The Aducanumab Saga and the Future of Antiamyloid Monoclonal Antibodies

BY DAVID S. KNOPMAN, MD

Inaugural Class Is Announced

New Treatments in Migraine: An In-Depth Review

BY ARATHI NANDYALA MD; AND JESSICA AILANI, MD

Updates in Dravet Syndrome: Entering a New Era

BY JOSEPH SULLIVAN, MD

Endoplasmic Reticulum and/or Mitochondrial-Dependent Neuronal Degeneration in ALS

BY JENNIFER S. SUN, PHD

CLINICAL VIEWPOINT

Stopping Neurological Disorders Before They Start

WITH IMAD NAJM, MD
INDICATION
ZEPOSIA® (ozanimod) 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-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker
• Patients with severe untreated sleep apnea
• Patients taking a monoamine oxidase (MAO) inhibitor

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.
PROTECT IT BEFORE IT’S GONE

WITH ZEPOSIA, YOU HAVE THE POWER TO HELP PRESERVE THEIR MOST VALUABLE RESOURCE

- Powerful efficacy in reducing ARR, GdE lesions, and new/enlarging T2 lesions vs Avonex
- Data on brain volume and cognitive processing speed (SDMT) in secondary, exploratory endpoints and post hoc analysis
- Safety comparable to Avonex in overall incidence of adverse reactions and generally similar safety demonstrated in the long-term extension study

*Study designs: SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-μg intramuscular injection. Primary endpoint: ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.181 vs 0.350, respectively) and by 38% at 2 years (0.172 vs 0.276, respectively). Secondary endpoints: ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.

*Brain volume loss was analyzed as secondary (whole brain volume loss) and exploratory endpoints (thalamic volume loss and cortical gray matter volume loss) in the SUNBEAM and RADIANCE trials. Volume loss endpoints were not part of the statistical analysis hierarchy. SDMT is a tool that measures cognitive processing speed and was analyzed in a post hoc analysis of SUNBEAM and DAYBREAK, an ongoing open-label extension study. The MSDT was a secondary endpoint made up of 3 components: 9-hole peg test (arm/hand function), timed 25-foot walk (ambulation), and SDMT (cognitive function). SUNBEAM SDMT post hoc: ZEPOSIA (n=427) Avonex (n=426) at Month 12. DAYBREAK SDMT post hoc (SUNBEAM participants only): ZEPOSIA (n=376) at Month 42. SDMT was not part of the statistical analysis hierarchy for SUNBEAM and was analyzed descriptively in DAYBREAK.

*Adverse reactions: Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 22%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartateaminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypotension. Severe adverse reactions: The rate of severe adverse reactions at 1 year for ZEPOSIA was 1.6% vs 2.2% for Avonex and the rate at 2 years for ZEPOSIA was 3.5% vs 4.3% for Avonex.

*Study design: DAYBREAK is an ongoing open-label extension (OLE) trial that enrolled participants from multiple randomized phase 1 to 3 studies, including SUNBEAM and RADIANCE. These data are presented as an interim analysis with a data cutoff of February 2, 2021. Patients evaluated in this analysis included those receiving ZEPOSIA 0.92 mg (n=681) who completed the randomized phase 1 to 3 trials. Primary objective was the long-term safety of ZEPOSIA. Secondary objectives included ARR, new/enlarging T2 lesions, and GdE lesions. Endpoints were analyzed descriptively.

*Treatment-emergent adverse events (TEAEs): At the data cutoff (up to 5 years), the overall incidence of TEAEs for ZEPOSIA in the DAYBREAK OLE trial was 84.7%. The most common TEAEs with an incidence of at least 4% in patients treated with ZEPOSIA, sorted by decreasing incidence, were as follows: nasopharyngitis, 19.3%; headache, 15.6%; upper respiratory tract infection, 10.9%; ALC decreased, 8.9%; lymphopenia, 8.7%; back pain, 8.1%; gamma-glutamyltransferase increased, 5.9%; bronchitis, 5.8%; urinary tract infection, 5.8%; hypertension, 5.4%; respiratory tract infection, 5.4%; viral respiratory tract infection, 5.0%; and depression-related TEAEs, 4.9%. The rate of TEAEs leading to permanent treatment discontinuation was 2.7%. Severe TEAEs: The rate of severe TEAEs was 6.0%.

*Additional Information

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

Infections (Continued):
- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P 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.
- 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 stopping ZEPOSIA. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

Progressive Multifocal Leukoencephalopathy (PML): 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. PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, 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.

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delay, 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 la 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 sino-atrial heart block

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

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

Increased Blood Pressure: Increase in systolic blood 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 symptoms 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 alemutzumab is not recommended.

Severe Increase in Multiple Sclerosis (MS) Disability After Stopping ZEPOSIA: In MS, 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.

Use in Specific Populations: Hepatic Impairment: Use is not recommended.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for additional important information.


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Recommended Dosage for Multiple Sclerosis

Initiate ZEPOSIA with a 7-day titration, as shown in Table 1 (see Warnings and Precautions). After initial titration, the recommended dosage of ZEPOSIA is taken orally once daily starting on Day 8.

Table 1: Dose Titration Regimen

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose (mg)</th>
<th>Days</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>0.23 mg once daily</td>
<td>5-7</td>
<td>0.46 mg once daily</td>
</tr>
<tr>
<td>8</td>
<td>0.82 mg once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liver Function Tests

With certain preexisting conditions, advice from a cardiologist should be sought (see Warnings and Precautions).

Cardiac Evaluation

Obtain a recent (i.e., within the last 6 months) electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with preexisting conduction conditions, advice from a cardiologist should be sought (see Warnings and Precautions).

In patients with a history of unexplained syncope, heart rates below 40 bpm should be reported (see Warnings and Precautions).

Infections

Known Risk Factors

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to approximately 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues (see Clinical Pharmacology (12.3) in Full Prescribing Information). ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature, 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.

Antineoplastic, 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.

Bradyarrhythmia and Atrioventricular Conduction Delays

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 and Clinical Pharmacology (12.2) in Full Prescribing Information). ZEPOSIA was not studied in patients who had:

- 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).
- A history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial block unless the patient has a functioning pacemaker (see Warnings and Precautions).
- Severe untreated sleep apnea (see Warnings and Precautions).
- A baseline QT interval >450 msec in males, >470 msec in females, or >480 msec in males, >500 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 (see Warnings and Precautions).

In MS Study 1 and Study 2, bradycardia was reported on the day of treatment initiation in 0.6% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.8% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Liver enzyme elevations were 1.1% of patients with MS treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a.

Patients with histories of heart failure should not be initiated on ZEPOSIA.

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 MS 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 1.1% of patients who received IFN beta-1a. Elevations of 5-fold the ULN or greater occurred in 0.5% of patients treated with ZEPOSIA and 0.3% 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 without an elevation to less than 3 times then ULN within approximately 2-4 weeks. ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic transaminase levels in patients with MS treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a.

