading to botulism.

Other notable AEs caused by incobotulinumtoxinA can include injury to the cornea in people treated for blepharospasm, as well as allergic reactions such as itching, redness, swelling, rash, wheezing, trouble breathing, or dizziness.

It is not known if the treatment is safe and effective in children aged less than 2 years for the treatment of chronic sialorrhea or upper limb spasticity, and in those aged less than 18 years for the treatment of cervical dystonia or blepharospasm.
"Having Xeomin approved to treat another symptom that children living with movement disorders experience is an important milestone for patients, caregivers, and health care providers," Elizabeth Moberg-Wolff, MD, pediatric and brain injury physical medicine and rehabilitation physician, Pediatric Rehabilitation Medicine Associates, said in a statement.

Oral Agent Shows Promise as Alzheimer Therapy

AB Science announced that its investigational oral agent masitinib met its primary end point in the phase 2b/3 AB09004 study (NCT01872598) in patients with mild-to-moderate Alzheimer disease (AD).1

Treatment with masitinib 4.5 mg/kg/day (n = 182) generated a significant treatment effect on the primary end point of change from baseline in the AD Assessment Scale-Cognitive Subscale (ADAS-Cog) compared with those in the control arm (n = 176; P = .0003). AB Science noted that it plans to present the full detailed results at an upcoming meeting.

In addition to the effect on cognition and memory, masitinib 4.5 mg/kg/day generated a significant change from baseline in the AD Cooperative Study Activities of Daily Living (ADCS-ADL) score, an instrument that assesses self-care and ADL (P = .0381).

“There is a vacuum of treatment options for patients with AD, and today, very few attempts [are made] to address the population with confirmed mild or moderate dementia associated with AD. These data are very encouraging and may provide new hope for patients with AD,” Bruno Dubois, MD, PhD, professor of neurology, Neurological Institute, Salpêtrière University Hospital, and coordinating investigator of study AB09004, said in a statement.

Among the notable data points presented, fewer patients who received masitinib 4.5 mg/kg/day reached severe dementia stage (defined as Mini-Mental State Exam [MMSE] score <10) compared with patients taking placebo after 24 weeks of treatment (P = .0446).

Dubois added, “The fact that masitinib could significantly reduce the proportion of patients reaching the stage of severe dementia is particularly interesting because this stage of the disease represents a significant burden [to] society.”

The safety analysis showed that masitinib 4.5 mg/kg/day was acceptable and consistent with its known tolerability profile. In total, 79.5% and 74.6% of patients in the masitinib and control arms, respectively, experienced at least 1 adverse event (AE). Serious AEs, which were nonfatal, were observed in 5.9% of patients in the masitinib arm compared with 2.9% in the control arm. Incidence of at least 1 serious AE was present in 18.9% of patients in the masitinib arm compared with 16.8% in the control arm.

Study AB09004 was a randomized, placebo-controlled trial that compared the efficacy and safety of masitinib relative to placebo after 24 weeks when administered as an add-on therapy to a cholinesterase inhibitor (donepezil, rivastigmine, or galantamine) and/or memantine. There was a 4.5 mg/kg/day masitinib group along with a 4.5 mg/kg to 6.0 mg/kg/day titrated dose group, each having an independent control arm along with it.

“The preliminary results from this study support efficacy on important outcomes assessing both cognition and function,” said AD expert Jeffrey Cummings, MD, ScD, in a statement. “The observed patient tolerability is encouraging. Masitinib’s mechanism is novel in its targeting of the innate immune system via mast cells and microglia. A growing body of evidence suggests that microglia play a central role in Alzheimer’s disease and other neurodegenerative disorders.”

Cummings is director emeritus of the Lou Ruvo Center for Brain Health, Cleveland Clinic, and vice chair, Department of Brain Health, University of Nevada – Las Vegas.

Proof of concept for masitinib in AD was established in a 35-patient, double-blind, placebo-controlled phase 2 study. Results from that study showed the rate of clinically relevant cognitive decline, or ADAS-Cog response, was significantly lower with masitinib compared with placebo after 12 and 24 weeks (6% vs 50% for both; P = .040 and P = .046, respectively).2

Patients in the placebo arm also experienced worsening mean ADAS-Cog, ADCS-ADL, and MMSE scores, whereas the masitinib arm reported statistically significant improvements at weeks 12 and 24.

Masitinib has been evaluated in other neurological disorders such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). In February 2020, AB Science announced that the treatment had met its primary end point in a phase 2b/3 study (AB07002) of patients with primary progressive MS and nonactive secondary progressive MS.3

In April, the FDA accepted an investigational new drug application for masitinib, allowing AB Science to proceed with a phase 3 study (AB19001) to test the agent in patients with ALS. The study was intended to confirm results from the first phase 2b/3 AB10015 study (NCT02588677) which demonstrated that masitinib, at 4.5 mg/kg/day in combination with riluzole, significantly slowed decline as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale – revised.4

Novel Agent Makes Progress in DMD Pipeline

Sarepta Therapeutics has announced that SRP-5051, its next-generation treatment for patients with Duchenne muscular dystrophy (DMD) that is amenable to exon 51 skipping, demonstrated proof-of-concept in the phase 2 MOMENTUM study (Study 5051-201; NCT04004065) with results supporting continued dose escalation.1

These were the first clinical data about SRP-5051, a treatment that uses Sarepta’s peptide phosphorodiamidate morpholino oligomer (PPMO) technology. Consistently higher tissue exposure, exon-skipping, and dystrophin production in patients taking a monthly dose of SRP-5051 was observed in Part A from the multisascending dose MOMENTUM study.

SRP-5051 was found to be generally well tolerated across all doses,
with no clinical or laboratory findings reported. Sarepta noted its belief that the findings support further clinical development of the agent.

“Sarepta’s PPMO RNA technology is a vital platform on which we design therapies to treat those with Duchenne muscular dystrophy. Our next-generation PPMO technology is designed to increase cell penetration with the goal of offering significantly improved efficacy with more convenient dosing in Duchenne patients amenable to exon skipping,” Doug Ingram, JD, president and chief executive officer of Sarepta, said in a statement.

Once-monthly dosing of SRP-5051 resulted in higher muscle concentration, increased exon-skipping, and increased dystrophin at 12 weeks when compared with a control group of patients with DMD from the PROMOVI study (NCT02255552), who received weekly 30 mg/kg doses of eteplirsen (Exondys 51) for 24 weeks.

The group of patients receiving a 20 mg/kg monthly dose of SRP-5051 for 12 weeks yielded a 1.6 times greater increase in exon skipping (n = 4) and a 5-fold increase in functional dystrophin (n = 2) when compared with the group taking eteplirsen, over 24 weeks.

Sarepta noted that the incidence of adverse events (AEs) in the MOMENTUM study were similar across all dose cohorts and did not suggest dose dependency. Furthermore, there was 1 treatment-emergent AE in the 4 mg/kg group, but it was deemed unrelated to the study drug.

SRP-5051 is designed to bind to exon 51 of dystrophin pre-RNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping.

The ongoing MOMENTUM phase 2 study was designed to not only investigate the safety and tolerability of SRP-5051 but to identify the maximum tolerated dose. The study will enroll up to 24 patients, both ambulant and nonambulant, who will receive monthly intravenous infusions of SRP-5051, starting at 4 mg/kg and ascending to 40 mg/kg.

MOMENTUM is composed of 2 parts. Participants in part A will receive the aforementioned ascending doses of SRP-5051 for 12 weeks. After an optimal dose is established, part B patients will receive that dose for 24 weeks.

“We know from our experience with PPMOs that exon-skipping and dystrophin increase over time, and these results, along with our preclinical experience, give us confidence as we dose escalate and continue to advance our PPMO exon-skipping therapies for Duchenne, including another 5 potential therapies that have already been designed, and explore the utility of the PPMO RNA platform for new disease indications,” Ingram added.

SRP-5051 is among the many RNA technologies from Sarepta. Its drug eteplirsen became FDA approved for the treatment of patients with DMD in September 2016. At the time, it was the first drug approved for DMD; it is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping.2

Sarepta’s second marketed DMD treatment, golodirsen (Vyondys 53), is an antisense oligonucleotide that was approved in December 2019 for the treatment of DMD with genetic mutations subject to skipping exon 53 of the dystrophin gene.3

READ MORE  neurologylive.com/SRP-5051-DMD

For a full list of references, see the article on NeurologyLive.com.
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CHALLENGES OF TREATING MIGRAINE
Richard B. Lipton, MD, the director of the Montefiore Headache Center, discussed the obstacles in addressing migraine for patients and how different treatments work for different patients with migraine.

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SEIZURES: SHORT, SUDDEN, STRANGE, SIMILAR SPELLS
Jacqueline French, MD, director, Translational Research and Clinical Trials in Epilepsy, NYU Grossman School of Medicine, discussed recently published data from part of the Human Epilepsy Project that suggests the delay in identifying nonvoter seizures can result in injury for the individuals experiencing them, and that earlier identification may prevent this issue.

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DIGITAL APPROACHES TO COMPREHENSIVE CARE IN MS
Leigh Charvet, PhD, clinical neuropsychologist, Division of MS, NYU Langone Health, spoke to the work she and colleagues have done in validating and assessing digital therapeutics and telemedicine approaches in MS, and how these interventions might make an impact on the invisible symptoms of the disease.

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Cannabidiol Maintains Long-Term Efficacy in Tuberous Sclerosis Complex

By Victoria Johnson

DATA FROM THE EXPANDED ACCESS PROGRAM (EAP) of cannabidiol (CBD; Epidiolex; GW Pharmaceuticals) presented at the American Epilepsy Society (AES) 2020 Annual Meeting, December 4-8, 2020, show that CBD provided sustained seizure reduction in patients with tuberous sclerosis complex (TSC) for up to 192 weeks with an acceptable safety profile.¹

The findings were presented by Arie Weinstock, MD, director of the Comprehensive Epilepsy Program at Oishei Children’s Hospital. “In the cohort of patients with TSC in the CBD EAP, add-on CBD produced sustained reduction in convulsive, focal, and total seizure frequency through 192 weeks,” he said.

This analysis focused on 34 patients with TSC of the 892 total patients in the safety analysis set of the GWPCARE6 EAP study (NCT02544763). These patients had a mean age of 12.4 years (range, 1.8-31.2) and were taking a median of 3 (range, 1-7) concomitant antiepileptic drugs (AEDs). Clobazam was the most common AED, used by 20 (59%) patients; 14 (41%) patients took lamotrigine, 11 (32%) patients took levetiracetam, and 6 (18%) took valproate.

Patients received plant-derived, highly purified CBD in doses of 2 to 10 mg/kg/day increasing to tolerance or a maximum of 25 to 50 mg/kg/day, depending on study site. The median maximum CBD dose was 40 (Q1-Q3 interquartile range [IQR], 25-50) mg/kg/day and the median duration of CBD use was 1102 (IQR, 414-1341) days. In that efficacy analysis set, the baseline median seizure frequency was 46 (IQR, 18-76) for convulsive seizures, 37 (IQR, 24-84) for focal seizures, and 64 (IQR, 31-148) for total seizures.

In the first 48 weeks, the median reduction in seizure frequency ranged from 48% to 55% for convulsive seizures, 61% to 75% for focal seizures, and 44% to 56% for total seizures. These patterns of seizure reductions were maintained through 192 weeks, with some variation due to decreasing sample size as some patients withdrew from the study. Seizure responder rates (≥50%) were also maintained through 192 weeks.

Of the 34 patients with TSC, 8 (24%) patients withdrew: 4 (12%) due to lack of efficacy, 1 (3%) due to diarrhea, and 3 (9%) due to other reasons. Adverse events (AEs) such as somnolence (32%), diarrhea (29%), convulsion (18%), and vomiting (18%) were reported by 94% of patients; 47% reported serious AEs. No deaths occurred. A liver-related AE occurred in 1 patient (3%) who had an abnormal liver function test.

“CBD was generally well tolerated with a safety profile similar to that seen in the previously reported EAP analyses and the TSC randomized controlled trial (GWPCARE6; NCT02544763). Results of this subgroup analysis from the final CBD EAP dataset support the long-term use of CBD in patients with TSC,” Weinstock and colleagues concluded.

Also presented at AES was a post hoc analysis of GWPCARE6 suggesting that the treatment is consistent in reducing seizures in patients with TSC with and without a history of infantile spasms (IS). Steven Sparagana, MD, pediatric neurologist, Texas Scottish Rite Hospital for Children, UT Southwestern Medical Center, and colleagues noted that in patients with a history of IS, percent reduction in seizure count from baseline was 45% for those on CBD 25 mg/kg/day, 43% in the CBD 50 mg/kg/day group, and 23% for placebo compared with 54%, 55%, and 32% in the respective dose groups for those without IS history.²

For a full list of references, see the article on NeurologyLive.com.
Perampanel Efficacious Regardless of Enzyme-Inducing Antiseizure Medications

By Marco Meglio

**DATA PRESENTED VIRTUALLY AT THE** American Epilepsy Society 2020 Annual Meeting, December 4-8, 2020, revealed that long-term adjunctive perampanel (Fycompa; Eisai) 4 mg/day is efficacious and generally well tolerated in patients from the Asia-Pacific region with or without secondarily generalized seizures (SGS), regardless of enzyme-inducing antiseizure medications (EIASMs).

Presented by Lynn Kramer, MD, chief clinical officer and chief medical officer, Neurology Business Group, Eisai, the results showed a higher median percent reduction in seizure frequency per 28 days in patients receiving non-EIASMs compared with EIASMs for both partial-onset seizures (POS; median difference, 28.3; 95% CI, 3.7-54.8) and SGS (median difference, 16.2; 95% CI, −54.9 to 94.7).

Eighty-five patients (mean [SD] age, 34.6 [13.55] years; 58.8% female) participated in the open-label extension phase of the Asia-Pacific Study 335 (NCT01618695) and received a modal dose of perampanel 4 mg/day.

EIASMs used in the study included carbamazepine, phenytoin, and oxcarbazepine. In total, 48 (56.5%) patients received concomitant EIASMs and 37 (43.5%) received non-EIASMs.

Patients included in the study presented with POS and were 12 years or older. The core study included 6-week prerandomization and 19-week randomization (6-week titration; 13-week maintenance) periods, while the open-label extension was composed of a 4-week preconversion period, a 6-week conversion period, and a maintenance period of at least 46 weeks.

The 50% responder rates, a study end point, were greater in the non-EIASMs group compared with the EIASMs group for both partial-onset seizures (POS; median difference, 28.3; 95% CI, 3.7-54.8) and SGS (median difference, 16.2; 95% CI, −54.9 to 94.7).

Seizure freedom rates, another topline end point of the study, were found to be greater in the non-EIASM group vs the EIASM group for both POS (2.7% [1/37] vs 0% [0/46]; RR data not available) and SGS (20% [2/10] vs 6.3% [1/16]; RR, 3.9; 95% CI, 1.5-10.2).

In terms of safety, the rates of treatment-emergent adverse events (TEAEs) and treatment-related TEAEs were slightly higher in the non-EIASM group (94.6% and 81.1%, respectively) compared with the rates in the EIASM group (85.4% and 72.9%, respectively). In contrast, the rate of serious TEAEs was higher in those with EIASMs (16.7%) compared with the non-EIASM patients (8.1%).

Dizziness was the most common AE, occurring in both the EIASM (45.8%) and non-EIASM (45.9%) groups. Other common AEs observed were somnolence, headache, nasopharyngitis, anxiety, convulsion, irritability, vertigo, aggression, suicidal ideation, and weight increase.

Kramer and colleagues concluded, “Patients receiving perampanel in combination with an EIASM may require a higher perampanel dose to achieve similar efficacy with only non-EIASMs.”