In individuals with an ALT or AST greater than 1.5 times ULN were excluded from MS Study 1 and Study 2. There were no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA. Use of ZEPOSIA in patients with hepatic impairment is not recommended (see Use in Specific Populations).

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.

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). Because it takes approximately 3 months to eliminate ZEPOSIA from the
**Increased Blood Pressure**

In MS 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 MS 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.

**Respiratory Effects**

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MS patients treated with ZEPOSIA compared to patients who received IFN-beta-1a. Upper abdominal pain 2 g 1

**Blood pressure should be monitored during treatment with ZEPOSIA and managed appropriately.**

**Macular Edema**

Sphingosine 1-phosphate (SIP) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In MS 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.

**Increased Blood Pressure**

In MS 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 MS 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.

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Sphingosine 1-phosphate (SIP) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In MS 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.

**Increased Blood Pressure**

In MS 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 MS 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.

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Sphingosine 1-phosphate (SIP) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In MS 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.

**Increased Blood Pressure**

In MS 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 MS 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.

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Sphingosine 1-phosphate (SIP) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In MS 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.

**Increased Blood Pressure**

In MS 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 MS 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.

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Sphingosine 1-phosphate (SIP) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In MS 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.

**Increased Blood Pressure**

In MS 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 MS 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.
Table 3: Clinically Relevant Interactions Affecting Drugs, Tyramine, and Vaccines Co-administered with ZEPOSIA (ozanimod)

| Prevention/Management | Clinical Impact | Oral administration of ozanimod (0, 0.2, 2, or 30 mg/kg/day) to male and female rats prior to and during mating and throughout gestation resulted in a marked increase of fetal body weight 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, CC12273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Clinical Data

- In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures.
- Metabolite CC112273 was negative in in vitro (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an in vivo chromosomal aberration assay in human (THK) cells but negative in an in vivo rat micronucleus/comet assay.

Strong CYP2C9 Inhibitors

- Co-administration of ZEPOSIA with strong CYP2C9 inhibitors increases the exposure of the active metabolites of ozanimod [see Clinical Pharmacology (12.3) in full Prescribing Information], which may increase the risk of ZEPOSIA adverse reactions.

Strong CYP2C8 Inducers

- Co-administration of ZEPOSIA with strong CYP2C8 inducers (e.g., rifampin) is not recommended.

USE IN SPECIFIC POPULATIONS

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, including, embryopathy, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity.

In rabbits, fetal blood vessel malformations were observed at oral doses approximately 1000 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC12273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

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

- Oral administration of ozanimod (0, 0.2, 0.5, or 5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/delayed ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. 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, CC12273 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. The no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, plasma ozanimod exposure (AUC) was approximately 11 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC12273 and CC1084037, were less than those in humans at the MRHD.

- Oral administration of ozanimod (0.2, 0.0, 2, or 2.0 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycles and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day) 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, CC12273 and CC1084037, were less than those in humans at the MRHD.

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.

Females and Males of Reproductive Potential

Contraception

Before initiation of ZEPOSIA (ozanimod) 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 Warnings and Precautions (7.25)]. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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. No clinically significant differences in the pharmacokinetics of ozanimod and CC12273 were observed based on age [see Clinical Pharmacology (12.3) in full Prescribing Information]. Monitor elderly patients for cardiac and hepatic adverse reactions, because of the greater frequency of reduced cardiac and hepatic function in the elderly population.

Hepatic Impairment

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of ozanimod (0, 0.2, 0.5, or 10 mg/kg/day) to B6C3F1 mice for 26 weeks resulted in an increase in 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, CC12273 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 micronuclear) assays. Metabolite CC12273 was negative in 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 (THK) cells but negative in an in vivo rat micronucleus/comet assay.

Impairment of Fertility

Oral administration of ozanimod (0, 0.2, 0.5, or 10 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 (50 mg/kg/day), pregnant rats and their offspring (AUC) was approximately 1600 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for metabolites, CC12273 and CC1084037, at 30 mg/kg/day were 13 and 3 times, respectively, those in humans at the MRHD.

PREGNANCY COUNSELING INFORMATION

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

Risk of Infections

Informed 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]. 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. Advise patients that if immunizations are planned, they should be administered at least 1 month prior to initiation of ZEPOSIA. Inform patients that the use of live attenuated vaccines should be avoided during and for 3 months after treatment with 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 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 and Warnings and Precautions].

Liver Injury

Informed 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 or dark urine [see Warnings and Precautions].

Fertility and Fetal Risk

Informed 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. For a female patient to informally inform her healthcare provider if she is pregnant or planning to become pregnant [see Warnings and Precautions and Use in Specific Populations].

Reproductive Effects

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

Mucosal Edema

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

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. Informed patients that delayed treatment could lead to permanent neurological consequences [see Warnings and Precautions].

Severe Increase in Multiple Sclerosis Disability after Stopping ZEPOSIA

Inform patients with multiple sclerosis that severe increase in disability has been reported after discontinuation of a SP1 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].

Immun System 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].

Manufactured for: Celgene Corporation

ZEPPOS® is a trademark of Celgene Corporation, a Bristol-Myers Squibb company.
The Aducanumab Saga and the Future of Antiamyloid Monoclonal Antibodies

BY DAVID S. KNOPMAN, MD
Professor and Consultant, Department of Neurology, Mayo Clinic

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BY JOSEPH SULLIVAN, MD
The Challenges Progress Poses

NEURODEGENERATIVE DISORDERS AND DISEASES have posed great challenges to the physician community for many years. The clinical care of these patient populations is complex and multifaceted, often requiring teams of a multidisciplinary nature to ensure proper management of patients’ needs. Despite these difficulties, improvements have been made to the care paradigm—as well as in therapeutic development—for many disease states.

One of the major areas that has seen advances is the Alzheimer disease (AD) field. Although it remains an extraordinary task to fully elucidate the pathophysiology and underpinnings of AD, the progress made in developing targeted therapeutic approaches has shown great promise in recent years, and the pipeline of hopeful agents reflects this. We would be remiss to avoid mention of aducanumab-avwa (Aduhelm; Biogen Inc) in this conversation. The anti–amyloid-ß therapy was approved for the treatment of AD in June 2021—the first such approval in 18 years—but its journey to the FDA, and since, has been one of ups and downs.

On page 21 of this issue of NeurologyLive®, David S. Knopman, MD, dives into the saga of aducanumab-avwa, from its beginnings in clinical development to the recently announced Centers for Medicare & Medicaid Services coverage determination. He shares his expert perspective on the therapy’s odyssey to this point and touches on what the medical field can learn from its successes and shortcomings to better prepare for the next potential approval for AD.

Further afield, experts in the treatment of migraine are facing their own challenges a few years after the first disease-specific therapies for the headache disorder came to market. After the approvals of the calcitonin gene-related peptide targeted therapies, these specialists experienced a newfound ability to offer efficacious options to their patients, but as Arathi Nandyala, MD, and Jessica Ailani, MD, point out on page 30, progress often “comes with a certain amount of pain.” The pair detail the currently available novel options for migraine, touching on their best practices for the optimal use of these drugs.