Initially, perampanel was approved in 2012 as an adjunctive therapy for POS, and the indication was later expanded to include patients 12 years and older with primary generalized tonic-clonic seizures. In 2017, perampanel received a monotherapy indication for POS with or without SGS in those with epilepsy 12 years and older.

The FDA then expanded the indication of perampanel for monotherapy and adjunctive use in pediatric patients 4 years and older for the treatment of POS with or without SGS in September 2018. The approval included both tablet and oral suspension formulations.

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

National Registry Data Shed Light on SUDEP Rates

By Matt Hoffman

**FINDINGS FROM A LARGE NATIONAL REGISTRY**, presented virtually at the American Epilepsy Society (AES) 2020 Annual Meeting, December 4-8, 2020, suggest that the occurrence of sudden unexpected death in epilepsy (SUDEP) is significantly more frequent than previously reported.

Additionally, the data from the National Institutes of Health (NIH) and CDC Sudden Death in the Young (SDY) Case Registry revealed that Black and multiracial infants and children (mortality, 38%; 0.32 per 100,000) have a SUDEP mortality rate 1.5 times higher than that of White infants and children (mortality, 58%; 0.22 per 100,000).

The overall rate of mortality was 0.26 per 100,000 infants and children. Previous literature has suggested that the mortality rate from SUDEP is 0.16 per 100,000 infants and children, markedly lower than this new research suggests.

The findings were presented by Vicky Whittemore, PhD, health science administrator of the NIH’s National Institute of Neurological Disorders and Stroke, who said in a statement that although “SUDEP is traditionally considered a more significant issue in adults, these findings add to the growing research that it is more common in infants and children than we believed, particularly for certain groups.”
CONFERENCE HIGHLIGHTS

This first-of-its-kind, population-based study included data on 1776 analyzable cases of patients aged 0 to 17 years, residing in 9 US states, who died between 2015 and 2017. Of these, 55 (3%) were deemed SUDEP and 11 (1%) were considered possible cardiac death or SUDEP. Possible cardiac/SUDEP was considered if the patient had a history of epilepsy and 1 or more of the following factors: family history of a heritable cardiac condition or a family member’s sudden death before age 50 years; personal history of cardiac disease; clinical history suggestive of a cardiac cause.

Additionally, the autopsy rates were lower for SUDEP (70%) compared with other categories of death in the Registry (range, 81%-100%). Of the 47 cases with an available autopsy, 10 (21%) had undergone neuropathological consultation while alive. In 71% of the deaths, death occurred unwitnessed, while the patients were sleeping or resting.

SUDEP was found to be as common among males as females. It was also observed to occur at all ages, with comparatively higher mortality rates between the ages of 0 to 2 years (0.51 per 100,000 live births and children) and 14 to 17 years (0.32 per 100,000 live births and children).

The mortality rate between the ages of 0 and 1 year was 0.53 per 100,000 (n = 12); between 2 and 5 years, 0.18 per 100,000 (n = 8), between 6 and 9 years, 0.26 per 100,000 (n = 12); between 10 and 13 years, 0.17 per 100,000 (n = 8); and between 14 and 17 years, 0.32 per 100,000 (n = 15).

“Physicians often don’t discuss SUDEP with parents because they consider it rare and don’t want to frighten them. But it’s important that physicians who have young patients discuss the risk with parents,” Whittemore added.

“This ongoing research is focused on understanding the underlying causes of SUDEP, the risk factors involved, and how the brain changes over time in people with chronic epilepsy, which can contribute to SUDEP,” Whittemore said. “Based on this information, prevention strategies can be developed and disseminated.”

Discussing SUDEP with patients and caregivers has been a topic of ongoing conversation at the AES Annual Meeting for some time. At the 2019 event, Jeffrey Buchhalter, MD, pediatric epileptologist and adjunct professor of pediatrics, University of Calgary, told NeurologyLive® that in the last decade, the amount of discussion has certainly increased, and patients and their families appear to want to know the risk. At this point, Buchhalter described, it is a “mandatory” conversation, particularly in light of practice guideline updates.

“If a child or an adult has ongoing tonic-clonic seizures, it needs to be brought to the attention of the patient and caregiver that they are at the highest risk for SUDEP,” Buchhalter said. “Some data suggest that nocturnal supervision can influence the risk and prevent death, but they need to know about it. Disclosure is mandatory not only for nocturnal supervision, but to be aggressive about their own care in terms of pursuing additional medications, or surgery, or vagus nerve stimulation, or ketogenic diet.”

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

Personalized Neuromodulation May Reduce Seizures in Drug-Resistant Epilepsy

By Victoria Johnson

DATA FROM A PATIENT WITH drug-resistant epilepsy (DRE) enrolled in a prospective multicenter trial, the Microburst Study (NCT03446664), suggest that individualized titration of stimulation parameters based on brain activation patterns resulted in a decrease in seizure frequency and severity following vagus nerve stimulation (VNS).1

These findings were presented virtually at the American Epilepsy Society (AES) 2020 Annual Meeting, December 4–8, 2020, by Kristl Vonck, MD, PhD, professor of neurology in Ghent University’s Laboratory for Clinical and Experimental Neurophysiology. Vonck and colleagues found that personalized, novel microburst stimulation may help in the reduction of seizures, potentially with minimal adverse effects.

Regarding VNS, “the optimal stimulation parameters for seizure control are unknown and may differ [among] patients. Novel stimulation paradigms such as microburst stimulation have been developed following previous preclinical research,” Vonck and colleagues commented. “We aimed to investigate the approach of individualized titration of stimulation parameters based on the effects of different stimulation parameters on central nervous system structures by means of functional imaging.”

Patients enrolled in Microburst were investigated with functional MRI (fMRI) using a series of standard and microburst stimulation parameters with titrated increases in output current. Stimulation parameters associated with the strongest thalamic activation when comparing VNS on/off fMRI microburst responses were selected post implantation at 2 weeks, 1 month, 3 months, and 6 months based on immediate postscanning fMRI analysis. Data presented at AES were from a 54-year-old patient with drug-resistant
juvenile myoclonic epilepsy with generalized tonic-clonic and myoclonic seizures.

VNS was first initiated 2 weeks after implantation of the VNS device. The parameters were associated with the strongest thalamic blood oxygen level dependent signal change: 1mA output current, 300Hz frequency, 250µsec pulse width, 7 pulses, and 0.5 seconds interburst intervals. VNS was cycled 30 seconds on and 5 minutes off. At the subsequent fMRI sessions at 1 month, 3 months, and 6 months, stimulation parameters were further adjusted based on the postscan fMRI analysis. At 3 months, stimulation parameters were 2mA output current, 300Hz frequency, 250µsec pulse width, 7 pulses, and 0.5 seconds microburst intervals. At 6 months, generalized tonic-clonic seizures had decreased by 91.5% (from 4.7 to 0.4) and myoclonic seizures had decreased by 52.0% (from 41.7 to 20.0) from baseline.

The patient’s overall Quality of Life in Epilepsy score decreased by 7.4% (from 71.9 to 66.6) but their mood parameter score improved by 57.5% (from 40.0 to 63.0). The patient reported a transient dizziness, which was resolved by the 6-month follow-up, and better tolerability to microburst stimulation vs standard stimulation.

“This personalized medicine approach of neuromodulation is unique and may further improve seizure control in patients treated with VNS,” Vonck and colleagues concluded.

NeurologyLive® has previously covered an investigation into the safety and efficacy of VNS conducted by Sandipan Pati, MD, assistant professor in the Department of Neurology at the University of Alabama at Birmingham, and colleagues. They found that of 27 patients with DRE treated with VNS, 15% (n = 4) were nonresponders, but 44% (n = 12) self-reported a 60% or greater reduction in seizures at follow-up visits occurring 8 or more months post implantation, although none were seizure free. The most tolerated stimulation current was between 1.5 and 2.25 mA.2

Pediatric Epilepsy Laser Ablation Shows Efficacy With Few Complications

By Victoria Johnson

PRELIMINARY DATA FROM THE North American Pediatric Epilepsy MRI-guided (MRg) Laser Interstitial Thermal Therapy (LITT, also known as laser ablation; PEP-LITT) registry presented at the American Epilepsy Society 2020 Annual Meeting, December 4-8, 2020, show that more than half of the children in the registry treated with MRgLITT achieved seizure freedom at 1 year follow-up, and permanent neurological deficits were rare.1

The findings were presented by Elysa Widjaja, MD, MPH, pediatric neuroradiologist at the Hospital for Sick Children and associate professor at the University of Toronto, and colleagues. “Although MRgLITT is a promising therapy, the effectiveness and complication rates of MRgLITT remain uncertain,” they wrote. “Understanding the benefits and risks of MRgLITT will assist with the decision-making process on treatment options.”

The PEP-LITT registry has enrolled 129 children treated with MRgLITT from 8 pediatric epilepsy surgery centers across North America, with a mean (SD) age of 10.7 (5.2) years. The mean (SD) age at seizure onset was 4.6 (4.6) years and the mean (SD) number of antiepileptic drugs was 1.9 (1.4). Abnormal MRI findings were seen in 86% (n = 111) of patients; the most common lesion was hypothalamic hamartoma (n = 33), followed by focal cortical dysplasia (n = 23).

Seizure outcome was available for 93 patients: After 1 year, 56% (n = 52) reported seizure freedom. More than 1 MRgLITT procedure was performed in 9% (n = 12) of patients, of whom 7 achieved seizure freedom. The mean (SD) length of hospital stay was 3.2 (3.7) days and the median was 1 day.

Of the 129 patients, 22% (n = 28) experienced complications relating to MRgLITT: 12% (n = 16) and 2% (n = 2) experienced transient neurologic deficits and permanent neurologic deficits, respectively. Post MRgLITT, 1 case of 30-day mortality was reported.

“The PEP-LITT registry will provide data for future analysis comparing seizure and health-related quality of life outcomes of MRgLITT to resective epilepsy surgery,” Widjaja and colleagues concluded.

NeurologyLive® has previously covered an investigation into the safety and efficacy of LITT in 42 adults conducted by Patrick Landazuri, MD, director of the Epilepsy Fellowship Program in the University of Kansas Department of Neurology, and colleagues. The team found that at 1 year follow-up, 64.3% (n = 27) of patients in the cohort were free of disabling seizures (reaching Engel I on the Surgery Outcome Scale) and more than 95% of patients had worthwhile seizure reduction (Engel I-III). The median length of stay after LITT was 32.7 hours, and head pain at discharge averaged 1.4 (SD, 2.1) on a scale from 1 to 10. Seizure worry (P = .0219) and social functioning scores (P = .0175) improved significantly at 1-year follow-up after treatment as measured by the Quality of Life in Epilepsy questionnaire.2

For a full list of references, see the article on NeurologyLive.com.
Multimodal Wristband Sensors May Predict Seizures

By Marco Meglio

**MULTIMODAL WRISTBAND SENSOR DATA** from easy-to-use, noninvasive devices in combination with deep learning may provide statistically significant and clinically useful seizure forecasting, according to study results presented virtually at the American Epilepsy Society 2020 Annual Meeting, December 4-8, 2020.¹

Lead author Christian Meisel, MD, PhD, of the Department of Neurology, Universitätätsmedizin Berlin, and the Berlin Institute of Health, and colleagues applied deep learning networks such as long short-term memory and one-dimensional convolutional neural networks on multimodal wristband sensor data from 69 persons with epilepsy (PWE) to assess the wristband’s capability to forecast seizures. The data for the study were collected by contributions from Tobias Loddenkemper, MD, director of clinical epilepsy research at Boston Children’s Hospital.

Using evaluations based on sensitivity, time in warning, and improvement over chance (IOC), results showed that the seizure forecasting was significantly better than chance for 43.5% of patients (n = 30), yielding a mean IOC of 28.5 (±2.6) and a mean sensitivity of 75.6 (±3.8).

Researchers also noted that the mean prediction horizon was 1896 (±101) seconds, a period that may be long enough to afford reasonable warning of seizures in advance.

“Our study was motivated by the potential benefits for patients and clinicians that seizure risk assessments or seizure forecasting may have. These benefits have long been known. If you ask a patient with epilepsy what they’re most concerned about within their disease, they will usually tell you that it’s the unpredictability of seizures,” Meisel told *NeurologyLive®*.

Each patient within the study was equipped with the Empactica E4 wireless multisensor device, which recorded temperature, photoplethysmography, electrodermal activity, and actigraphy, all during long-term, continuous video-electroencephalography monitoring.

The E4 wristband is a medical-grade wearable device that offers real-time physiological data acquisition, enabling investigators to conduct in-depth analysis and visualization. It is equipped with several different sensors, including a photoplethysmogram sensor (to measure blood volume pulse [BVP], from which heart rate variability can be derived) and an electrodermal activity sensor (to measure the constantly fluctuating changes in certain electrical properties of the skin).²

The device also has a 3-axis accelerometer to capture motion-based activity, an infrared thermopile to read peripheral skin temperature, an event mark button that tags events and links them to physiological signals, and an internal real-time clock.

Meisel and colleagues applied a leave-one-subject-out cross-validation approach in which matched preictal/interictal data were used for training, and testing was done on the remaining out-of-sample patient dataset.

Additional control analyses using time-matched seizure surrogate data showed that forecasting seizures was not simply based on time of day or vigilance state. To better understand how each sensor plays a role into predicting seizures, the researchers performed analyses by removing each sensor’s data individually; these indicated that all data streams contributed to seizure forecasting.

Although the study included 69 PWEs, prediction performance increased with size of the training dataset, which may point to future studies that include larger datasets.

“These initial results may provide the basis for future reevaluation, algorithm improvement, and benchmarking as a step toward patient empowerment and objective epilepsy diagnostics for broad application,” concluded Meisel and colleagues.

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

More on NeurologyLive.com

FINDING THE RIGHT AEDS FOR PATIENTS WITH EPILEPSY

Pavel Klein, MD, director of the Mid-Atlantic Epilepsy and Sleep Center, urged physicians to catch refractory epilepsy early and look for the most efficacious treatments for their patients.

View video: neurologylive.com/Klein-AED-Epilepsy
Tapping Into the Potential of Cell and Gene Therapy

By Larry Hanover

EXCITEMENT TOOK WING IN THE scientific community in the early 1990s, when the first gene therapy trial showed significant success, only to crash at the end of the decade with a patient’s tragic death.

Twenty years later, the excitement is back and greater than before. Although safety remains a concern, investigators are breaking ground in cell and gene therapy, and many believe that ultimately, a string of cured cancers will follow.

“We can absolutely cut the number of cancer deaths down so that one day in our lifetimes it can be a rare thing for people to die of cancer,” said Patrick Hwu, MD, president and CEO of Moffitt Cancer Center in Florida and among gene therapy’s pioneers. “It still may happen here and there, but it’ll be kind of like people dying of pneumonia. It’s like, ‘He died of pneumonia? That’s kind of weird.’ I think cancer can be the same way.’”

The excitement returned in spades in 2017 when the FDA signed off on a cell-therapy drug for the first time, approving the chimeric antigen receptor (CAR) T-cell treatment tisagenlecleucel (Kymriah; Novartis) for the treatment of B cell precursor acute lymphoblastic leukemia. At last, scientists had devised a way to reprogram a person’s own T cells to attack tumor cells.

“We’re entering a new frontier,” said Scott Gottlieb, MD, then-FDA Commissioner, in announcing the groundbreaking approval.

Gottlieb wasn’t exaggerating. The growth in CAR T-cell treatments is exploding. Although only a handful of cell and gene therapies are on the market, the FDA has projected that it will receive more than 200 investigational new drug applications per year for cell and gene therapies over the next few years, and by 2025, it expects to have accelerated to 10 to 20 cell and gene therapy approvals per year.