Another area of care that has been fortunate to experience advances is the rare epilepsy field, specifically Dravet syndrome. This rare epilepsy syndrome that once proved nearly impossible to manage has been the subject of a decade of rapid forward momentum in both treatment and diagnosis. On page 34, Joseph Sullivan, MD, reviews the past 5 years of progress and dives into ongoing research for this patient population. He shares an in-depth view of the field’s positioning as it approaches a new era of therapeutics and management and the potential for disease-modifying approaches to the rare disease.

As we strive to keep you abreast of the latest research and tools to improve your clinical practice, we always welcome your feedback. If you have any comments or thoughts about our coverage or would like to contribute to NeurologyLive®, please email Managing Editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.

Mike Hennessy Jr
President and CEO, MJH Life Sciences®
Achieving Greater Diversity in Dementia Research: A Call to Action

By R. Scott Turner, MD, PhD,* and Charlyn Gomez, BS**

*Professor of Neurology and Director, Memory Disorders Program, Georgetown University Medical Center
**Clinical Trials Coordinator, Memory Disorders Program, Georgetown University Medical Center

THE FINAL CENTERS FOR Medicare & Medicaid Services (CMS) decision regarding the anti–amyloid-ß (Aß) monoclonal antibody aducanumab-avwa (Aduhelm; Biogen Inc) for mild cognitive impairment and Alzheimer disease (MCI/AD) on April 7, 2022, provides coverage only with evidence development—namely, a requirement to further evaluate the clinical efficacy of aducanumab in a phase 4 trial,1 which David S. Knopman, MD, addresses in this issue of NeurologyLive®. Due to inadequate diversity in the agent’s 2 completed phase 3 studies, ENGAGE (NCT02477800) and EMERGE (NCT02484547), the CMS decision further stipulates that greater diversity must be achieved in the study population so that “patients are representative of the national population with MCI due to AD or mild AD dementia.”1 This diversity can be accomplished by increasing enrollment of individuals in underrepresented racial and ethnic groups (URGs).

In the US, individuals in URGs are defined as Black or African American, Hispanic/Latinx, Indigenous and Native American, Asian, Native Hawaiian and other Pacific Islander, and as other individuals of color (self-identified).2 To match the diversity of the US population,3 a goal of at least 31% enrollment from URGs is targeted in the phase 4 aducanumab trial, ENVISION (NCT05310071).

Achieving greater diversity in study populations is a focus of increasing scrutiny, priority, and funding in all medical research, including studies enrolling individuals on the continuum of prodromal AD, MCI, and AD. Although many individuals in URGs have a higher risk of developing AD, these same individuals may also be under- and misdiagnosed,4 underscoring the urgency of achieving greater health care access as well as research enrollment.

To successfully create a more inclusive environment, we must consider the following questions.

How will large numbers of interested and eligible individuals and their study partners from URGs be screened, recruited, and retained in clinical research? The number of individuals required to enroll in typical phase 3 trials of AD is large—in part because of variability of outcome measures (of cognition, function, and behavior, or their composite), an approximate 20%-per-year dropout rate, and a minimum trial duration of 12 to 18 months (much longer for prevention studies). Given the high screen-fail rate of approximately 80% for many modern studies (by design), far greater numbers of individuals must be screened to identify potential candidates to enroll. In other words, the funnel of potential research candidates must be much wider and larger. Our current track record is dismal, with URGs typically comprising less than 5% of study participants.4

Which biomarkers of prodromal AD/MCI/AD may be employed to screen and identify eligible individuals—including those from URGs—for clinical trials? Driven by the development of increasingly sensitive methods such as single-molecule array technology, the field of dementia research is rapidly discovering and validating plasma biomarkers useful for screening. In selected individuals, these results may be followed by more established, well-studied biomarkers (either costly positron emission tomography (PET) neuroimaging or invasive cerebrospinal fluid [CSF] proteomic analyses). Neither PET imaging nor CSF collection is feasible for population screening because neither is scalable to match even current demands. With safe and effective disease-modifying therapies now on the horizon, demand will only further outstrip supply. Furthermore, cost will be prohibitive and may disproportionately exclude individuals, including those in URGs, facing socioeconomic barriers.

What is known about plasma biomarkers of prodromal AD/MCI/AD? Are there differences in plasma biomarker results from URGs compared with other populations? Biomarker cutoffs are typically defined in cohorts of non-Hispanic White individuals and then applied to all individuals. Yet applying cutoffs established for non-Hispanic White individuals to groups in which the biomarker has not been studied may be misleading—potentially resulting in higher proportions of false positives (with additional...
FROM THE EDITOR

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Neurologists must also reflect the diversity of the population targeted for enrollment. The staff of research programs must appropriately consider potential ethnoracial differences, must then be educated regarding motivations, barriers, and strategies. Best practices, which currently are not implemented widely to meet diversity goals, must advance as a science—testing hypotheses regarding the potential genetic or environmental factors leading to different biomarker cutoffs among groups.

Achieving adequate diversity, equity, and inclusion in prodromal AD/MCI/AD research will enable answers to questions regarding potential group differences in biomarkers (as above), as well as in drug safety and efficacy. Participant and study partner recruitment and retention in medical research, including dementia research, must advance as a science—testing hypotheses regarding motivations, barriers, and strategies. Best practices, which appropriately consider potential ethnoracial differences, must then be implemented widely to meet diversity goals. The staff of research programs must also reflect the diversity of the population targeted for enrollment.

Maintaining the status quo is not an option. Once validated and approved, new biomarkers and new treatments in the pipeline will potentially benefit individuals in all groups, including those in URGs.

REFERENCES


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REFERENCES


FDA Approves New Option for Generalized Myasthenia Gravis
By Marco Meglio
Ravulizumab-cwvz (Ultomiris; Alexion Pharmaceuticals, Inc), a terminal complement C5 inhibitor, has been approved by the FDA for the treatment of patients with generalized myasthenia gravis who are anti-acetylcholine receptor antibody–positive. With the decision, ravulizumab becomes the first approved long-acting C5 complement inhibitor for this patient population.1

The approval was based on data from the phase 3 CHAMPION MG trial (NCT03920293), in which treatment with ravulizumab resulted in rapid and sustained improvement of symptoms in patients with generalized myasthenia gravis for up to 26 weeks. At the end of the treatment period, investigators observed statistically significant improvements on the primary end point of Myasthenia Gravis Activities of Daily Living total score compared with placebo (−3.1 vs −1.4; *P* < .001).2

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

ALS Oral Therapy Receives FDA Approval
By Alicia Bigica
The FDA has approved an oral formulation of edaravone (Radicava ORS; Mitsubishi Tanabe Pharma America, Inc) for the treatment of amyotrophic lateral sclerosis (ALS). The formulation can be given by mouth or feeding tube, expanding upon the usage of a previously approved intravenous version.1

The drug is meant to slow loss of physical function in ALS and can now be administered several ways to best accommodate the different needs of patients with ALS. The new oral formulation—which offers the same efficacy as the intravenous version—is designed for ease of use, with a 5-mL dose in a portable bottle that does not require refrigeration or reconstitution.1

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

NIH Launches Epstein-Barr Virus Vaccine Trial
By Marco Meglio
Months after data further confirmed the link between multiple sclerosis and Epstein-Barr virus (EBV), the National Institute of Allergy and Infectious Diseases (NIAID) announced a new phase 1 study evaluating an investigational preventive vaccine for the virus. Participants will be followed for 18 to 30 months, and the trial is expected to last 4 years.1

Led by Jessica Durkee-Shock, MD, an assistant research physician in the Laboratory of Infectious Diseases at NIAID, the study “will assess safety and immune response of a gp350-Ferritin nanoparticle vaccine with a saponin-based Matrix-M adjuvant.”1 The vaccine is designed to target “EBV glycoprotein gp350, which is found on the surface of the virus and virus-infected cells.”1

For a full list of references, see the article on NeurologyLive.com.
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THE NEW BAR IS SET FOR THERAPIES IN TREATMENT-RESISTANT EPILEPSY: JACQUELINE A. FRENCH, MD
The codirector of epilepsy clinical trials at NYU Langone Health speaks about the progress that’s been made in treating refractory epilepsy and her hopes for the future of drug development in this area of medicine.
+ VIEW VIDEO neurologylive.com/new-bar-epilepsy

ALIGNING PATIENT, CLINICIAN, AND CAREGIVER GOALS IN ALZHEIMER DISEASE: SHARON COHEN, MD, FRCP
The neurologist and assistant professor at the University of Toronto discusses why elevating the voices of patients and caregivers is important to understanding and treating an individual with Alzheimer disease.
+ VIEW VIDEO neurologylive.com/goals-care-ad

MOVING MIGRAINE TOWARD PERSONALIZED CARE
Jessica Ailani, MD, director of MedStar Georgetown Headache Center and associate professor of neurology at MedStar Georgetown University Hospital, talks about some recent data in headache medicine that have provided evidence of the in-clinic experience and how the migraine treatment landscape has shifted almost continuously the past several years.
+ LISTEN neurologylive.com/mm-ep-63

ADVANCED THERAPEUTICS IN PARKINSON AND MOVEMENT DISORDERS
Yasar Torres-Yaghi, MD, director of the Parkinsonism and Dementia Clinic and assistant professor of neurology at MedStar Georgetown University Hospital, discusses the current state of therapeutic intervention for movement disorders and the first Advanced Therapeutics in Movement & Related Disorders Congress being put on by the Parkinson & Movement Disorder Alliance in June 2022.
+ LISTEN neurologylive.com/mm-ep-62

TOP TWEETS

Amy Brin, MSN, MA, PCNS-BC | @winwithbrin
Really appreciated the opportunity to chat with @neurology_live about how honest conversations can lead to better care for children. @Child_Neurology

Parkinson & Movement Disorder Alliance | @PMDAlliance
Jill Farmer, DO, MPH, one of our ATMRD Congress Faculty, spoke with @neurology_live for #ParkinsonsAwarenessMonth about exciting emerging therapies for movement disorders. neurologylive.com/pd-awareness-farmer @jillfarmmovedoc

UCLA Neurology | @UCLANeurology
Check out this @neurology_live Peer Exchange featuring Dr Andrew Charles providing an overview of the optimal management of acute and preventative #migraine. neurologylive.com/optimal-migraine

AASM Membership | @AASMmembership

CURE Epilepsy | @CureEpilepsy
Epilepsy does not have a “one size fits all” treatment. Each case of epilepsy is complex in its own way. That is why an individualized approach to epilepsy treatment can be key for many patients. Learn more in this article from @neurology_live. https://bit.ly/3ke2mLk #epilepsy

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Congratulations to our 2022 inductees:

- Victor M. Rivera, MD, FAAN
  Global Impact
- Frederick W. Foley, PhD
  Mental Health
- David Li, MD, FRCPC
  Neuroimaging
- Thomas John (Jock) Murray, OC, MD
  Neurology
- Valerie Stickel-Diehl, MS, MSCN, RN
  Nursing
- Ellen S. Lathi, MD
  Patient Care
- Nancy Ross, PharmD, BCACP, MSCS, CSP
  Pharmacy
- Peter A. Calabresi, MD
  Research
- Kathleen Brandfass, MS, PT
  Rehabilitation

Legacy Award
Susan E. Bennett, PT, DPT, EdD, NCS, MSCS

The 2022 Visionary Award
June Halper, MSN, APN-C, MSCN, FAAN

A very special thank you to our corporate sponsors!

Keep an eye out for 2023 nominations—opening soon!
The 1st annual awards ceremony was held during the CMSC Annual Meeting in National Harbor, Maryland.

NEUROLOGYLIVE, IN PARTNERSHIP WITH the Consortium of Multiple Sclerosis Centers (CMSC), is thrilled to announce the inaugural class of inductees for the Giants of Multiple Sclerosis™ recognition program.

The Giants of Multiple Sclerosis™ recognition program is a premier neuroscience award that recognizes and celebrates the pioneers, innovators, and difference makers who have achieved landmark successes and have significantly contributed to the betterment of care for people with multiple sclerosis.

Staying true to the mission of CMSC by helping foster a team-based approach to care, the peer-nominated and peer-voted program recognizes health care professionals across the breadth of multiple sclerosis, including neurologists, researchers, nurses, rehabilitation specialists, mental health providers, pharmacists, and more.

The 2022 call for nominations received more than 100 submissions from the greater multiple sclerosis community. Nominations were then vetted and voted upon by an esteemed steering committee made up of leaders in the MS clinical care space: Committee Chair Scott Newsome, DO, MSCS, FAAN, FANA; and committee members Nora Fritz, PhD, PT, DPT, NCS; Bryan Walker, MHS, PA-C; Amy Perrin Ross, MSN, APN, CNRN, MSCN; Patricia Bobryk, MHS, PT, MSCS, ATP; Jacquelyn L. Bainbridge, PharmD, BSPharm, FCCP, MSCS, FAES; Terry Lee-Wilk, PhD; and Flavia Nelson, MD.

Ultimately, the 2022 Giants of Multiple Sclerosis™ class included honorees in 9 categories: Neurology, Neuroimaging, Research, Patient Care, Nursing, Rehabilitation, Pharmacy, Global Impact, and Mental Health. Honorees were announced during an awards ceremony on June 2, 2022, at the Gaylord National Hotel and Conference Center in National Harbor, MD, during the 2022 CMSC Annual Meeting, which took place from June 1 to 4, 2022.

In addition, NeurologyLive® and the Giants of Multiple Sclerosis™ steering committee recognized 2 individuals with special awards for their unique contributions to the field of multiple sclerosis.

Nominations for the 2023 class of Giants of Multiple Sclerosis™ will open in Summer 2022. More information can be found on NeurologyLive.com/giantsofms.

On behalf of NeurologyLive®, MJH Life Sciences®, and CMSC, congratulations to the honorees on this monumental achievement!