“Essentially, you can kill any cancer cell that has an antigen that is recognized by the immune cell,” Hwu said. “The key to curing every single cancer, which is our goal, is to have receptors that can recognize the tumor but don’t recognize the normal cells.” Receptors recognizing and then attacking normal cells is what can cause toxicity.

In neurology, a number of neuromuscular diseases, most prominently spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD), have already begun to assess gene therapies (TABLE). In SMA, Novartis Gene Therapies’ intrathecal (IT) onesemogene abeparvovec (Zolgensma) is already approved for use. In October 2020, more data were announced from the phase 3 STR1VE-EU trial of the therapy, suggesting it offered significant benefit in patients with SMA type 1. Of the 32 patients in the study, 31 had survived event-free by the data cutoff point. Additionally, 21 (65.6%) achieved motor milestones not seen in the natural history of the disease, including 6 patients (18.8%) who sat independently for ≥10 seconds.

Also in SMA, Biogen recently dosed the first patient in a phase 4 trial of usinersen (Spinraza) in patients who have unmet needs despite treatment with onesemogene abeparvovec, with plans to evaluate 60 patients aged up to 3 years. The primary study group is expected to include 40 infants aged 9 months or younger (at the time of first nusinersen dose) who have 2 copies of SMN2 and received nusinersen at 6 months and older. A second study group will include 20 children within a broader age range (up to 3 years).

In DMD, microdystrophin gene transfer using recombinant adeno-associated virus serotype rh74 (rAAVrh74) driven by a skeletal and cardiac muscle-specific promoter with enhanced cardiac expression (MHCK7) is being evaluated as effective therapy. As well, Sarepta Therapeutics recently announced the first clinical data for SRP-5051, which demonstrated proof-of-concept in in the phase 2

TABLE. Select Gene Therapies in Neurology

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MOMENTUM study (NCT04004065) in DMD. The results supporting continued dose escalation, and the therapy was found to be generally well-tolerated across all doses administered. Likewise, a number of gene-based treatments are being assessed and showing promise in diseases such as SCN1A-positive epilepsy, Parkinson disease, and Alzheimer disease, among others.

Juliette Hordeaux, PhD, senior director of translational research for the University of Pennsylvania’s gene therapy program, is cautious about the FDA’s predictions, saying she’d be “thrilled” with 5 cell and/or gene therapy approvals annually.

“For monogenic diseases, there are only a certain number of mutations, and then we’ll plateau until we reach a stage where we can go after more common diseases,” Hordeaux said.

Safety has been the main brake around adeno-associated virus vector (AAV) gene therapy,” added Hordeaux, whose hospital’s program has the institutional memory of both Jesse Gelsinger’s tragic death during a 1999 gene therapy trial as well as breakthroughs by Carl June, MD, and others in CAR T-cell therapy. “Sometimes there are unexpected toxicity [events] in trials....I think figuring out ways to make gene therapy safer is going to be the next goal for the field before we can even envision many more drugs approved.”

Natural killer (NK) cells are the research focus of Dean Lee, MD, PhD, a physician in the Division of Hematology and Oncology at Nationwide Children’s Hospital. He developed a method for consistent, robust expansion of highly active clinical-grade NK cells that enables repeated delivery of large cell doses for improved efficacy. This finding led to several first-in-human clinical trials evaluating adoptive immunotherapy with expanded NK cells under an FDA investigational new drug application. He is developing both genetic and nongenetic methods to improve tumor targeting and tissue homing of NK cells. His efforts are geared toward pediatric sarcomas.

“The biggest emphasis over the past 20 to 25 years has been cell therapy for cancer, talking about trying to transfer a specific part of the immune system for cells,” said Lee, who is also director of the Cellular Therapy and Cancer Immunology Program at Nationwide Children’s Hospital, at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital, and at the Richard J. Solove Research Institute.

### The Pivot To COVID-19 and Other Diseases

However, Lee said, NKs have wider potential. “This is kind of a natural swing back. Now that we know we can grow them, we can reengineer them against infectious disease targets and use them in that space,” he said.

Lee is part of a coronavirus disease 2019 (COVID-19) clinical trial, partnering with Kiadis, for off-the-shelf K-NK cells using Kiadis’ proprietary platforms. Such treatment would be a postexposure preemptive therapy for treating COVID-19. Lee said the pivot toward treating COVID-19 with cell therapy was because “some of the very early reports on immune responses to coronavirus, both original [SARS-CoV-2] and the new [mutation], seem to implicate that those who did poorly [overall] had poorly functioning NK cells.”

The revolutionary gene editing tool CRISPR is making its initial impact in clinical trials outside the cancer area. Its developers, Jennifer Doudna, PhD, and Emmanuelle Charpentier, PhD, won the Nobel Prize in Chemistry 2020. For patients with sickle cell disease (SCD), CRISPR was used to reengineer bone marrow cells to produce fetal hemoglobin, with the hope that the protein would turn deformed red blood cells into healthy ones. National Public Radio did a story on one patient who, so far, thanks to CRISPR, has been liberated from the attacks of SCD that typically have sent her to the hospital, as well from the need for blood transfusions.

Ten patients with SCD or transfusion-dependent beta-thalassemia treated with promising results, as reported by the New England Journal of Medicine. Two different groups, one based in Nashville, Tennessee, and another based at Dana-Farber Cancer Institute in Boston, Massachusetts, have reported on this technology.

Stephen Gottschalk, MD, chair of the department of bone marrow transplantation and cellular therapy at St Jude Children’s Research Hospital, said, “There’s a lot of activity to really explore these therapies with diseases that are much more common than cancer.”

Animal models use T cells to reverse cardiac fibrosis, for instance, Gottschalk said. Using T cells to reverse pathologies associated with senescence, such as conditions associated with inflammatory clots, are also being studied.

Hordeaux said she foresees AAV being used more widely to transmit neurons to attack neurodegenerative diseases.

“The neurons are easily transduced by AAV naturally,” she said. “AAV naturally goes into neurons very efficiently, and neurons are long lived. Once we inject genetic matter, it’s good for life, because you don’t renew neurons.”

### Logistical Issues

The process of working out all kinks in manufacturing also remains a challenge. Rapid production is difficult, too, because of the necessary customization of doses and the need to ensure a safe and effective transfer of cells from the patient to the manufacturing center and back into the patient.

Other factors that slow down launches include insurance coverage, site certification, staff training, reimbursement, and patient identification. The question of how to reimburse has not been definitively answered; at this point, insurers are being asked to issue 6- or even 7-figure payments for treatments and therapies that may not work.

“CAR T, I think, will become part of the standard of care,” Gottschalk said. “The question is how to best get that accomplished. To address the tribulations of some autologous products, a lot of groups are working with off-the-shelf products to get around some of the manufacturing bottlenecks. I believe those issues will be solved in the long run.”

For a full list of references, see the article on NeurologyLive.com.
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How Big Data Can Drive Advancements in MS Research

Big data is in on the precipice of revolutionizing multiple sclerosis knowledge and treatment.

By Nicola Davies, PhD

ABOUT 2.8 MILLION INDIVIDUALS WORLDWIDE, including 1 million in the United States, currently live with multiple sclerosis (MS), the leading cause of nontraumatic neurological disability.¹ Investigators have been striving for decades to find more effective ways to diagnose and manage MS, but the “gold standard” of evidence-based care—use of randomized controlled trials—has not been as beneficial for this disease as it has for others. “MS is a condition that has a great degree of variability across people and across time,” said Aaron Boster, MD, president of the Boster Center for Multiple Sclerosis in Columbus, Ohio. As such, he explained to NeurologyLive®, it can be difficult to draw evidence from the relatively small number of patients recruited for clinical trials and standard observational studies, as they do not accurately reflect the status of the disease in the real world.

Could big data provide a solution to this problem? Big data refers, essentially, to a large volume of data that can either be structured or unstructured. In the medical context, these data are obtained from a variety of sources: medical records, hospital records, or data generated from wearable devices and health care apps. Over the past few years, efforts by players in the field have focused on creating repositories of information by establishing online registries for MS.

“A large volume of information is not normally accessible to the average neurophysician, who, over the course of 20 to 30 years, usually ends up seeing only a couple of thousand patients with MS,” Boster said.

When analyzed statistically, big data can be used to spot patterns and generate evidence that is applicable to the entire MS population. “Big datasets essentially help us understand health. The greater the number of data points involved, the greater the learning,” explained Ava Battles, MPsyChSc, chief executive officer of Multiple Sclerosis Ireland.

Big Data’s Potential in MS Management

Multiple factors play a role in the severity of MS, a disease that is not completely understood. Its exact cause is poorly grasped as well, and boundaries remain extremely blurred between the 2 distinct disease forms: relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS). These deficits, understandably, can hinder disease management.

MS registries can collect patient details and synthesize them into information that can help improve understanding of the disease process. For example, Boster cites the most accepted definition of SPMS, which was created by identifying 576 versions of the definition and comparing them with a cohort of patients from MSBase, an international database that contains information on patients with MS throughout the world.² The definition that performed the best in terms of timely diagnosis, disease activity, and overall disease burden was selected from the data. Using the Expanded Disability Status Scale (EDSS), SPMS is defined by: a disability progression of 1 step in patients with EDSS 5.5 or less, and of 0.5 step in patients with EDSS 6 or higher in the absence of a relapse; a minimum EDSS score of 4; a pyramidal functional system (FS) score of 2; and confirmed progression over 3 months, including confirmation within the leading FS.

Big data may also help in the identification of various factors that can predict disease progression. “Currently, the standard for
monitoring patients with MS is through clinical assessments and radiographic monitoring using MRI scans. This needs to be done yearly to look for the formation of new lesions,” Gauruv Bose, MD, clinical research fellow in MS at the Brigham Multiple Sclerosis Center in Boston, Massachusetts, explained to NeurologyLive®.

However, meeting this standard may not be feasible in locations where access to care is limited. MRI scans, in particular, can be expensive and are not always covered by insurance. Another use for these datasets is to identify cost-effective prognostic markers to help predict disease progression in different individuals. For instance, results of a longitudinal observational study published in 2020 explored risk factors for conversion of RRMS to SPMS by utilizing datasets from more than 15,000 patients. The investigators found that older age, a longer duration of illness, higher disability scores, and more relapses in the previous year could predict progression to SPMS. Conversely, other factors that were previously thought to be associated with progression, including oligoclonal bands in cerebrospinal fluid and evidence of spinal cord lesions, were found to not be associated with progression.

Another recent observational study attempted to identify early clinical markers for aggressive MS by collating data from MSBase datasets. After screening almost 10,000 patients whose data were recorded over 10 years, specific markers were pinpointed: older age at symptom onset and higher disability scores and occurrence of pyramidal signs during the first year of MS. Based on these data, clinicians encountering these features in a patient may choose to be more aggressive in their early intervention.

Patients with MS often suffer from other medical comorbidities, which may or may not influence MS progression, and big data helps comprehend the various effects of these comorbidities. For instance, an observational study identified that patients with psychiatric comorbidities such as mood or anxiety disorders were more likely to have increased neurological disability. Another recent cohort study retrieved data from MSBase and explored the association between pregnancy and clinically isolated syndrome (i.e., the first episode of neurological symptoms in MS). Preliminary findings from this study suggest that pregnancy can forestall the onset of MS.

The detection increased risk of certain comorbidities in patients with MS may offer another role for these large datasets. A matched cohort study from 2 different databases showed that patients diagnosed with MS have a 2-fold increase in rates of venous thromboembolism and peripheral vascular disease when compared with patients without MS. Additionally, the incidence of myocardial infarction in female patients with MS was 2.5 times higher than in those without MS.

Increasingly, decision-making is a process shared between physician and patient. Patients cannot make informed treatment choices unless they are aware of the risks and prognosis of their condition. Particularly in young patients who are newly diagnosed with MS, the risks may not be immediately apparent. “There is a significant disease lag in MS,” Boster explained. “The brain damage that occurs in a 30-year-old does not cause clinical concern at that time because of neuroplasticity and a large neurological function reserve. Although there might be temporary loss of function, this is usually regained—but the brain damage is permanent. Over the years, increasing bouts of brain damage will eventually lead to accelerated volume loss and progression of disability.” Study results corroborate that MS risk knowledge can be relatively low among patients, confirming the importance of educating patients on self-care. Results gleaned from large datasets of patients with MS can be valuable in this endeavor.

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― AARON BOSTER, MD

One such tool that can be used to educate patients is the MS Severity Rank Calculator, developed by investigators at MSBase by plotting the EDSS scores of a consolidated large volume of patients over time. The calculator can be used to categorize individual patients into a specific decile. Patients can be shown where they rank on the graph, which is a powerful indicator of the severity of their disease status. “Showing patients their own natural history over the course of time is extremely valuable in terms of treatment adherence,” said Boster.

Randomized trial results may not always represent the real-world efficacy of a drug, but for MS agents, the differences may be even starker. Patients in randomized trials are usually treatment-naïve and therefore have less potential for interactions that could impact the efficacy of a drug. Assessment of the real-world efficacy of a given MS medication can be done on a much larger scale through big data than is possible with...
randomized trials. For example, research from registry datasets show that ocrelizumab is more associated with respiratory infections than are other drugs for MS—a finding that was not apparent in clinical trials.\(^{10}\)

"As opposed to almost no treatments 20 years ago, we now have 24 FDA-approved therapies to treat MS. But we still don’t know the best way of using them all," said Boster. This situation is due in large part to the drugs’ diversity. "While some drugs have similar mechanisms of action, many have unique pharmacological properties, which in turn creates differences in efficacy, as well as different adverse effect risks, routes of administration, and monitoring requirements," added Bose.

Consequently, patients aren’t always prescribed the medication that is best for them. "Not all countries allow patients to have the medication their neurologist recommends, without first ‘failing’ another choice, one that is often cheaper and relatively safer," said Bose. "If clinicians could use evidence derived from big data to characterize and prognosticate their patients’ condition accurately, policy makers could be persuaded to [pay for] the right medication for higher-risk patients when it is first prescribed."

All of these factors—correctly diagnosing and prognosticating the patient, educating patients about the importance of adhering to treatment, and choosing the right drug for treatment—contribute to making informed health care decisions. "With appropriate data, a clinician can take an individual’s physiology and lifestyle into account, and they can potentially provide a detailed, holistic treatment plan for a person living with MS," said Battles.

Making informed treatment choices also includes timing treatments correctly. Although disease-modifying therapy is often only initiated after obvious neurological disability, such as walking issues, information from big data has shown that cognitive decline—a relatively less visible parameter—can often signal the beginning of MS.\(^{11}\) This is an emerging advance for care, in that it offers parameters to assess cognitive function earlier in the disease process.

Platforms Dedicated to Collating MS Data
While data is obtainable from various sources, the key sources of these datasets thus far for MS research have been disease registries. Unlike patient and hospital records, which capture data passively, disease registries actively encourage data entry and the sharing of information, and while relatively small, they have been growing. Several European MS registries have more than 500,000 total patients in their databases, potentially covering a large swath of the estimated 700,000 people with MS on the continent. As well, attempts have been made to harmonize the data between registries for additional insight, with the EUREMS and BMSD projects currently analyzing the results of this for datasets from over 60,000 and 100,000 patients, respectively.\(^{12}\) North America has been catching up slowly, and now several registries capture information from patients on this continent as well.

Four of the key big data sources for MS are as follows:

- **MSBase.** An international registry, MSBase is open to neurophysicians worldwide. Patient data can be shared on this registry with appropriate consent, and these data can be used by investigators to track and evaluate outcomes. "The MSBase registry has capture visits from sites across many countries, and several excellent analyses have been done using this and similar datasets," said Bose. MSBase currently has records from approximately 74,000 patients in 38 countries.

- **Atlas of MS.** Supported by the MS International Foundation, this database actively collects epidemiological information on MS worldwide. In addition to prevalence across various patient demographics, the database also offers information on health care resources’ availability and accessibility.