For more information, visit neurologylive.com/giantsofms
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University of British Columbia

NEUROLOGY
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Dalhousie University MS Research Unit

NURSING
Valerie Stickel-Diehl, MS, MSCN, RN
Ruan Neurology At MercyOne Hospital

PATIENT CARE
Ellen S. Lathi, MD
The Elliot Lewis Center for Multiple Sclerosis

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Susan E. Bennett, PT, DPT, EdD, NCS, MSCS
Bennett Rehabilitation Institute

2022 VISIONARY AWARD
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Consortium of Multiple Sclerosis Centers

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The Multiple Sclerosis Center of Atlanta

RESEARCH
Peter A. Calabresi, MD
The Johns Hopkins University School of Medicine

REHABILITATION
Kathleen Brandfass, MS, PT
UPMC/Centers for Rehab Services
Ozanimod Treatment Results in Higher Rates of No Evidence of Disease Activity vs Interferon Beta-1a

By Marco Meglio

IN A POST HOC ANALYSIS of the phase 3 RADIANCE trial (NCT02047734) and its open-label extension DAYBREAK (NCT02576717), a higher proportion of patients with relapsing multiple sclerosis (MS) achieved no evidence of disease activity status 3 or 4 (NEDA-3 and NEDA-4) following treatment with oral ozanimod (Zeposia; Bristol Myers Squibb) vs intramuscular interferon beta-1a.

At months 12 and 24 of the RADIANCE trial, investigators observed NEDA-3 rates of 31.2% and 24.6% (P < .05) for ozanimod-treated patients vs 26.9% and 17.0% for those on interferon beta-1a, respectively. In the DAYBREAK trial, rates were 16.2% (P < .05), 13.4% (P < .05), and 10.7% with continuous ozanimod at months 12, 24, and 36, respectively, compared with rates of 9.8%, 8.6%, and 7.4% for those on/transitioned from interferon beta-1a.

These findings were presented at the American Academy of Neurology 2022 Annual Meeting in April by lead investigator Ludwig Kappos, MD, a professor of neurology in the Department of Biomedical Engineering at University of Basel in Switzerland. “We see the effects in the first year were repeated over time and that a significant number of patients remained disease activity free under these quite strict criteria,” he told NeurologyLive.

“Those who had evidence of disease activity mainly had this through MRIs—so through lesions that occurred in their regularly repeated and standardized assessments.”

Ozanimod, a sphingosine-1-phosphate receptor modulator, has been FDA approved to treat relapsing forms of MS since March 2020. In this analysis, NEDA-3 was defined as no new gadolinium-enhancing lesions, no new/enlarging T2 lesions, no relapses, and no progression on Expanded Disability Status Scale scores from baseline. Achieving NEDA-4 required NEDA-3 status plus annualized whole-brain volume loss of less than 0.4%.

For those on continuous ozanimod, 21.5% and 14.0% (P < .05) of patients achieved NEDA-4 in the RADIANCE trial at months 12 and 24, respectively, compared with rates of 16.3% and 7.8% for those on interferon beta-1a. The therapeutic effect of ozanimod continued to show greater results than interferon beta-1a in DAYBREAK, with NEDA-4 rates of 10.0%, 10.4%, and 10.3% for ozanimod-treated patients in months 12, 24, and 36 vs rates of 5.9%, 6.2%, and 6.3% for those on/transitioned from interferon beta-1a, respectively.

Rebaselining to month 12 resulted in greater rates of achieving NEDA-3 and NEDA-4 for patients on continuous ozanimod vs those who transitioned from interferon beta-1a. After rebaselining, the NEDA-3 rate in the RADIANCE trial at month 24 was 52.6% (P < .05), and the NEDA-3 rates in the DAYBREAK trial at months 12, 24, and 36 were 33.1% (P < .05), 26.3% (P < .05), and 21.3% in ozanimod-treated patients, respectively. For those on/transitioned from interferon beta-1a in DAYBREAK, NEDA-3 rates were 33.4%, 20.5%, 17.4%, and 14.8%, respectively, at RADIANCE month 24 and DAYBREAK months 12, 24, and 36. Rebaselined rates of NEDA-4 were 33.5% (P < .05), 20.0% (P < .05), 16.7%, and 14.1% for continuous ozanimod and 19.7%, 11.7%, 11.2%, and 11.0% for those on/transitioned from interferon beta-1a, respectively.

RADIANCE was a multicenter, double-blind, double-dummy
study that randomly assigned patients with MS in a 1:1:1 fashion to either daily ozanimod 1.0 mg or 0.5 mg or weekly intramuscular interferon beta-1a 30 μg, with annualized relapse rate (ARR) as the primary end point. After 24 months of treatment, adjusted ARRs were 0.17 (95% CI, 0.14-0.21) for ozanimod 1.0 mg, 0.22 (95% CI, 0.18-0.26) for ozanimod 0.5 mg, and 0.28 (95% CI, 0.23-0.32) for interferon beta-1a, with rate ratios vs interferon beta-1a of 0.62 (95% CI, 0.51-0.77; \( P < .0001 \)) and 0.79 (95% CI, 0.65-0.96; \( P = .0167 \)) for the ozanimod 1.0 mg and 0.5 mg groups, respectively.

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

**Ubrogepant Demonstrates Several Positive Real-World Migraine Effects in Patients With Prior Treatment Failure**

By Marco Meglio

**REAL-WORLD DATA FROM** the observational, cross-sectional UNIVERSE study (NCT03732638) showed that treatment with ubrogepant (Ubrelvy; AbbVie) was associated with a high satisfaction for achieving pain relief, ability to think clearly, and return-to-normal function among patients with migraine who switched to the treatment following prior therapy failure.1

Presented at the American Academy of Neurology 2022 Annual Meeting in April, the results also showed that 91.7% of patients reported they were likely to continue ubrogepant use. An oral calcitonin gene-related peptide antagonist, ubrogepant has been approved for the acute treatment of migraine with or without aura since 2019.

Senior investigator Richard B. Lipton, MD, professor, Edwin S. Lowe Chair in Neurology, vice chair of the Saul R. Korey Department of Neurology, and director of Montefiore Headache Center at Albert Einstein College of Medicine in Bronx, New York, and colleagues analyzed 302 respondents to the Migraine Buddy app who self-reported using ubrogepant for at least 4 prior migraine headaches, including at least 1 dose in the preceding 14 days. They completed a 29-question survey assessing patient characteristics, treatment patterns, outcomes, and satisfaction with ubrogepant.

In this analysis, investigators looked at a subgroup of patients (n = 264; 87.4%) who switched to ubrogepant due to their prior treatment’s lack of efficacy. More than one-third (35.6%) of the subgroup had chronic migraine, and more than half (55.9%) previously tried at least 3 triptans. At 2, 4, and 24 hours post dose, 76.1%, 83.3%, and 78.4% of patients, respectively, reported satisfaction with ubrogepant for achieving pain relief.

In total, 85.2% of ubrogepant-treated patients reported satisfaction in the ability to think clearly, and 84.8% were reportedly satisfied with their return-to-normal function. In addition to a large majority of patients claiming they were likely to continue treatment, an analysis of prior and concurrent acute medication revealed reduced use of opioids (~28%), barbiturates (~25%), ergots (~15%), nonsteroidal anti-inflammatory drugs (~38%), and other acute medication classes (~37%). Notably, the odds of triptan use were also reduced by 55%, the largest reduction of any medication assessed.

Since the approval of ubrogepant, several analyses have further demonstrated the agent’s positive effects for patients with migraine. Results of a 2021 post hoc analysis of the phase 3 ACHIEVE 1 and 2 studies (NCT02828020; NCT02867709), which led to ubrogepant’s approval, demonstrated that the drug is safe and effective for patients with perimenstrual migraine (pmM) attacks.2

Findings were presented at the American Headache Society 63rd Annual Scientific Meeting in 2021. The 52-week study randomly assigned those who completed 1 of 2 lead-in ACHIEVE trials 1:1:1 to usual care (n = 417), ubrogepant 50 mg (n = 417), or ubrogepant 100 mg (n = 420). Among all female participants, 1329 pmM attacks and 16,145 non-pmM attacks were treated with ubrogepant.

At 2 hours post dose, 28.7% and 29.7% of patients in the 50- and 100-mg dose groups experienced pain freedom from pmM, and 22.1% and 25.3%, respectively, experienced pain freedom from non-pmM. Pain relief of pmM and non-pmM was experienced by 64.8% and 65.2% of patients in the ubrogepant 50-mg group and by 67.1% and 68.4%, respectively, in the 100-mg group.

For a full list of references, see the article on NeurologyLive.com.
CNM-Au8 Shows Survival Benefit for Patients With ALS in Phase 2 Extension Trial

By Matt Hoffman

CLENE NANOMEDICINE INC HAS announced new interim data from the open-label extension of its phase 2 RESCUE-ALS trial (NCT04098406), which evaluated the investigational oral suspension of gold nanocrystals, known as CNM-Au8, in patients with amyotrophic lateral sclerosis (ALS). The data suggest that those treated with the therapy experienced a 70% survival benefit.1,2

Presented at the American Academy of Neurology 2022 Annual Meeting in April by study investigator Matthew Kiernan, MBBS, PhD, DSc, FRACP, FAHMS, the data demonstrated an HR of 0.3 (log-rank \( P = .006 \)) for those treated with the study drug compared with the estimated mean survival from the European Network for the Cure of ALS survival prediction model.1 In total, the extension included 90% of eligible patients (n = 36) from the base trial.

“Following the 36 weeks of placebo versus active compound, we put everyone on the active compound, and we’ve been following them up,” Kiernan told NeurologyLive®. “We did the census of the data in March, and it really is quite dramatic, showing that the survival in patients is improved on nanocrystalline gold, CNM-Au8. And that was the case whether the patients were on the active part in the trial or indeed on the placebo and then switched to the active part.”

Kiernan added that, importantly, the data show not only an improvement in survival, but a noteworthy improvement in quality of life. “There are less events for patients, less complications, more survival, and less deaths on the active compound, nanocrystalline gold. Really, this is quite a dramatic finding in ALS patients,” Kiernan said.

Kiernan is Bushell Chair of Neurology, professor of medicine at Central Clinical School, and codirector of discovery and translation at the Brain and Mind Centre of the University of Sydney. He is also a neurologist in the Institute of Clinical Neurosciences at Royal Prince Alfred Hospital in Australia.

RESCUE-ALS was a phase 2 multicenter, randomized, double-blind, parallel-group, placebo-controlled trial designed to assess efficacy, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8 in 45 participants with early ALS over 36 weeks of treatment. Among that cohort of 45 participants (CNM-Au8, n = 23; matched placebo, n = 22), 96% of patients who received the study drug completed the 36-week observation period.1,3 That original blinded period revealed significant results, with CNM-Au8 found to be associated with slowed disease progression (\( P = .0125 \)), a decreased proportion of participants with a 6-point decline in the ALS Functional Rating Scale-Revised (\( P = .035 \)), and improved quality of life as measured by the ALS Specific Quality of Life questionnaire (\( P = .018 \)).

CNM-Au8 was well tolerated with no safety signals identified during 96 weeks of treatment. At the end of the 36-week period, there was 1 (4%) recorded mortality event in the active-treatment arm and 2 in the placebo-treated group. In total, 86% of those on placebo completed the study period, with the remaining 14% attributable to death or withdrawal due to disease worsening. Of the participants who completed the double-blind portion, 1 participant on CNM-Au8 was ineligible for the open-label extension (OLE) due to relocation from Australia, and 4 elected not to continue in the OLE (1 active, 3 placebo), resulting in 90% of eligible participants in the OLE.2

“This approach—nanocrystalline gold—is really a complete framework in thinking about neurodegenerative disease,” Kiernan told NeurologyLive®. “The way it works is that it supports energy processes; it restores energy in brain cells in neurons in the brain. It does this through effects by mitochondria, but also it stops the accumulation of TDP-43, the protein compound that spreads through the brain causing disability and deficits for patients with ALS. In addition, it seems to have an antioxidant effect through superoxide dismutase.

“It is a paradigm shift,” he added. “A lot of this has come through understanding the disease itself. TDP-43 and the connections to ALS [were] a relatively recent discovery in the last decade. Then there’s been a lot of interest in ALS with the Ice Bucket Challenge and...a lot of support from industry and philanthropy—and that’s driven the science through the roof. As a result, now we have a lot of compounds coming through.”

Rob Etherington, president and CEO of Clene Nanomedicine, noted in a statement that the company is looking forward to the HEALEY ALS Platform Trial (NCT04297683) results because survival is a prespecified key secondary end point in that trial. “HEALEY participants will also be offered long-term, open-label extension for 52 weeks following the 6-month blinded study duration, allowing for long-term assessment of survival,” Etherington said.1 “Our growing body of evidence from the RESCUE-ALS open-label extension—and soon from the HEALEY trial—could potentially change the treatment paradigm for people living with the devastating diagnosis of ALS.”

CNM-Au8 is also being evaluated in other conditions such as multiple sclerosis (MS) in the REPAIR-MS study (NCT03993171) and Parkinson disease (PD) in the REPAIR-PD trial (NCT03815916). These 2 sequential group studies examine the brain metabolic effects, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8 in patients who received a diagnosis of MS within 15 years of screening or in patients with PD who received a diagnosis within 3 years of screening. In August 2021, Clene announced positive topline results from the trials, which showed that the investigational agent significantly improved brain energetic metabolism in both patient groups.4

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

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

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

MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.
Pepinemab Demonstrates Improved Cognition in Subgroup Analysis in Huntington Disease

By Marco Meglio

IN A SUBGROUP ANALYSIS of the phase 2 SIGNAL-HD study (NCT02481674), patients with Huntington disease (HD) treated with pepinemab (Vaccinex, Inc), a novel monoclonal antibody, displayed cognitive benefits after 18 months of treatment. Investigators concluded that these results encourage the continued evaluation of pepinemab in HD and related conditions such as Alzheimer disease.