- **The North American Registry for Care and Research in MS.** This database links MS centers across the United States and Canada. A collaborative registry, it has repositories of clinical, genetic, and radiographic data of more than 800 patients with MS from 24 institutions.

- **COViMS.** This new registry, whose name is an acronym for COVID-19 Infections in MS & Related Diseases, was formed in wake of the coronavirus disease 2019 (COVID-19) pandemic. It was established by the Consortium of Multiple Sclerosis Centers and the National Multiple Sclerosis Society to help investigate how COVID-19 affects the MS population, and it already contains data from about 900 patients with MS who have had COVID-19.

Challenges in Using Big Data for MS Research
The most common fear shared by both physicians and patients regarding these collections of information is breach of privacy. "Sharing your most private, most intimate information about your health has fear attached to it," said Boster. "First is the fear that your data might fall into the wrong hands or be used inappropriately, and second, that datasets might actually limit your options for treatment." Clinicians can mitigate patient fear by being open about how big data is used. Indeed, Battles stressed, "People consenting to their data being shared should be informed of who will have access to the data and what [they] will be used for. They should also know how to have their data removed, should they wish to do so at any time."

Another key challenge is the inherent bias that these datasets may have. "There may be differences in the examination and rating tools used, although efforts are underway to standardize these," said Bose. He added that incomplete or missing data can also create a bias. For
instance, not all countries have the resources to allow frequent MRI examinations. Certain countries may not contribute to databases at all, creating a geographical bias. The Atlas of MS database records data from 138 countries, but it has excluded at least 80 countries where coordinators could not be identified. The world’s largest MS database, MSBase, has data from only 38 countries.

Despite these challenges, most patients are inclined to share their experiences and health data on global registries. “We see that patients are willing to fight back and do what it takes to contribute toward the understanding of the disease, whether this is participating in clinical trials or sharing their health information,” said Boster.

**The Future of Big Data and Advances in MS**

The wealth of insights that big data has the potential to offer is exciting, experts agree. According to Bose, one avenue of future research could be developing analytical tools that can be applied to big data to create and refine specific treatment algorithms. Another focus should be toward consolidating information across different databases, said Boster. “Increasing efforts at consolidating databases is essential, so that we can have larger, robust, homogenous datasets to work from,” he noted.

Boster also expresses hope that consolidated big data can be applied to studying the prodromal stage of MS. “We know from the literature that for almost 5 years leading up to an MS diagnosis, patients have certain abnormal patterns, such as increased emergency [department] visits, pain, or psychiatric complaints. If we are ever to a priori identify certain abnormal patterns, such as increased emergency [department] visits, pain, or psychiatric complaints. If we are ever to a priori identify the trappings of an MS prodrome, it is going to be through mining big data for clues and tips that lead us there,” he says. Identifying patients in the preclinical stages could certainly revolutionize management of the disease, as the next logical step would be to identify treatment strategies that can stave off the clinical course altogether.

**REFERENCES**

Indication
ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

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

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.
Study designs: Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.

Contraindications:

Confirmed disability between ZEPOSIA and Avonex. 1-3

9 of 10 patients showed no confirmed 3-month disability of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. ZEPOSIA reduced the number of new or enlarging T2 lesions 38% at 2 years (0.17 vs 0.28, respectively).

Secondary endpoints:

ZEPOSIA reduced dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-/uni03BCg (2 years; N=1313) were multicenter, randomized, double-blind, SUNBEAM (1 year; N=1346) and RADIANCE 4%

Follows: upper respiratory infection, 26% (vs 23%); hepatic enzyme increased, liver function test abnormal, and laryngitis. Hepatic transaminase elevation includes hepatitis, jaundice, transaminase increased. Hypertension includes hypertension, orthostatic hypertension. Overall discontinuation rates vs Avonex Consistently low of Adverse Reactions in Overall Incidence Safety Profile vs Avonex COMPARABLE.

• Patients taking a monoamine oxidase (MAO) inhibitor

Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations. 1 Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation. 1 For patients with a history of uveitis or macular edema, an ophthalmic assessment is required. 1 An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur. 1

*Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA. 1

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

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

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

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

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

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

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:
- with significant QT prolongation
- with arrhythmias requiring treatment with Class Ia or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome, or sinoatrial heart block

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

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

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

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

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

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

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alentuzumab is not recommended.

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

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

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

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.


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ZEPOSIA® (ozanimod) capsules, for oral use

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

1 INDICATIONS AND USAGE

ZEPOSIA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of ZEPOSIA

Before initiation of treatment with ZEPOSIA, assess the following:

- Complete Blood Count
  - Obtain a recent (i.e., within the last 6 months or after discontinuation of prior MS therapy) complete blood count (CBC), including lymphocyte count [see Warnings and Precautions (5.1)].

- Cardiac Evaluation
  - Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought [see Warnings and Precautions (5.2)].

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

- Ophthalmic Assessment
  - In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula [see Warnings and Precautions (5.7)].

Current or Prior Medications

- If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].

- Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction [see Warnings and Precautions (5.2) and Drug Interactions (7.2)].

Vaccinations

- Test patients for antibodies to varicella zoster virus (VZV) before initiating ZEPOSIA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.3)].

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

2.2 Dosing Information

2.2.1 Maintenance Dosage

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

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

Treatment Initiation

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

| Days 1-4 | 0.23 mg once daily |
| Days 5-7 | 0.46 mg once daily |
| Day 8 and thereafter | 0.92 mg once daily |

Table 1: Dose Titration Regimen

2.3 Reinitiation of ZEPOSIA After Treatment Interruption

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

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

4 CONTRAINDICATIONS

ZEPOSIA is contraindicated in patients who:

- In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure [see Warnings and Precautions (5.2)].

- Have the presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker [see Warnings and Precautions (5.2)].

- Have severe untreated sleep apnea [see Warnings and Precautions (5.2)].

- Are taking a monoamine oxidase (MAO) Inhibitor [see Drug Interactions (7.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of Infections

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues [see Clinical Pharmacology (12.2)]. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature.

Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA.

Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA.

Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved.

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

The proportion of patients who experienced lymphocyte counts less than 0.2 x 10^9/L was 3.3%. These values generally returned to greater than 0.2 x 10^9/L while patients remained on treatment with ZEPOSIA. After discontinuing ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was 38 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)].

Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection.

Because the elimination of ZEPOSIA after discontinuation may take up to 3 months, continue monitoring for infections throughout this period.

Herpes Viral Infection

In Study 1 and Study 2, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients who received IFN beta-1a. Herpes simplex encephalitis and varicella zoster meningoencephalitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA [see Vaccinations below].

Cryptococcal Infection

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with S1P receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. ZEPOSIA treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leukenoencephalopathy

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

PML has been reported in patients treated with S1P receptor modulators and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., Immunocompromised patients, polytherapy with immunosuppressors). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

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

Prior and Concomitant Treatment with Anti-neoplastic, Immunosuppressive, or Immune-modulating Therapies

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

Vaccinations

Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA, following which initiation of treatment with ZEPOSIA should be postponed for 4 weeks to allow the full effect of vaccination to occur. No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Vaccinations may be less effective if administered during ZEPOSIA treatment.

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

5.2 Bradycardia and Atrioventricular Conduction Delays

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

ZEPOSIA was not studied in patients who had:

- A myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months
- New York Heart Association Class III / IV heart failure
- Cardiac conduction or rhythm disorders, including sick sinus syndrome, significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that in the opinion of the treating investigator could jeopardize the patient’s health
- Other pre-existing stable cardiac conditions without clearance from a cardiologist
- Severe untreated sleep apnea
- A resting heart rate less than 55 beats per minute (bpm) at baseline

Reduction in Heart Rate

Initiation of ZEPOSIA may result in a transient decrease in heart rate. In Study 1 and Study 2, after the initial dose of ZEPOSIA 0.23 mg, the greatest mean decrease from baseline in heart rate of 1.2 bpm occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. With continued up-titration, the maximal heart rate effect of ozanimod occurred on Day 8. The utility of performing first-dose cardiac monitoring when initiating ZEPOSIA in patients with characteristics similar to those studied in the clinical trials of ZEPOSIA is unclear. Heart rates below 40 bpm were not observed.

Initiation of ZEPOSIA without titration may result in greater decreases in heart rate [see Dosage and Administration (2.2)].
5.5 Liver Injury
Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain transaminase and bilirubin levels, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. In Study 1 and Study 2, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients who received IFN beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ZEPOSIA and 3.1% of patients who received IFN beta-1a. The median time to an elevation of 3-fold the ULN was 6 months. The majority (79%) of patients continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2-4 weeks. In clinical trials, ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked, and ZEPOSIA should be discontinued if significant liver injury is confirmed. Individuals with an AST or ALT greater than 1.5 times ULN were excluded from Study 1 and Study 2. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA, caution should be exercised when using ZEPOSIA in patients with a history of significant liver disease.

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

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

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

5.6 Respiratory Effects
Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in patients treated with ZEPOSIA in early as 3 months after treatment initiation. In pooled analyses of Study 1 and Study 2, the decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV1 at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.8, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and %predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a (60 mL, 95% CI: [-110, -10]); 1.4%, 95% CI: [-2.6, -0.2]), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation. One patient discontinued ZEPOSIA because of dyspnea. Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

5.7 Macular Edema
S1P modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA. Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient. Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

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

5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment with Immunosuppressive or Immune-Modulating Drugs
When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating ZEPOSIA. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended [see Drug Interactions (7.1)].

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

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

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

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

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ZEPOSIA was evaluated in two randomized, double-blind, active comparator-controlled clinical studies in which 882 patients received ZEPOSIA 0.92 mg [see Clinical Studies (14)].

Table 2 lists adverse reactions that occurred in at least 2% of ZEPOSIA-treated patients and greater than comparator. The most common adverse reactions that occurred in at least 4% of ZEPOSIA-treated patients and greater than in patients who received IFN beta-1a were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.
Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a (Pooled Study 1 and Study 2)

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

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

^b Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.

^c Includes the following terms: alanine aminotransferase increased, gamma-glutamyl transpeptidase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.

^d Includes hypertension, essential hypertension, and orthostatic hypotension.

Reducions in Heart Rate

Inhibition of ZEPOSIA may result in transient decrease in heart rate [see Warnings and Precautions (5.2)].

Respiratory Effects

Dose-dependent reductions in absolute FEV1 and FVC were observed in patients treated with ZEPOSIA [see Warnings and Precautions (5.6)].

Malignancies

Malignancies, such as melanoma, basal cell carcinoma, breast cancer, and seminoma, were reported with ZEPOSIA in the active-controlled trials for ZEPOSIA. An increased risk of cutaneous malignancies has been reported with another S1P receptor modulator.

Hypersensitivity

Hypersensitivity, including rash and urticaria, has been reported with ZEPOSIA in active-controlled MS clinical trials.

7 DRUG INTERACTIONS

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

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

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

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

ZEPOSIA has not been studied in patients taking QT prolonging drugs. Class 1a (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought.

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

7.3 Vaccination

During, and for up to three months after, discontinuation of treatment with ZEPOSIA, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ZEPOSIA treatment and for up to 3 months after discontinuation of treatment with ZEPOSIA [see Warnings and Precautions (5.1)].

7.4 Strong CYP2C8 Inhibitors

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

7.5 Breast Cancer Resistance Protein (BCRP) Inhibitors

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

7.6 Strong CYP2C8 Inducers

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

7.7 Monoamine Oxidase (MAO) Inhibitors

Co-administration of ZEPOSIA with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, the active metabolites of ozanimod inhibit MAO-B [see Clinical Pharmacology (12.3)].

The potential for a clinical interaction with MAO inhibitors has not been studied; however, the increased risk of nonselective MAO inhibition may lead to a hypertensive crisis. Therefore, co-administration of ZEPOSIA with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors.

7.8 Adrenergic and Serotonergic Drugs

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

Opioid Drugs

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

Serochemical Drugs

Although a small number of patients treated with ZEPOSIA were concomitantly exposed to serotonergic medications, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration.

7.9 Tyramine

MAO in the gastrointestinal tract and liver (primarily type A) provides protection from exogenous amines (e.g., tyramine). If tyramine were absorbed intact, it could lead to severe hypertension, including hypertensive crisis. Aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines (e.g., aged cheese, pickled herring) may cause release of norepinephrine resulting in a rise in blood pressure (tyramine reaction). Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ZEPOSIA [see Warnings and Precautions (5.5)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

Oral administration of ozanimod (0.2, 0.1, 0.5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/deflagged ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. At the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day.

Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

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

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

8.2 Lactation

Risk Summary

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

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

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of ozanimod (0, 8, 25, or 80 mg/kg/day) to Tg.rasH2 mice for 26-weeks resulted in an increase in hemangioma and hemangiosarcoma (combined) in males and females at the mid and high doses tested.

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

Mutagenesis

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

Impairment of Fertility

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

17 PATIENT COUNSELING INFORMATION

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

Risk of Infections

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

Cardiac Effects

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

Liver Injury

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

Pregnancy and Fetal Risk

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

Respiratory Effects

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

Macular Edema

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

Posterior Reversible Encephalopathy Syndrome

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

Severe Increase in Disability After Stopping ZEPOSIA

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

Immunosystem Effects After Stopping ZEPOSIA

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

Manufactured for: Celgene Corporation
Summit, NJ 07901
Patent: www.celgene.com/therapies
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**PACAP Pathway and Its Role in Migraine**

By Jennifer S. Sun, PhD

**MIGRAINE IS A HERITABLE,** complex brain disorder that produces an assortment of neurological and systemic effects. Diagnosis is based on criteria related to the number and duration of attacks, as well as headache characteristics and the presence of accompanying symptoms. These symptoms are often debilitating and can be triggered by hormonal fluctuations or stress. Further, patients with migraine are more likely to experience medication overuse headache and comorbidities such as insomnia, depression, anxiety, gastric ulcers, and gastrointestinal bleeding.

Despite the prevalence and significant burden of migraine, the majority of patients living with the disorder are overlooked or treated unsatisfactorily. This is due in part to the challenge of identifying effective treatment to address the complex pathophysiology of migraine. Lack of efficacy and the development of adverse effects (AEs) often result consequent in patients’ dissatisfaction with medications, particularly before the recent advent of more targeted preventive migraine treatments. The continued development of such agents promises to change this landscape.

Investigational migraine therapeutics focus on receptors of the trigeminovascular system, the activation and sensitization of which yields migraine headaches. Eptinezumab (Vyepti, Lundbeck Seattle BioPharmaceuticals), a humanized monoclonal antibody (mAb) inhibitor of the calcitonin gene–related peptide (CGRP), received FDA approval in February 2020 as the first intravenous migraine prophylactic in adults. Clinical trials, along with an open-label safety study and pharmacokinetic data, show that quarterly infusions of eptinezumab achieve 100% bioavailability after administration and significantly decrease the number of migraines experienced per month. Modulation of other signaling systems and factors which are involved upstream or alongside the trigeminovascular system (the endocannabinoid system) are also being considered for therapy development. These factors can potentially be used in combination therapy with CGRP active agents. Of particular recent interest is the pituitary adenylate cyclase–activating peptide (PACAP) signaling pathway.

PACAP is a pleiotropic signaling neuropeptide belonging to the glucagon-growth hormone–releasing factor-secretin superfamily. It exists in 2 biologically active forms, PACAP-27 and PACAP-38. PACAP-38 is the predominant form, shows a remarkable degree of evolutionary conservation, and PACAP is known to regulate learning, memory, and behavior through its modulation of neuronal growth, development, and repair. It shares important close anatomical similarities with CGRP in central nervous system regions associated with migraine pathophysiology, suggesting that PACAP may play a role similar to that of CGRP in its contribution to migraine. Preclinical data, however, indicate that PACAP and CGRP have differentiated pharmacology with respect to migraine-associated symptoms.