The results were presented by lead author Elizabeth Evans, PhD, MS, chief operating officer and senior vice president of discovery and translational medicine of Vaccinex, at the American Academy of Neurology 2022 Annual Meeting in April. Vaccinex previously reported topline findings from the SIGNAL-HD trial in September 2020, noting that despite not reaching its prespecified coprimary end points, the investigational agent had a direct impact on cognitive assessments that reflect changes in planning ability and memory associated with disease progression.

In cohort B of this study, 179 patients with early-manifest HD were randomly assigned 1:1 to either pepinemab or placebo for an 18-month period. Investigators used a combination of the HD Cognitive Assessment Battery and Clinical Global Impressions of Change (CGI-C) as the primary end point.

At the conclusion of the analysis, those in a subgroup with Montreal Cognitive Assessment scores less than 26 demonstrated enrichment for treatment-related cognitive benefit. Additionally, pepinemab-treated patients with baseline total functional capacity (TFC) scores of 11 had reduced disease progression on CGI-C relative to placebo ($P = .041$); however, this was not the case for those with less advanced forms of the disease, indicated by TFC scores of 12 to 13.1

Both apathy and increases in fluorodeoxyglucose (FDG) as measured by FDG-positron emission tomography (FDG-PET) were correlated with disease progression and cognitive decline. Evans et al also identified a significant reduction in apathy severity related to treatment with pepinemab ($P = .0291$). Metabolic activity, assessed using FDG-PET, was slowed or reversed in all 26 brain regions examined, with significant benefit in 15 of the 26 (57%; $P \leq .05$). Treatment with pepinemab also resulted in reduced caudate atrophy ($P = .017$) and a trend of reduced ventricular expansion ($P = .06$) on MRI imaging analysis.

In the originally reported analysis of cohort B, the results of each of the 2 cognitive assessments demonstrated a strong trend for beneficial change on the One Touch Stockings of Cambridge ($P = .028$) and Practice Transition Accreditation Program ($P = .06$) tests.2

Previously reported results of cohort A, which evaluated the safety of pepinemab, met the primary end point. Additionally, those from cohort A treated with pepinemab (n = 11) demonstrated an increase in FDG uptake on FDG-PET in multiple cortical regions of interest relative to placebo, with estimated differences of 0.78 (standard error, 0.31; 95% CI, 0.11-1.40; $P = .025$). Preservation of brain matter, represented by reduced atrophy, and improvements in multiple motor and cognitive assessments were also observed in cohort A.3

Pepinemab is also being evaluated in several other neurological diseases, including Alzheimer disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis. A phase 1b/2a trial, SIGNAL-AD (NCT04381468), has been initiated and is planned to enroll 40 patients randomly assigned to either pepinemab or placebo for 48 weeks. Vaccinex has also successfully completed a phase 1 placebo-controlled, single-ascending dose study of pepinemab in 50 adult patients with MS. ■

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

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The Story of Aducanumab-AVWA

Aducanumab (Aduhelm; Biogen) is a tortured one. It started with promise after a phase 1 study in 2016 demonstrated that the drug dramatically reduced amyloid-β peptide levels in the brain and appeared to slow cognitive decline in a dose-dependent manner. However, it quickly descended into controversy with a wrongly conceived interim analysis, followed by the agent’s resurrection and favorable treatment by the FDA, its disastrous reception by an FDA advisory committee, and its controversial accelerated approval. The rejection by Canada and the European Union and the very restricted coverage offered by Medicare were further blows to the drug. Then, on May 3, 2022, Biogen Inc announced that it was “substantially eliminating commercial infrastructure related to Aduhelm.”

This review describes a few of the many issues that were part of this chain of events.

Aducanumab is an anti–amyloid-β (Aβ) monoclonal antibody that targets amino acids 3 through 7 of the Aβ peptide. With the promising phase 1 clinical trial results, Biogen chose to launch 2 large, identically designed, pivotal phase 3 studies dubbed EMERGE (NCT02484547) and ENGAGE (NCT02477800) in 2015. The trials had 3 arms: placebo, low dose, and high dose. Patients were stratified according to APOE genotype. Because of concerns about Aβ-related imaging abnormalities (ARIA) especially in the APOE ε4 allele carriers, the highest dose in the ε4 genotype group was restricted to 6 mg/kg monthly. A dose escalation to 10 mg/kg for APOE ε4 carriers in the high-dose arms was introduced midway through the trials in March 2017.

A preplanned interim analysis for futility was carried out based on data available in December 2018. Unfortunately, the timing failed to consider the dose escalation, and the findings of this interim analysis led Biogen to terminate the 2 studies in March 2019. According to the interim analysis, ENGAGE failed to show any benefit and EMERGE was trending toward a small clinical benefit.

The fate of aducanumab was revisited when 3 months of additional data became available. The EMERGE study that had been trending positive for the high-dose group showed a statistically significant benefit on the primary outcome measure—the Clinical Dementia Rating Scale sum of boxes—but the results from the high-dose group in ENGAGE continued to show no benefit.

Biogen adopted a strategy after viewing the revised futility analysis that touted the positive EMERGE study and devised several post hoc analyses to demonstrate how the same benefits could have occurred in the ENGAGE study. The FDA acknowledged this approach and gave Biogen permission to file a new biologics license application. Biogen presented its version of the results of the 2 trials at a public meeting in December 2019, after which commentators questioned the validity of Biogen’s claims.

The FDA convened a public advisory committee hearing on November 6, 2020. For the record, this writer, who had been a member of the FDA Peripheral and Central Nervous System Drugs Advisory Committee, was recused from that meeting because he was an investigator in one of the aducanumab clinical trials. The position of Biogen, supported by the FDA, was to accept the results of the EMERGE trial as compelling evidence of efficacy and to question the failure of the ENGAGE trial to
provide a similar outcome. This was opposite of the usual approach that the FDA takes when presented with studies claiming benefit—because it typically looks for flaws in claims of efficacy. It was even more unusual because the FDA statistician highlighted numerous substantive deficiencies in the 2 trials.9

The FDA advisory committee voted 10 to 0 with 1 abstention to reject the claim that aducanumab showed substantial evidence of effectiveness.10 The combination of the small effect size in the nominally positive EMERGE trial and the null result in the ENGAGE trial clearly did not provide confidence for clinical benefits. Moreover, from an interpretive perspective, it should be the totality of the results from both studies that counts. Taking the 2 studies jointly, either by frequentist11 or Bayesian12,13 statistical analyses, compelling evidence for benefit from aducanumab was not demonstrated by these phase 3 trials.

The conflicting results did not meet the usual FDA standards of convincing evidence of efficacy, as eventually acknowledged by the agency.14 On the other hand, the findings from the EMERGE trial clearly justified pursuing development of aducanumab by conducting another trial with the 10 mg/kg dose that took advantages of the lessons learned. That did not happen.