Human studies confirm PACAP as a key player in migraine pathophysiology. Intravenous administration of PACAP-38 caused headache in all healthy subjects and migraine-like attacks in 58% of patients with a history of migraine without aura (NCT00380263). However, administration of a functionally related neuropeptide, vasoactive intestinal peptide (VIP), did not induce migraine-like attacks in patients with migraine. PACAP-38 is released from both the parasympathetic and sensory system. Consequently, PACAP-38-induced migraine in the sensory system is attributed to modulation of nociceptors outside the blood-brain barrier. PACAP-38-mediated vasodilation through the sensory nerves that innervate the cranial vasculature may contribute to pain during migraine attacks. Moreover, a clinical trial demonstrated that plasma PACAP-38 levels were increased after PACAP-38 infusion in patients who subsequently experienced migraine attacks (NCT01471990), suggesting de novo synthesis or release of PACAP-38 during migraine. PACAP may therefore be useful as a biomarker of primary headaches.

PACAP’s actions are mediated through 3 G protein-coupled receptors: VIP type 1 receptor, VIP type 2 receptor, and PACAP type 1 (PAC1) receptor. Studies indicate that the PAC1 receptor is the most important mediator of PACAP signaling, perhaps due to its 1000-fold higher affinity for PACAP than for VIP.

**FIGURE. How Antibodies Developed for Prophylactic Antimigraine Treatment Target PACAP or Its Receptors, Disrupting Signaling**

**NeurologyLive.com**
Both PACAP and the PACR receptor have thus been suggested as novel targets for migraine treatment, which might provide new therapeutic options for patients who do not respond to CGRP-blocking drugs (FIGURE). Unfortunately, no statistically significant differences in mean monthly migraine days were found in a phase 2a, randomized, double-blind, placebo-controlled study of the safety and efficacy of 12 weeks of treatment with AMG 301 (Amgen; NCT03238781),28 a PACR receptor–targeting mAb. However, anti-PACAP antibodies still have the potential to be effective in the treatment of migraine.4

ALD1910 (Alder BioPharmaceuticals)24 is a potent, selective, high-affinity, neutralizing mAb that targets both PACAP-271 and PACAP-38,12 to block PACAP signaling, offering a new mechanism-specific approach for migraine therapy. ALD1910 recognizes a nonlinear epitope within PACAP-38 and effectively blocks its binding to its cell-surface receptors in a dose-dependent manner.1 A first-in-human, randomized, double-blind, placebo-controlled study (NCT04197349)24 in a healthy population began in September 2019 to assess the safety, tolerability, and pharmacokinetic profile of ALD1910 at 7 ascending doses. This study was completed in August 2020, with results forthcoming.

Considering the prevalence and heterogeneity of migraine,15,6 the development of therapeutic agents with mechanistically diverse targets will lead to more treatment options. A number of migraine regulators have been identified as promising targets. Targeting multiple levels in the same pathway might lead to more effective prevention of migraine.5 However, selective antibodies have the greatest therapeutic potential; such agents should reduce potential AEs while maintaining efficacy for most patients with migraine.15 mAbs that block activation of the trigeminovascular system should potently prevent the onset of migraine attacks.2,16 The ideal agent would exhibit limited drug-drug interactions, an important consideration in a patient population susceptible to polypharmacy.4

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REFERENCES

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Expert Perspectives: Advances in the Management of Acute Migraine

A pair of migraine experts explores several topics in the acute treatment of migraine, including recent therapeutic innovations.

By Matt Hoffman

MIGRAINE CARE HAS BENEFITED in recent years from the introduction of novel therapeutics aimed at preventing attacks by targeting calcitonin gene-related peptide (CGRP) and the corresponding receptors. Acute management, too, has benefited from these developments.

In a recent NeurologyLive® Insights discussion, Wade M. Cooper, DO, associate professor of neurology, Michigan Medicine, and Amaal J. Starling, MD, assistant professor of neurology, Mayo Clinic Scottsdale, offered their perspectives on how this has impacted the care of their patients, such as how the shift in expectations outcomes has impacted treatment selection, and shared some of their best practices in migraine treatment. Additionally, they spoke to the intricacies of measuring pain relief and monitoring the onset of action of therapy, and the vital nature of doctor–patient communication when optimizing the efficacy of treatment.

Pain Relief and Treatment Onset Inquiry
According to Cooper, the best question the treating physician can ask is about the control of a patient’s migraine. He noted that the responses of treated patients may vary, but they often will note that their headache is reduced or that they’re feeling better, but that they haven’t quite achieved their desired outcome.

“One of the things I like to ask, if I’m assessing someone for their headache [therapy] effectiveness, is, ‘How many times in the last month have you been disabled or incapacitated from an acute migraine?’” Cooper said. “Meaning, how many times did they have to stop their plans [relating to] work, family, or social events? Incapacity—taking people out of their daily lives—is a huge issue for people with migraine.”

Probing about the onset of action for a given medication can be tricky, Cooper added. The inquiry itself relies on the assumption that patients are taking medicines at the onset of symptoms. With triptans, for example, the literature is most supportive of efficacy when they’re administered as close as possible to the beginning of an acute headache, Cooper noted. The same appears to be true for the newer medications, as well. A further complicating factor, Cooper explained, is that patients’ response times vary—from as short as 10 to 15 minutes to as long as 4 to 6 hours, or even a full day.

“We know that triptans and some of the gepant-class medicines work on the lining of the brain, where the meningeal pain through...
the trigeminal fibers is sent deep into the brain itself,” Cooper said. “If you wait too long, and that signal from the lining of the brain becomes amplified and it gets reactivated back into the brain stem itself, you’ve lost your opportunity for medications that work in the periphery to have [efficacy].”

Importantly, many patients need to ration their acute treatments because usage should be limited to 2 to 3 days per week. A patient with 15 headache days per month may hold off on administering medication, to save it for the days and times when they most cannot afford to be incapacitated. In some circumstances, Cooper explained, patients tend to wait because of the prodrome period. This can cause some confusion and awareness impairment for patients, which can delay the time they take to recognize that they are headed for an attack.

Delays in treatment can also be due to fear of adverse effects or to a perceived lack of efficacy. The consequences of such delays are, mainly, more severity and longer duration of migraine, as well as incomplete response to therapy.

The Importance of Patient Communication

“Our patients with migraine [often] come to us with a history of stigma: a history of family members, the lay public, [people at] their workplace, and even their medical and health care providers not listening to them and not communicating with them. That’s why it’s so important that once they come to us, as their neurologists and their headache treatment providers, that we emphasize how dedicated we are to communicating with them,” Starling explained.

Communication is essentially the key to the entire patient–doctor relationship, Starling emphasized, beginning with the first appointment and extending through follow-up and every subsequent visit.

Part of establishing a strong relationship includes properly describing the treatment plan with the patient. This includes giving them a plan for when medication does not achieve the required efficacy; being sure they know when to contact the physician or to potentially head to the emergency department; and outlining what to expect in all of these situations.

“You want to make sure that the patient has a plan [for different scenarios] because those events can be really scary, and often they’re not in a position where they can appropriately advocate for themselves,” Starling said. They should also have a follow-up plan, detailing when to update their doctor and how soon they should anticipate another visit to the office. Additionally, providing the patient with the information the physician will require for the visit can help with the efficiency and accuracy of both the visit and communication.

Starling said that going over all these specific factors helps optimize the treatment plan, and also reinforces the importance of monitoring pain relief and therapeutic effect onset. She also noted that when the patient keeps a reliable headache diary, it not only helps patient–doctor communication but provides valuable information about attack patterns, such as clustered attacks or unbroken attacks, which require distinct therapy approaches.

“A reason that many patients find keeping a headache diary to be frustrating is that their doctor doesn’t ask to look at it,” Starling said. “If you ask for it and [actually] look at it, they’re more motivated to keep it.” And it’s not necessarily difficult to keep a diary, she added: “They can keep it on their phone, using any type of app. A lot of my patients like using the app Migraine Buddy. Or, they can use an old-school [paper] calendar that you can just flip through. I usually have patients tick the days when they’re taking a medication, or the days when they’re debilitated by a migraine attack and they took medication.”

Solid communication between doctor and patient can also lead to patients using as-needed acute therapies for migraine in the early stages of an attack—something both Starling and Cooper advocate.

Recent Approvals for Acute Migraine

Along with these strategies are the therapeutic advances for migraine and headache disorders that have emerged since 2018, providing migraine specialists with novel tools and marking a new era in treatment. The agents mainly target CGRP, but new targets to explore have been identified as well.

“We know that in this country, about 1 in 1000 people have multiple sclerosis (MS). We also know that [the same number]—about 1 in 1000 people in the United States—are on a CGRP monoclonal antibody for prevention of headache.

The same number of people with MS in the entire country are on the preventive CGRP monoclonal antibodies.” Cooper exclaimed. “It’s [very] rapid adoption.”

In addition to the therapies that focus on the CGRP inflammatory cascade or inflammation, lasmiditan (Reyvow), a therapy targeted to the 5-HT1F receptor, has been introduced. Lasmiditan’s benefits not only include the lack of blood vessel constriction, but having some targets located centrally in the nervous system, said Cooper.

Further, clinical trials, and often the primary end points required by the FDA, are experiencing a shift toward acute treatment. This includes explorations of some patients’ most vexing symptoms, including photophobia, phonophobia, and nausea.

“I really appreciate that [these are now] end points in clinical trials because migraine is not just a headache. Migraine is not synonymous with ‘head pain.’ There are so many other disabling symptoms in migraine,” Starling said. Consequently, these end points have translated into real-world patient experience, she explained, in part because it is now expected that medications will address these issues.

“I think this is a good shift in the field of headache medicine, in the research world, the clinical world, and the patient advocacy world, that we should all be expecting more from our medications,” Starling said. And, “patients should be expecting more from not only their medications,” she concluded, “but from their headache treatment providers.”

View the full series: neurologylive.com/perspectives-migraine-management
ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease.4

A novel RNAi-based approach that may transform the future for your patients.1,4-6

Patients and their families face a future of functional decline.1-3

Important Safety Information

Infusion-Related Reactions (IRRs)
In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Reduced Serum Vitamin A Levels and Recommended Supplementation
ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g. night blindness).

Adverse Reactions
The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

Please see brief summary of full Prescribing Information following this ad.
ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease\textsuperscript{4}

A novel RNAi-based approach that may transform the future for your patients\textsuperscript{1,4-6}

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Study Design
The efficacy of ONPATTRO was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adults with hATTR amyloidosis with polyneuropathy. Patients were randomized to receive ONPATTRO 0.3 mg/kg (N=148) or placebo (N=77) via intravenous infusion once every 3 weeks for 18 months.

Primary endpoint: The modified Neuropathy Impairment Score + 7 (mNIS+7) is an objective 304-point assessment of neuropathy that measures cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology.

Key secondary endpoint: The Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) scale is a patient-reported assessment that evaluates neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy (score range -4 to 136).

Select secondary endpoint: The Composite Autonomic Symptom Score 31 (COMPASS 31) is a patient-reported questionnaire that evaluates 6 autonomic domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor (score range 0 to 100).

At 18 months, ONPATTRO demonstrated:

- Reversal in neuropathy impairment\textsuperscript{4}
  - Mean change from baseline in mNIS+7 of -6.0 points vs 28.0 with placebo, a treatment difference of -34 points (95% CI: -39.9, -28.1; p<0.001)

- Improvement in quality of life\textsuperscript{4}
  - Mean change from baseline in Norfolk QoL-DN score of -6.7 points vs 14.4 with placebo, a treatment difference of -21.1 points (95% CI: -27.2, -15.0; p<0.001)

- Reduction in autonomic symptoms\textsuperscript{6,7}
  - Mean change from baseline in COMPASS 31 of -5.3 points vs 2.2 with placebo, a treatment difference of -7.5 points (95% CI: -11.9, -3.2; p<0.001)

\textsuperscript{CI}=confidence interval; RNAi=ribonucleic acid interference.

Visit www.onpattrohcp.com to get your patients started.
ONPATTRO® (patisiran) lipid complex injection, for intravenous use
Initial U.S. Approval: 2018
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

DOSEAGE AND ADMINISTRATION
Dosing Information
ONPATTRO should be administered by a healthcare professional. ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight. For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks. For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

Missed Dose
If a dose is missed, administer ONPATTRO as soon as possible. If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient’s original schedule. If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter.

Required Premedication
All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) [see Warnings and Precautions (5.1) in the full Prescribing Information]. Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion: intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent); oral acetaminophen (500 mg); intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent); and intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent).

For medications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent. Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs [see Warnings and Precautions (5.1) in the full Prescribing Information].

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were dyspnea, arthralgia, or pain in muscle or joint, and erythema or injection site redness. Most of these symptoms were reported in less than 1% of patients.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs [see Dosage and Administration (2.2) in the full Prescribing Information].

Reduced Serum Vitamin A Levels and Recommended Supplementation
ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum vitamin A levels do not reflect the total vitamin A in the body. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of ONPATTRO cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

A total of 224 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received ONPATTRO in the placebo-controlled and open-label clinical studies, including 196 patients exposed for at least 1 year. 137 patients exposed for at least 2 years, and 52 patients exposed for at least 3 years. In the placebo-controlled study, 148 patients received ONPATTRO for up to 18 months (mean exposure 17.7 months).

Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.

Table 1 lists the adverse reactions that occurred in at least 5% of ONPATTRO-treated patients and at least 3% more frequently than in placebo-treated patients.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONPATTRO N=148 %</th>
<th>Placebo N=77 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections a</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Infusion-related reaction b</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea c,d</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms c</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia c</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Erythema c</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Bronchitis c</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Vertigo c</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

a Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.

b Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea, and headache [see Adverse Reactions (6.1) in the full Prescribing Information]. One patient in the ONPATTRO expanded access program had a severe adverse reaction of hypotension and syncope during an ONPATTRO infusion.

Patients should receive premedication on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion [see Dosage and Administration (2.2) in the full Prescribing Information]. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Extravasation was observed in less than 0.5% of infusions in clinical studies, including cases that were reported as serious. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to
ONPATTRO during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the program by calling 1-877-256-9526 or by contacting alnylampregnancyprogram@iqvia.com.

Risk Summary

There are no available data on ONPATTRO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ONPATTRO treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking ONPATTRO. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by ONPATTRO and of vitamin A supplementation are unknown [see Clinical Pharmacology (12.2), Warnings and Precautions (5.2) in the full Prescribing Information].

In animal studies, intravenous administration of patisiran lipid complex (patisiran-LC) to pregnant rabbits resulted in developmental toxicity (embryofetal mortality and reduced fetal body weight) at doses that were also associated with maternal toxicity. No adverse developmental effects were observed when patisiran-LC or a rodent-specific (pharmacologically active) surrogate were administered to pregnant rats [see Data in the full Prescribing Information].

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

Data

Animal Data

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 15 mg/kg) or a rodent-specific (pharmacologically active) surrogate (15 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

Intravenous administration of patisiran-LC (0, 0.1, 0.3, or 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis produced no adverse effects on embryofetal development. In a separate study, patisiran-LC (0.3, 1, or 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 15 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Lactation

Risk Summary

There is no information regarding the presence of ONPATTRO in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not detected in milk; however, the lipid components (DLin-MC3-DMA and PEG2000-C-DMG) were present in milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No dose adjustment is required in patients ≥65 years old [see Clinical Pharmacology (12.3) in the full Prescribing Information]. A total of 62 patients ≥65 years of age, including 9 patients ≥75 years of age, received ONPATTRO in the placebo-controlled study. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤1 x ULN and AST ≤1 x ULN, or bilirubin >1.0 to 1.5 x ULN) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <60 mL/min/1.73 m²) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions (e.g., flushing, dyspnea, chest pain, rash, increased heart rate, facial edema). Advise patients to contact their healthcare provider immediately if they experience signs and symptoms of infusion-related reactions [see Warnings and Precautions (5.1) in the full Prescribing Information].

Recommended Vitamin A Supplementation

Inform patients that ONPATTRO treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms [see Warnings and Precautions (5.2) in the full Prescribing Information].

Pregnancy

Inform patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO [see Use in Specific Populations (8.1) in the full Prescribing Information].

Manufactured for: Alnylam Pharmaceuticals, Inc.

300 Third Street, Cambridge, MA 02142

By: Alnylam Atthea, Inc.

11040 Roselle Street, San Diego, CA 92121

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TTR02-USA-00517

Recommended Vitamin A Supplementation

Inform patients that ONPATTRO treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms [see Warnings and Precautions (5.2) in the full Prescribing Information].

Pregnancy

Inform patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO [see Use in Specific Populations (8.1) in the full Prescribing Information].
Aducanumab and the Alzheimer Disease Treatment Landscape

By Matt Hoffman

THE GLOBAL PANDEMIC BROUGHT with it an enormous challenge for health care workers. But for the Alzheimer disease (AD) community, the past several months also brought the ongoing conversations around aducanumab, Biogen's investigational amyloid-targeting agent, to the forefront. After its 2 phase 3 trials were cut short and a complex analysis suggested the therapy may offer benefit to patients, the therapy is awaiting an approval decision from the FDA—potentially a landmark moment for AD—a decision the agency recently delayed 3 months out to June 2021.

While the discussion about aducanumab's potential has dominated conversations in the space of late, determining if this agent offers benefit is far from the community's only challenge. To find out more about what a possible approval might mean for AD and for the physicians treating it, as well as what impact it may have on some of those obstacles, NeurologyLive® spoke with the principal investigator in the aducanumab trials, Stephen Salloway, MD, MS, director of neurology and of the Memory and Aging Program, Butler Hospital, Providence, Rhode Island.

Q: What impact do you believe an approval of aducanumab would have for AD?

My take is that it would open a new modern treatment era for AD. It would just be the beginning—a stepping stone, rather than the final breakthrough. There was a really good quote the other day, from a colleague of mine, who said, “In order to get the best-in-class drug, we must have the first-in-class drug.” That’s how I see this.

It’s akin to azidothymidine (AZT) for HIV. There was no treatment for HIV, and when AZT was approved, it had limited use, but it stimulated the community to really get going with developing better treatments, and now they have developed really potent treatments that affect the disease course for HIV. I’m hoping the same thing would happen for us, and AD. No drug has been approved for 17 years for AD. The need is much greater now than it was back then, and this would be the first indication for mild cognitive impairment. There is no current indication for the earlier stage of the disease. And it’d be the first drug that actually targets the core pathology of the disease. There are a lot of great things on that side.

But where I see it as really being beneficial and moving the field is that it would then require us to use the modern tools. We’d have to screen for amyloid status. Right now, we’d be using amyloid PET and cerebrospinal fluid, but soon we’ll have blood tests to do the same thing. That will get us on the move to figure out how to use those. We’ll have to screen for appropriate eligibility, making sure people meet the disease stage, making sure their MRI is doesn’t show extensive cerebral amyloid angiopathy. We’d have to learn how to monitor for and manage amyloid-related imaging abnormalities, which is a common adverse effect of AD therapies. On all those fronts, it would be a major advance in moving us forward.

If aducanumab became the standard of care, we’d have to [work on] add-on studies for people with early AD who had access to aducanumab. I imagine most [people] would want to go on aducanumab, rather than go into a clinical trial and [possibly] be on placebo. We’d have to show added benefit of a new treatment—or really, a combination treatment—with aducanumab plus something else, or aducanumab compared with something else.

Q: Do you think that that would happen relatively quickly, if aducanumab is ultimately approved?

Well, I think it’ll be determined based on the uptake. If there is full FDA approval for the indication that we used to test the drug—which I would recommend that it be—that would be the label, and [then there would be widespread] reimbursement. Then I think
there would be pretty broad uptake. Patients would have access to it, there’ll be a high demand for it, and then there will be pretty brisk uptake. We’ll figure out how to administer it to a larger number of people. That’s going to be a challenge, but I think we can overcome that. Once that happens, then that basically establishes it as the standard of care.

Then you have an ethical problem, or [at least] a recruitment problem—you can debate whether it’s an ethical problem. If someone has access to a drug with some positive chance of benefit vs nothing, they’re going to choose [the drug], especially for a serious disease like AD. It’s a big commitment to be in these studies. You don’t want to dedicate yourself to something and turn down a treatment that might be of benefit to you. I think that will happen over the course of a year. It’ll take time to retool our trials to factor in aducanumab. Then, there is the whole issue of coverage—who pays for that? If we’re testing, let’s say, a tau drug plus aducanumab, and everyone is guaranteed to get aducanumab—some will gettau and some will get placebo—who pays for the aducanumab? Is it the sponsor of the tau trial? Is it Medicare? A combination? I don’t know. That’s another factor.

What’s likely to happen, or could, is approval of aducanumab in the United States, but no approval for a while outside the United States. Then, the trials of monotherapy, without aducanumab, would be conducted in other countries, which is good and bad. The rigor of US trials is pretty reliable, and I get more nervous the less developed the country is. [For instance,] we had a positive drug, Dimebon, many years ago, when it was tested in Russia, with a really great result. Then, when we tested it outside of Russia, we saw no benefit. We couldn’t replicate the findings. So, it just makes me nervous if we rely on other medical systems, especially less developed medical systems, to prove the benefit of the drug.

**Q:** Do you think that the scales that are currently being used are adequate?

We always want the most sensitive and reliable measures we can develop, for sure. That’s especially challenging when we go earlier in the disease. Let’s say someone is showing pathological changes of AD with amyloid or tau buildup and no symptoms. Detecting change on a cognitive scale in that case is very challenging. The more impaired the patient, the easier it is to detect the change. And patients change more during the trials. That’s a very important factor: the rate of change. If you get a lot of people in a trial who are stable, then it’s very hard to show a drug’s benefit. You need at least a substantial group of people who are progressing in a detectable way during the trial.

We’ve made a lot of advances that I’m really excited about. One is that we can visualize the amyloid plaques safely now, and [do so] early on in the disease process. We can see the tau tangles, as well, with a brain scan. The blood tests and the plasma test [to detect plaques] look really good and they are coming on quickly—much more quickly than almost all of us expected. [Those tests will] be a real game-changer. Once we have a plasma test that’s reliable for detecting the disease state, and also helping to measure progression of change, that will be really helpful. [We’ll be able to] define a population that is amyloid positive, and we can target whatever stage of the disease—either preclinical, or early AD, or later AD—and verify that they have AD pathology. That’s really good.

Now we have drugs in development like aducanumab and others—it’s not alone—that actually target the plaques and can lower them demonstrably. That’s a big advance; don’t take that for granted. The FDA’s question is whether we can show a correlation between the lowering of the amyloid plaques and a clinical benefit, and that’s where there’s a debate. Aducanumab has had mixed results, but [there are some explanations]. First of all, the trials got interrupted. That made data interpretation more challenging. And then there was a dose adjustment for a large segment of the population—the APOE4 carriers—midway through. Dose is important for these drugs, and a lot of [the trial participants] didn’t get to the highest dose and have full exposure to that, which makes interpretation difficult. One study clearly showed a benefit, and one study didn’t. I think it’s open to interpretation.

**Q:** How would you describe the impact of the technological and diagnostic advances you alluded to earlier?

We have made major, major advances on the diagnostic side and biomarker side. I would consider the blood biomarker to be a major, game-changing breakthrough. Once that comes into clinic—it’s already coming into research—and we start using it for research, to screen, that will be the first major test for this. If we can reliably use that to screen, especially for the preclinical population—so we don’t have to do a PET scan on everybody to figure out who’s likely to be positive—that will be huge. At least initially, we’ll use PET scans to verify [status]. But if [the biomarker] is good enough, you won’t even need the PET scan unless you want to measure the change in amyloid-PET. That would be our first clinical use, in a research setting. If that’s good and reliable, then it’ll go into clinical practice, and then we’re in a whole new world. Then, any doctor who treats older patients will need to become familiar with it because they’ll need to know how to use it. That will be driven by therapy, if we have one. A doctor is going to be motivated if there’s something they can do. If there’s nothing you can do about, [say], prostate cancer, there’s much less motivation to screen. But now there are a lot of treatments for prostate cancer, colon cancer, breast cancer—all of the other cancers that have routine [screening] now. It will be the same thing for AD. That’s why it’s important to have at least 1 drug approved, because that will motivate the clinical community to get more engaged.
Parkinson Disease Treatment Tavapadon Aims to Benefit From Unique Multitrial Designs

Tavapadon’s rare combination of efficacy and minimal adverse effects may indicate a step forward in the treatment of Parkinson disease.

By Marco Meglio

RESULTS OF THE TEMPO TRIALS, a combination of three phase 3 studies and an open-label extension, will be used to examine the effects of tavapadon, a Parkinson disease (PD) drug designed by Cerevel Therapeutics, in patients with early-onset PD and those with late-stage PD.

Approximately 1200 individuals, aged 40 to 80 years, will be enrolled in the 3 trials; the first patients were dosed in November 2020. TEMPO-1 (NCT04201093) and TEMPO-2 (NCT04223193) will include patients with early-onset PD and, to determine tavapadon’s efficacy, will use change from baseline in the Unified Parkinson’s Disease Rating Scale (UPDRS) part 2 and part 3 combined score (FIGURE).

Patients included in TEMPO-1 and TEMPO-2 may not be on levodopa but can be on a monoamine oxidase type B inhibitor, such as rasagiline, and still qualify for the trials. TEMPO-1 will be a fixed-dose trial, while TEMPO-2 and TEMPO-3 will feature flexible dosing.

The TEMPO-3 (NCT04542499) trial will differ from the other 2 in that it will assess patients with late-stage PD, a population whose disease is severe enough to require the introduction of levodopa. The primary end point of TEMPO-3 is the change from baseline in “ON” time without troublesome dyskinesia.

All 3 trials are supported by a 58-week open-label trial that will continue to gather information on safety that will be needed for an eventual FDA submission.

Raymond Sanchez, MD, chief medical officer of Cerevel Therapeutics, told NeurologyLive®, “We are trying to understand the benefits that tavapadon may bring to PD patients as both a stand-alone treatment in early stages of PD and as a potential adjunctive treatment to levodopa in more advanced stages of the disease.”

Tavapadon was designed as an orally bioavailable, once-daily partial agonist that selectively targets dopamine D1 and D5 receptor subtypes. The agent differentially activates the direct motor pathway, potentially driving motor benefit while minimizing the adverse effects (AEs) typical of drugs that nonselectively stimulate dopamine.

Across phase 1b and phase 2 trials conducted to date, tavapadon has demonstrated this motor control benefit with an improved tolerability profile relative to that of D2/D3-prefering agents.

Positive results from the phase 2 assessment showed that tavapadon met its primary end points by showing a statistically significant improvement in motor symptoms after 15 weeks. Researchers found a change of –9.0 points in UPDRS Part 3 scores for those treated with tavapadon, compared with –4.3 for those administered placebo (leastsquares mean, –4.8; $P = .0407$). Additionally, treatment compliance was high in both groups, and 82% of patients who received tavapadon completed the trial.

The randomized, flexible-dose study included 57 patients aged 45 to 80 years with PD and varying disease severity (their Hoehn and Yahr stage ranged from 1 to 3). The study included a 9-week dose optimization period followed by a 6-week period of stable dosing. In the phase 1 study, tavapadon doses were 0.75 mg, 1.5 mg, 3 mg, 6 mg, and 9 mg, and included an open-label multiple ascending dose study, which gave once-daily doses with up-titration to 5 mg, 15 mg, and 25 mg.

After 15 weeks, 50% of those treated with the study agent reported Patient Global Impression of Change statuses of either much improved or very much improved. In comparison, 25% of patients in the placebo group reported this status. There were no effects of significance on Epworth Sleepiness Scale score in either the placebo or tavapadon groups.

Tavapadon also showed a favorable tolerability and safety profile. Most of the AEs were deemed mild or moderate; the most common were nausea, headache, somnolence, and tremor.

Sanchez hopes that “even when [tavapadon] is introduced as an adjunct treatment to levodopa, given its long half-life and partial agonist mechanism of action, it can sustain motor control, allow practitioners to reduce the levodopa dose, reduce the dyskinesia burden, and still [give patients] the needed motor control.”

The data readouts for these trials will emerge collectively by the end of 2023. Sanchez noted that if the trials are successful, Cerevel Therapeutics plans to submit a new drug application to the FDA shortly thereafter. It will include all 3 TEMPO trials and the open-label extension.

For a full list of references, see the article on NeurologyLive.com.
Sonja W. Scholz, MD, PhD, on Advancing Genomics Against Complex, Polygenic Neurodegenerative Disorders

Kenneth Bender, PharmD, MA

Sonja W. Scholz, MD, PhD, an investigator in the Neurodegenerative Diseases Research Unit in the Division of Intramural Research at the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH), was the recipient of the annual Soriano Lectureship Award at the 2020 American Neurological Association (ANA) virtual meeting. The award acknowledges, according to the ANA, a “brilliant lecture delivered by an outstanding scientist.”

Scholz was recognized for her application of advanced genetic techniques to the study of neurodegenerative disorders, including dementia with Lewy bodies, multiple system atrophy, frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. She welcomed the opportunity, utilizing the occasion to describe how advances in genetics are likely to impact daily clinical practice with patients afflicted with these types of disorders.

While much of the recent excitement in this field has resulted from identification of single-gene defects or deficiencies underlying rare monogenic disorders such as Batten disease and Rett syndrome, and from the emerging technologies to deliver gene replacement, Scholz emphasized the importance of also pursuing the genetic components of more common and more complex polygenic, age-related neurodegenerative disorders.

“A lot of the work in genetics has traditionally been done in the pediatric population, where you have the single-gene disorders. But increasingly in our adult population, we are recognizing that genetics also play a role,” Scholz told NeurologyLive®. “It shouldn’t really surprise us; our genes don’t stop working just because we’re growing up. But it becomes more complicated. There are more risk factors rather than causative genetic factors, and it’s usually a combination of many.”

“While I think that most of the immediate translations are going to happen in the Mendelian diseases, the monogenic diseases, I think there’s also a lot of hope that this knowledge can be leveraged for the more complex genetic disorders,” Scholz commented.

After presenting her Soriano Award lecture, “Genomic Approaches Paving the Way for Precision Neurology,” Scholz spoke with NeurologyLive® regarding her work and the opportunity to pursue it in collaboration with scientists both in and outside of the NIH. That discussion has been edited and abridged, and the lecture excerpted for this profile.

Pursuing Research to Improve Clinical Outcomes

Scholz obtained her medical degree from the Medical University of Innsbruck, Austria, in 2004, after which she completed a fellowship at the Laboratory of Neurogenetics in the NIH National Institute of Aging. In 2010, she earned her PhD in neurogenomics from University College London in the United Kingdom. Before returning to the NIH, Scholz added to the clinician component of her physician-scientist background by completing her neurology residency at Johns Hopkins University School of Medicine in Baltimore, Maryland.

In 2015, Scholz received the McFarland Transition to Independence Award for Neurologist-Scientists and rejoined the
NIH to lead a team of researchers in applying advanced genetic techniques to the study of neurodegenerative disorders. She established the Atypical Parkinsonism Clinic at the NIH Clinical Center to study the natural history and molecular characteristics of patients suffering from these conditions.

Scholz described the decision to complete her neurology residency even as she had established her path in research directly from medical school.

“I think the ideal scenario is to combine the clinical work with research. They’re 2 worlds that sometimes live by themselves, and I think I see myself as kind of a bridge builder between those worlds,” she recounted.

“I really enjoy the basic sciences side, asking questions and learning more about very complicated diseases, but also kind of crystallizing out the important, translatable parts of the knowledge that we’re generating, and communicating that to the clinicians who are working with these patients. And, hopefully, contributing to the new therapies that we’re hoping to develop for patients with very complex, neurodegenerative conditions,” Scholz said.

After the completing her neurology residency and receiving the McFarland Award, Scholz proposed that the NINDS establish a genetics research unit dedicated to neurodegenerative diseases. Scholz found the leadership at NINDS to be “very open to the idea” and to have already recognized the need for additional physician-scientists to work in that area.

“With the population aged more than 65 years growing quite rapidly, we’re seeing an increase in patients with neurodegenerative diseases, and that puts a huge socioeconomic burden on the society. There is a need to come up with better insights into what is actually causing these very challenging diseases, and [into] treatments,” Scholz pointed out.

Scholz integrated the Neurodegenerative Diseases Research Unit into the Laboratory of Neurogenetics, an established genetics research laboratory within the Intramural Research Program. The stated primary mission of the laboratory is to unravel the molecular genetic mechanisms that underlie these devastating diseases and identify targets for drug development.

Scholz’s efforts to focus the direction of genetic research and accelerate the attainment of meaningful findings were aided by the emphasis on collaboration in the Laboratory of Neurogenetics and at the Intramural Research Program, and her research has proceeded with national and international partners.

“Everything that we do is part of team science and team research. Nobody can do any of this by themselves,” Scholz declared. “It has to be an effort that involves the entire research community: patients, caregivers, researchers, and clinicians.”

**FIGURE 1. The Future Focus: Complex Disease**

The range of genetic investigations that derive from the linkage studies used to characterize rare monogenic disorders, such as Batten disease, and genome-wide association studies that are helping to uncover polygenic foundations of complex disorders such as Parkinson disease and Alzheimer disease.

Source: Sonja W Scholz, MD, PhD, investigator, Neurodegenerative Diseases Research Unit, NINDS, NIH. Presented in her Soriano Award Lecture at the 2020 American Neurological Association virtual meeting. Used with permission.
Scholz encourages clinicians to tell patients of diverse backgrounds and ethnicity about openings in clinical trials, as well as opportunities to provide biosamples for genomic studies.

“We have great opportunities to use genomics, [and] not just for identifying underlying genetic defects that may help with the diagnosis,” Scholz explained. “By enrolling many individuals from varied backgrounds into the research studies, we can learn more about them and build a health care system that becomes more open and more equitable, as well as more precise and more personalized.”

Tallying the Polygenic Risk Score

Scholz emphasized the utility of the polygenic risk score (PRS) to distill genome-wide association study (GWAS) locations of loci with possible links to pathogenesis into a cumulative risk metric. In her area of research, the PRS is used to sum up the identified loci from the GWAS and weigh them by their relative effect sizes to estimate an individual’s risk for complex, polygenic degenerative neurologic disorders.

Clinical correlations of PRS for some disorders have included estimated age at onset and the rapidity of the degenerative course.

In Alzheimer disease (AD), for example, Scholz has noted that individuals in the highest decile of PRS have onset more than a decade earlier than those in the lowest decile. In the genetic assessment of age-associated AD risk cited in her lecture, the investigators demonstrate that polygenic factors beyond APOE contribute to modifying AD risk.\(^1\)

Scholz pointed to similar associations established for patients with Parkinson disease (PD), with patients in the highest polygenic risk category presenting with earlier disease onset. Those investigators underscore the evidence that early-onset forms of PD cannot be exclusively attributed to highly penetrant Mendelian mutation, but to an accumulation of common polygenic alleles with relatively low effect size.\(^2\)

Scholz is also interested in applying PRS to better differentiate patient groups from controls to increase the precision of clinical trials. She pointed to a successful example of case-control status prediction in PD that was accomplished by combining PRS with smell test data and demographics.\(^3\) She said she anticipates that the approach can help not only to distinguish participants with PD from controls, but that it will also progress to aid early diagnosis in individuals with prodromal features.

“There’s a lot of variability in the symptoms and signs that the patients present because they’re all individuals, and that can make the diagnosis very challenging,” Scholz commented. “I think anything that can help with identifying the underlying disease mechanism will also help with instituting appropriate treatments.”

ML, machine learning; PRS, polygenic risk score.

Source: Sonja W Scholz, MD, PhD, investigator, Neurodegenerative Diseases Research Unit, NINDS, NIH. Presented in her Soriano Award Lecture at the 2020 American Neurological Association virtual meeting. Used with permission.
Finding Interrelationship of Complex Neurodegenerative Disorders

Scholz is a principal investigator of new research that applied genetic risk scores established for AD and PD to a large cohort of patients with Lewy body dementia. She and her colleagues showed that patients with Lewy body dementia have a higher risk for both AD and PD. She pointed out that the interrelationship was present even after analysis corrected for the most common high-risk alleles (APOE, GBA, SNCA, and LRRK2).

Scholz and colleagues used GWAS analysis to identify 5 independent risk loci, with genome-wide gene-aggregation tests implicating mutations in the gene GBA. Scholz suggested that the shared risk profiles and pathways of these conditions, previously considered disparate, provide a deeper molecular understanding of the complex genetic architecture of the age-related neurodegenerative conditions.

Scholz also considered these findings as immediately clinically relevant, since a therapeutic agent that targets mechanisms for PD or AD could be a candidate for Lewy body dementia as well. Trials that provide evidence for “repurposing” a therapeutic agent could hasten the possibility of effective intervention, she suggested.

“Imagine, for example, that there is a drug that targets this specific pathway, and it shows a promising result in AD. The very obvious next thought should be, ‘Well, we’ve shown that pathway also has a defect in Lewy body dementia, so we should really try that disease population next,’” Scholz explained. “So, in a way, that can also help to accelerate the field, because we already know that these molecular overlaps exist.”

Scholz also anticipated that her team’s work in demonstrating overlapping pathways in the conditions, previously considered distinct, will help prioritize the pathway targets for intervention. For example, Scholz and colleagues suspected from their mapping that SNCA-AS1 may prove to be “a more amenable therapeutic target” than SNCA itself due to its neuronal specificity.

Lecture (excerpted):

IN A STUDY THAT WE RECENTLY PERFORMED, we applied Alzheimer disease and Parkinson disease genetic risk scores to a large cohort of patients with Lewy body dementia. And what we were able to show is that patients with Lewy body dementia have a higher risk for Alzheimer disease and for Parkinson disease, and that was present even after correcting for the most common high-risk alleles. This suggests that Lewy body dementia, on a molecular basis, intersects with the pathogenesis of Parkinson disease and Alzheimer disease. And that is immediately clinically relevant because any drug that works for Parkinson disease or Alzheimer disease should be tried in the Lewy body dementia population as well. So, for drug repurposing, this knowledge is really very valuable.

As part of their study on overlapping risk factors in patients with AD and PD and Lewy body dementia, Scholz and colleagues created a foundational resource, the largest whole-genome sequence repository in Lewy body dementia to date, which they anticipate will facilitate the study of molecular mechanisms across a broad spectrum of neurodegenerative diseases. This resource includes approximately 2000 elderly individuals who are neurologically healthy who could serve as control subjects for study of other neurological diseases.

“Determining shared molecular genetic relationships among complex neurodegenerative diseases paves the way for precision medicine and has implications for prioritizing targets for therapeutic development,” Scholz and colleagues observed.

For a full list of references, see the article on NeurologyLive.com.
Sparing the Hippocampus in Epilepsy Surgery: Critical Decisions for Outcome Optimization

Marcia Morita-Sherman, MD, PhD; Lara Jehi, MD, MHCDS

© Cleveland Clinic Epilepsy Center, Cleveland, Ohio.

THE EFFICACY OF SURGICAL TREATMENT in pharmacoresistant temporal lobe epilepsy is well established. In the majority of cases, there is clear involvement of the mesial structures, and therefore a standard temporal lobectomy, including the removal of the hippocampus, ends up being the surgery of choice. However, whenever the preoperative evaluation indicates that the hippocampus is normal on brain imaging, we are faced with a dilemma: to spare or not to spare the hippocampus. The resolution of this impasse is not straightforward. To provide the best treatment plan and surgical strategy, numerous clinical and nonclinical factors must be taken into account:

1. Neuropsychological Data
Since the resection of the hippocampus is associated with decline in episodic memory and language functions, the primary reason to spare the hippocampus is to attempt to prevent postoperative cognitive decline. This concern is most relevant when surgery is performed on the dominant hemisphere (usually left), since there is evidence that cognitive outcomes are better among patients whose hippocampus was spared.

The literature on rates of cognitive decline in cases in which the hippocampus is spared is sparse. A study on MRI-normal hippocampus cases showed that on the dominant side, those whose hippocampus was spared had lower rates of clinically meaningful postoperative declines in verbal memory (39.7% vs 70.4%; \( P = .03 \)) and confrontation naming (40.7% vs 79.2%; \( P < .01 \)) compared with those whose hippocampus was resected. However, when counseling patients, it is important to highlight that even when the dominant hippocampus was spared, the rates of decline of domain-specific memory and naming were rather substantial (39%-41%).

On the other hand, when surgeries sparing vs resecting the hippocampus were compared, the differences in memory decline on the nondominant side were not as evident. This finding could be explained by functional MRI evidence suggesting a more bilateral representation of visual memory and by the fact that visual memory deficits, traditionally associated with nondominant hemisphere epilepsies, could be compensated for by the use of verbal strategies.
The disrupting of the functional memory network in surgeries that spare the hippocampus could explain not only the observed memory decline, but also the postoperative hippocampal volume loss as reported by some studies.\(^7,8\) The effects of this network disruption on long-term postoperative neuro-psychological and seizure outcomes remain to be determined.

2. Surgical Outcome
The disadvantage of sparing the hippocampus is the theoretical higher risk of postoperative seizure recurrence. The literature comparing seizure outcome when one spares vs resects the hippocampus is controversial. Some studies found no difference between the 2 procedures,\(^4,9,10\) while other studies focusing on specific etiologies (eg, tumors or cavernomas) demonstrated higher rates of freedom from seizure whenever the hippocampus was resected.\(^11,12\) Data from a recent study suggest a more nuanced picture, with seizure outcomes being better 2 years after resection when the hippocampus was resected, but this advantage was not sustained, such that outcomes were similar at 5 years.\(^3\) In general, the seizure outcome is either better or similar when the hippocampus is resected as opposed to being left behind.

When discussing risk of seizure recurrence, a possible argument in favor of a more tailored resection is that in cases of seizure recurrence, a second resection can always be performed. However, after a first “unsuccessful” procedure, not infrequently, patients may be lost to follow-up or do not want to undergo a second surgery for various reasons, such as the fear of another failure and/or other medical complications as well as financial and personal issues.

3. Other Outcome Predictors
The strategic surgical decision is based not only on the risk of cognitive decline vs the odds of seizure freedom overall. Studies have shown that other variables are also important in defining surgical outcome, making it much more difficult to precisely delineate the risks and benefits of each procedure.

Some predictors of cognitive and seizure recurrence outcomes are described in the literature. One study comparing patients in whom the hippocampus was resected vs spared found that better baseline performance, higher age at surgery, left-sided surgery, lower preoperative IQ, and resection of the hippocampus predicted changes in verbal memory.\(^1\) Another study evaluating patients with normal-looking hippocampus on MRI found that longer epilepsy duration, normal MRI, history of invasive evaluation, and the presence of acute postoperative seizures were associated with a higher risk of seizure recurrence.\(^3\)

Other variables not listed here might also influence the overall outcome. These include, for example, electroencephalogram findings, seizure semiology, magnetoencephalographic data, and PET and ictal single-photon emission computed tomography results. However, studies with larger sample sizes are needed to further evaluate the association between other likely predictors and outcome, especially those related to the extent of the epileptogenic zone.

4. Patient’s Goals, Personality, and Expectations
Other factors that need to be taken into account when counseling patients are their social characteristics. The acceptable risk of cognitive decline and risk of seizure recurrence will depend on individual needs; these vary according to, for example, occupation, family dynamics, and future goals.

5. Development of Predictive Models
In clinical practice, when evaluating candidates for hippocampus-sparing surgery, all preoperative findings are taken into consideration to define the treatment that can be most highly recommended. However, based on the lack of consensus observed among clinicians whenever the management of those cases is discussed, the accuracy of this traditional assessment lacks precision.

Although the use of predictive models is not currently a part of standard clinical care, its utility is clearly promising, particularly in this scenario. At a minimum, predictive models have the potential to mitigate subjective interpretive biases.

We recently published a statistical model to predict seizure outcome in temporal lobe epilepsy patients with a normal-looking MRI who are undergoing epilepsy surgery.\(^7\) The model simultaneously provides the risk of seizure freedom 1 year after surgery with either treatment option: sparing vs resecting the hippocampus.

Although the model does not take into account all the factors discussed above, it optimizes the decision by providing calculated risks, at least for some of the primary outcomes. A risk calculator may also provide a level of comfort to the patient: They would be in receipt of objective data, along with expert clinical information, when making the decision to undergo surgery. New, collaborative studies, with bigger sample sizes, are needed to further enhance the model’s performance. Nevertheless, this is clearly an important step toward optimizing the decision to spare or not to spare the hippocampus.
Compounding Challenges: Conducting Clinical Trials in Alzheimer Disease

Treating Alzheimer disease presents a spider web of complexity for physicians, and its intricacies have made assessing therapies equally puzzling.

By Matt Hoffman

CLINICAL TRIALS HAVE COME A LONG WAY since the first systematic trial was conducted in the mid-1740s by Scottish physician James Lind, MD. Modern trials now consist of more rigorous design than their predecessors, in part spearheaded by the 1920s Principles of Experimental Design, which included the ideas of randomization, result replication, group blocking, and factorial experimentation. These trial tenets have helped prove the efficacy of innumerable therapies across the vast spectrum of disease since, including some conditions previously thought to be incurable or untreatable. Trial designs have pushed science forward and, as they have been refined over time, have helped researchers see the fruits of their labors blossom. Still, the success of trials still depends on the efficacy of the therapies being assessed, the recruitment of the correct patients, and the understanding of the disease in question, among other factors—including the challenge of showing clinically meaningful change, which presents itself as somewhat subjective in a practice that requires objectivity.

Ultimately, when it comes to determining which of these—clinically meaningful change or simply conducting the trials—is the biggest challenge for physicians in the development of therapies for Alzheimer disease (AD), the physician-scientist is faced with a chicken-or-egg question. As Lon Schneider, MD, MS, stated simply to NeurologyLive®, “They’re both the same.”

“The concept of clinical importance is, in this kind of discussion, a regulatory concept,” said Schneider, a professor of psychiatry and the behavioral sciences, and the Della Martin Chair in Psychiatry and Neuroscience, at the University of Southern California’s Keck School of Medicine.

“We know what properly designed, unbiased trials should be, and what they should look like. But we don’t do that.

“FDA has a phrase: ‘Adequate and well-controlled trials.’ That comes from at least the 1997 Drug and Cosmetic Act, but probably goes back a little further. It’s actually in the act, and then it was brought into regulation as well. It’s a term of art. It’s not a statistical concept,” Schneider added.

The Tools
For AD, these trials have proven to be as complex to conduct as the disease itself is to understand. Although progress has been made in the scientific understanding of AD’s pathology, much remains to
A large number of cardiovascular drugs have this level of effect. "Fundamentally, the designs of trials historically have been the standard parallel-group, randomized, controlled trials that really are looking for an average effect in an average patient. But I'm still waiting to meet an average patient," Steven Arnold, MD, told NeurologyLive®. "The heterogeneity is a real problem. Many of our outcome measures are too insensitive and too infrequently given."

Arnold, a professor of neurology at Harvard Medical School, and managing director and translational neurology head of the Interdisciplinary Brain Center at Massachusetts General Hospital, is also an investigator in the phase 2 PEGASUS trial (NCT03533257) of AMX0035, an investigational agent being assessed in AD. He noted that more frequent incorporation of digital technologies might help bolster the regularity of monitoring of patients in trials.

"People have good days and bad days," Arnold explained. "You do a test at baseline and the person does well, and then you do a test at the end of the trial. [But let's] say they slept poorly the night before. They blow the test. Even though they may have been improved all that time, you missed the ability to detect a benefit."

To overcome that amount of noise, the trials that need to be conducted require large numbers of patients, which are enormously expensive and utilize very blunt measurements. Schneider echoed this sentiment, noting that one must first consider that the measures being used in trials are continuous in nature, and are measuring, mostly, group means. But with a disease as heterogeneous as AD, determining whether there is benefit or worsening on an individual level can be difficult.

"When you're discussing clean outcomes, like death, or survival vs not survival, the concept of clinically important is very different. Count that 10 people vs 9 people survive—that is clinically meaningful for the 1 person who didn't," Schneider said. In fact, he noted, a large number of cardiovascular drugs have this level of effect.

Similarly, when looking at studies of cancer therapies in which a new combination, or a new therapeutic, is being added on top of the standard, any discrete and clean effect is considered clinically meaningful. The mitigating factors, in that case, are adverse events and the level of performance for the study. This challenge has existed for quite some time in AD. In 1993, the first therapy approved for AD was tacrine (Cognex; Shinogi) based on phase 2 and phase 3 studies; it has since been discontinued. Prior to tacrine's approval, the conversations at its 3 different FDA Advisory Committee meetings were dominated by what specific point-difference in means actually determined meaningful change. The scale used in those trials was the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog), a brief neuropsychological assessment utilized to assess the severity of cognitive symptoms of dementia that's still in use today.

Although the community finally came to an agreement of sorts on that matter, Schneider said, "the FDA has never said that there needs to be a minimal difference on a continuous measure. What came out of that was the need for a global measure—the clinical global impression of change—or what's been used more recently in longer-term studies, the Clinical Dementia Rating (CDR) Scale-Sum of Boxes."

"Historically, ADAS was it," Marwan Sabbagh, MD, director of the Cleveland Clinic Lou Ruvo Center for Brain Health, told NeurologyLive®. "Now we're seeing CDR—I think that's a good movement. It's funny because BAN2401, in its phase 2 studies, used ADCOMS [Alzheimer Disease Composite Score], which is a kind of a hybrid scale of CDR, and ADAS, and other things. These are easier instruments to derive clinical meaningfulness."

The CDR, which was utilized in the EMERGE (NCT02484547) and ENGAGE (NCT02477800) clinical trials of Biogen's investigational (and somewhat controversial) agent, aducanumab, has, in fact, offered a more ordinal measure. Patients change by strata on the clinical global impression of change, with the least amount of change possible being 1 point. Patients can go from "no change" to "minimal change," with minimal being defined as detectable by clinician—ergo, clinically meaningful change.

This kind of scale, Schneider said, offers the ability to separate patients into groups according to who worsened and who improved, and then leads to 2 possibilities of comparison: chi-square or categorical statistical analysis, or analysis by means. This, in part, has driven some of the discussion around the analysis for aducanumab. When using means, the meaning of the analysis becomes less clear, Schneider explained. That, in turn, presents a possible problem.

"You don't know whether there have been X number more people who were responders in the other group," Schneider said. "The FDA has been easy-going and liberal on that, and saying, 'You have the scales that measure the absolute change in individuals, and you take the average of them.' That means that more people, at whatever level you choose, are benefiting from the drugs and placebo. So, this becomes a lot of the quest for clinical meaning."

Despite the FDA previously refusing to approve AD therapy based on a cognitive test measurement, because of the inconclusive nature of these measurements' meaning and generally small effect sizes, that rule was relaxed slightly in the mid-2010s. Now, cognitive testing results can be provided as a provisional sign of efficacy in those who have disease that is considered mild with few symptoms. This is in part due to the FDA's recognition of the practical difficulty in...
The expectation is that these comparison analyses of mean values allow for the marketing of therapies for preclinical AD, with the necessary analyses being done in postmarketing studies to count individual benefits.

Most of this complication, Schneider explained, has not yet been widely realized, as only a handful of studies have been conducted in individuals with preclinical disease and a biomarker of increased risk, but no cognitive impairment. Under that circumstance, a neuropsychological composite score, which he described as a “work in progress” has been developed for use, called the Preclinical Alzheimer Cognitive Composite. It is currently being used in the A4 study of solanezumab (NCT02008357).

Fundamentally, the designs of trials historically have been the standard parallel-group, randomized, controlled trials that really are looking for an average effect in an average patient. But I’m still waiting to meet an average patient [with Alzheimer disease].

— STEVEN ARNOLD, MD

“For this kind of an early-stage AD study, you can get away with 1 outcome that is a global composite, that brings together both a memory or cognition test and a functional outcome,” Schneider said. “And the poster child for that is the CDR, because the scale has memory orientation, judgment, and problem-solving. There’s the cognitive stuff. And then it has social activity, basic activities, and community or in-house activities. You can average all those; you can add all those together into the sum of the box score.”

The FDA has noted that a composite of that nature, consisting of activities and cognitive function, such as memory and orientation, can be accepted as a single outcome without the need for a global or an individual patient outcome, because the CDR can be considered an individual patient outcome. “That’s what you now see with aducanumab. You could also have seen it with other drugs in the past, if we had chosen to make a big deal about it,” Schneider said.

Ultimately, the tools may not be the problem. For Schneider, the instruments used in AD clinical trials—which have been the same for approximately 3 decades—are fairly sensitive measures. “If you can’t tell the difference, or if you need a very large number of patients to tell the difference, then the drug is not [particularly] effective, and probably not effective enough to market,” he said. Perhaps, he admitted, the tools are not advanced, but the genuine feeling in the field seems to be that they are good enough.

“We complain about them,” Schneider explained. “But we use them. So, if you can’t find a difference with these instruments, [and] you can find efficacy with these instruments, probably there isn’t much there to deal with.”

The Timing

Another leading challenge in conducting AD trials is the timing related to the disease’s progression. In the discussions surrounding the proper targets for therapeutics and the different pathologies of the disease, many experts have posited, over the years, that earlier treatment would offer more benefit to patients. This is also reflected partially by the currently approved therapies, all of which are indicated for mild, mild to moderate, or moderate to severe stages of disease.

“What happens with clinical trials is that there’s always a delay. [In other words,] people may have some early mild symptoms, but there really isn’t a push to get people [with AD] enrolled in clinical trials until those symptoms are causing more and more of a problem,” Richard S. Isaacson, MD, told NeurologyLive®. “As we know, AD starts in the brain decades before the first symptom of memory loss. By the time someone already has dementia, that means the pathophysiology has been going on for a very long time. It’s a lot harder to make any sort of tangible progress in terms of a therapeutic or in terms of clinically meaningful change. I think it just makes sense, based on how [AD] progresses, to get people enrolled in clinical trials as early as possible.”

Isaacson, who is director of the Alzheimer’s Prevention Clinic at Weill Cornell Medicine in New York, noted that the need to evaluate patients earlier in the disease course is paramount—which is no small task, because this requires a clinical picture made clear by the presence of a biomarker. But for Isaacson, it offers a much more robust time point to show potential clinical benefit.

That time point “is when someone is starting to have cognitive changes, but they’re still able to take care of themselves,” said Isaacson. The cognitive changes must be “proven to be due to AD. [That would] mean there’s an amyloid biomarker, or tau, whether it’s through a brain imaging study or a spinal fluid test, or maybe one day in the future—pretty soon actually—a blood test,” he said. However, that time point might nonetheless still be too late, although “hopefully [it would] not.”

Isaacson noted that in this sense, treating mild cognitive impairment could operate essentially as tertiary prevention of dementia due to AD. Current estimates suggest that 47 million people in the United States have preclinical AD, which would offer quite a large group of potential individuals for trials. “That is a striking number. Maybe that’s when we need to try to study disease-modifying therapies, when the pathology has started but the symptoms haven’t begun yet,” Isaacson said.

However, attempting to assess therapies prior to even that point could produce additional issues, even if the measures of the...
disease were the most sensitive and reliable available. On top of that, developing these scales can become even more difficult when done earlier in the disease process, according to Stephen Salloway, MD, MS, director of the Neurology and the Memory and Aging Program at Butler Hospital, Providence, Rhode Island.

“Let’s say someone is showing pathological changes of AD with amyloid or tau buildup and no symptoms. In that case, detecting change on a cognitive scale is very challenging,” Salloway told NeurologyLive®. “The more impaired the patient, the easier it is to detect the change—and patients change more during the trials. A very important factor is the rate of change. If you get a lot of people in a trial who are stable, then it’s very hard to show a drug’s benefit. You need at least a substantial group of people who are progressing in a detectable way during the trial.”

Salloway noted that a number of advances have been made that might help address this difficulty, particularly the ability to visualize amyloid plaques more safely as well as earlier in the disease process. He explained that the progress made with brain scans, blood tests, and plasma tests have been surprisingly quick—more rapid, even, than what much of the field anticipated. The plasma tests, though, might offer the biggest advantage.

“Those will be a real game-changer. Once we have a plasma test that’s reliable for detecting the disease state and also helping to measure the progression of change, that will be really helpful,” he said. Such a test could “define a population who is amyloid positive, and then you can target whatever stage of the disease—either preclinical, early AD, or later AD—and verify that they have the pathology.”

As Salloway pointed out, much of the challenge of timing goes hand-in-hand with the challenge of identifying AD, and the earlier that AD can be detected, the earlier clinicians can intervene. However, this raises more questions: What is the optimal time to intervene? What is the correct dose of an agent? Is there a single correct mechanism of action? Can the intervention be used alone, or does it require accompanying lifestyle changes?

The questions don’t end there, unfortunately, Isaacson noted. “We have the amyloid hypothesis, and tau, and glucose, and hypometabolism, inflammation, and infection. Then, insulin resistance and vascular disease—the list just goes on and on and on,” he said. “The number of things that can promote AD progression and fast-forward decline is high. We have to be cautious about how much we invest our efforts into 1 specific mechanism.”

Of course, progress has been made in certain areas that warrant continued research, Isaacson explained, while plenty of failures have occurred as well. Fortunately, in Isaacson’s view, the overall result is an increased understanding that simplicity is never going to be the answer. A complex disease like AD will require complex trials and complex therapeutic tactics.

“We need to kind of have an all-hands-on-deck approach, and really keep hitting this just like any chronic condition that’s associated with aging,” Isaacson said. “High blood pressure, diabetes—you don’t treat these with just 1 magic drug or pill or infusion. It’s multiple, with blood pressure control, [angiotensin-converting enzyme] inhibitors, calcium channel blockers, and other drugs. And then we need to do some dietary changes, like a low-salt diet, and exercise and losing weight. There is just no perfect answer for these complex diseases, especially when they involve the brain. AD is as much a medical condition as it is a neurological condition, in my opinion, anyway, and we need to treat it accordingly.”

For a full list of references, see the article on NeurologyLive.com.
Donald S. Wood, PhD, is Elected MDA President, CEO

The Muscular Dystrophy Association (MDA) announced Donald S. Wood, PhD, as the organization’s new president and chief executive officer. Wood previously served as vice chairman of the board, and his experience with the MDA dates back nearly 40 years. He is perhaps best known for launching and managing the MDA’s Task Force on Genetics, which led to the discovery of the genetic cause of muscular dystrophy in 1986. Wood began his career as a postdoctoral research fellow in neurology for the National Institutes of Health at what was then known as Columbia-Presbyterian Medical Center in New York. Lynn O’Connor Vos, who served as MDA’s president and chief executive officer until recently, said in a statement, “With this foundation now set and the long-term strategy clearly paved, I have determined that now is a good time for me to pass the baton and pursue new and different opportunities.”

Tracy Dixon-Salazar, PhD, is Named Executive Director of LGS Foundation

The Lennox-Gastaut Syndrome (LGS) Foundation announced Tracy Dixon-Salazar, PhD, as its new executive director; since 2017, she has served as the foundation’s director of research and strategy. The Board of Directors selected her after a nationwide search and the review of more than 100 applicants. After earning her bachelor’s degree and her PhD in neuroscience, Dixon-Salazar conducted postdoctoral work in neurogenetics at the University of California, San Diego. Prior to joining the LGS Foundation, she worked as the associate research director of CURE Epilepsy. Dixon-Salazar’s ties with LGS are also personal as well as professional, stretching back more than 2 decades to when she became the mother of a child with LGS.

NeurAegis Appoints Renowned Neurology Experts to Scientific–Medical Advisory Board

Michel Baudry, PhD; Imad Najm, MD; and Barry Jordan, MD, MPH, are the 3 initial appointments to NeurAegis’ Scientific–Medical Advisory Board, which will help advance the company’s preclinical and clinical development activities and product pipeline. Baudry, a professor at Western University of Health Sciences, has more than 400 publications and was recently named a Fellow of the American Association for the Advancement of Science for his contributions in the field of molecular and cellular neuroscience. Najm currently serves as the director of the Epilepsy Center at the Cleveland Clinic Neurological Institute. He brings more than 22 years of experience in epilepsy and has conducted multiple research projects dedicated to exploring the mechanisms of epilepsy and malformations of cortical dysasia. Jordan is a board-certified neurologist with specialized expertise and interest in traumatic brain injury, sports neurology, and Alzheimer disease; he also serves as the chief medical officer of Rancho Los Amigos Rehabilitation Center.

Caroline Tanner, MD, PhD, Wins Robert A. Pritzker Prize for Parkinson Disease Research

The Michael J. Fox Foundation for Parkinson’s Research awarded the 2020 Robert A. Pritzker Prize for Leadership in Parkinson’s Research to Caroline Tanner, MD, PhD, for her contributions to Parkinson disease (PD) research and commitment to mentoring the next generation of PD scientists. Tanner, a professor of neurology at the Weill Institute for Neurosciences at the University of California, San Francisco, has been at the forefront of research efforts to understand how environmental factors contribute to the disease, including efforts to examine the links between increased risk of PD and exposure to commonly used pesticides such as rotenone and paraquat. She has also made efforts to chronicle the experience of PD, serving as the principal investigator of MJFF’s online clinical study Fox Insight. With Tanner’s leadership, Fox Insight’s base of volunteer patients with PD, who contribute valuable health and wellness data, has grown to nearly 50,000.

AHA/ASA 2020 Stroke Progress and Innovation Award Winner Is Selected

Brian Mac Grory, MB BCh BAO, was named the winner of the American Heart Association (AHA)/American Stroke Association’s (ASA) 2020 Stroke Progress and Innovation Award for his research examining treatment for central retinal artery occlusion (CRAO), a rare form of stroke that affects the eye. With colleagues, Mac Grory conducted a study finding that “clot-busting” medications, if given within 4.5 hours of the eye stroke, improve the chances of vision recovery for patients with CRAO. The award is given to recognize clinicians whose research encourages new paths, new methods, and new ways of thinking. Mac Grory’s award, in addition to those of the second- and third-place winners, will be presented at the International Stroke Conference in March 2021. Mac Grory plans to build off the findings of his study at the Duke Eye Stroke Center, to be established soon, which will treat CRAO and other stroke forms that affect vision.
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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Director, Goldberg Migraine Program
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Los Angeles, CA

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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