Six months after the advisory committee meeting, the FDA announced in June 2021 that it was granting aducanumab accelerated approval based on the dramatic reduction in Aß levels at the high dose. Based on the belief that the strength of the amyloid cascade hypothesis was sufficiently compelling, the FDA stated that it was reasonably likely that Aß lowering would result in clinical benefits.15 Accelerated approval was a strategy given to the FDA by Congress to speed up access to medications when a drug showed promising results but the time frame for obtaining definitive evidence of efficacy was felt to be too long, and it has been used in cancer treatments with mixed success.16 Biogen agreed to perform a phase 4 trial as part of the accelerated approval decision, but the status of this trial is now in doubt with the announcement in May 2022 about the company’s elimination of the aducanumab program.

The basis for the accelerated approval decision by the FDA was the prediction that reduction in brain Aß was reasonably likely to provide clinical benefit at some point in the future.14 The amyloid cascade model of Alzheimer disease (AD) asserts that Aß is the key molecule in the development of the neurodegeneration in AD.4,17 There is no question that dominantly inherited AD is caused by mutations in genes involved in the cleavage of amyloid precursor protein that ultimately leads to Aß deposition.17 In addition, brain Aß level is an outstanding biomarker for AD that tracks its severity and downstream consequences.18

But the ultimate proof of the model lies in therapeutic Aß removal producing clinical benefit. Previously, ß-site amyloid precursor protein cleaving enzyme-inhibitors such as verubecestat showed that Aß reduction itself does not necessarily result in clinical benefit,19 and clinical benefits were not present with aducanumab despite very robust Aß lowering. Aducanumab is the first of the monoclonal antibodies (mAbs) with potent Aß lowering effects that was subject to an 18-month large-scale trial6; 3 others that dramatically lower Aß have unique molecular targets and may exhibit different outcomes.4 We will learn within the next year whether other anti-Aß mAbs that induce substantial Aß lowering produce clinical benefits, which in turn would support this mechanism of action as a therapeutic strategy. Prior anti-Aß therapies that barely reduced Aß may be inappropriate for claiming failure of the amyloid-lowering model as many earlier trials lacked confirmatory information on the presence of Aß pathology in the study cohorts.

A few weeks after the FDA’s accelerated approval decision, the Centers for Medicare & Medicaid Services (CMS) announced the initiation of a review of coverage for aducanumab therapy. The CMS decision was more complicated because the agency chose to address anti-Aß mAbs as a class.

While the saga of aducanumab was playing out, the other 3 anti-Aß mAbs were moving through the phase 3 pipeline, with results expected to be reported at the end of 2022 or early 2023. Their outcomes will be equally as or more important than aducanumab because those agents and their sponsors are in the position of seeking regular FDA approval. One of them, gantenerumab, uses a subcutaneous route of administration.21 Another one, donanemab, for which phase 2 results were reported in 2021,22 was so effective in lowering brain Aß that it was discontinued in a large number of patients within the first year because their brain Aß levels had decreased into the background range. The third drug, lecanemab, which also has reported phase 2 results,23 has a lower rate of amyloid-related imaging abnormalities (ARIA) than others in the class; however, lecanemab’s ARIA rate must be viewed with caution due to a restriction on using the highest dose in APOE ε4 carriers in the phase 2 trial.

In the final CMS decision memo issued April 7, 2022,24 Medicare agreed to provide coverage for aducanumab or any other agent in the class that was approved on the basis of accelerated approval, but only in the setting of a randomized, controlled trial. This effectively made aducanumab accessible on a very limited basis in the United States. CMS stated that for other anti-Aß mAbs that obtained regular FDA approval based on clinical efficacy, coverage would be available in the context of prospective observational registries. It is not entirely clear how restrictive or expansive access might be in the CMS-mandated observational registries. Further, CMS restricted coverage to persons with mild cognitive impairment and mild dementia due to AD.

The CMS decision reflected a much greater concern about the adverse consequences of aducanumab treatment, mainly ARIA. Approximately 40% of those treated with aducanumab experienced some form of ARIA, with higher rates in APOE ε4 carriers.25 Most ARIA edema (ARIA-e) occurred within the first 8 doses of treatment. The number of serious complications from aducanumab-related ARIA was low (1.4%).25 If ARIA-e is promptly recognized and aducanumab therapy paused or discontinued, ARIA-e often will resolve spontaneously over weeks to months. In many patients, aducanumab can be restarted without recurrence of ARIA-e.
Microhemorrhages are a different matter. Microhemorrhages occur in untreated persons with AD dementia—at a rate of 6.6% in the placebo groups in the aducanumab trials—but at 3 times that rate in aducanumab-treated patients. Excess microhemorrhages were typically associated with ARIA-e. Although there is no evidence on how many new microhemorrhages represent a higher risk of future macrohemorrhage in the context of anti-Aβ mAb treatment, caution would dictate that if even a few new microhemorrhages occur, an anti-Aβ mAb should be permanently discontinued.

Appropriate-use recommendations have been formulated that call for a conservative approach to screening for cortical microhemorrhages or other lesions indicative of amyloid angiopathy and that 3 T MRI should be performed every 12 weeks for the first year after initiating aducanumab treatment. The concern of both proponents and opponents of aducanumab use is that the level of neuroradiological expertise available in the clinical trial setting (with skilled central readers) is not readily available even in academic settings outside a clinical trial and would likely be unavailable in community care settings. If ARIA-e were overlooked and dosing continued, a rapid expansion of the area of edema may become life threatening. Therefore, if aducanumab were prescribed, a high level of neuroradiological expertise must be engaged. This necessarily places some constraints on where it would be feasible to administer aducanumab and who could prescribe it—a restriction that will apply to other agents of the class as well.

The decision by Biogen to suspend commercialization of aducanumab would appear to seal the agent’s fate. If none of the other anti-Aβ mAbs show benefit, that will raise serious questions about the conceptual model on which therapy with anti-Aβ mAbs is based and seriously threaten the future of this class of treatments. On the other hand, if at least one of the other drugs shows a benefit on clinical grounds, the debate will shift to the magnitude of the clinical benefit in relation to risks.

A genuine clinical benefit, however modest, would be a powerful selling point for a successful anti-Aβ mAb. This writer hopes that these future discussions will be conducted in a thoughtful and collegial manner. A full appraisal of the evidence must be the starting point, but weighing the benefits vs the risks is a matter of judgment that should be dictated by the needs of our patients.

The sudden realization that there may be a therapy that could be prescribed to a large number of patients with mild cognitive impairment and AD in the US revealed a striking lack of preparedness and highly unequal access in our health care system. There are not enough dementia care specialists with the expertise to make an accurate diagnosis and manage aducanumab therapy. There are also unmet needs for infrastructure that will limit access in underserved rural areas and in diverse urban communities, including prompt access to 3 T MRI scanners, infusion centers, and neurological intensive care units in the rare instances when ARIA becomes symptomatic in a serious way. Addressing these challenges will be a necessary step forward for the care of this patient population, regardless of what the future hold for the anti-Aβ class of medicines.

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

TESTING FOR EARLY DIAGNOSIS OF ALZHEIMER DISEASE

In this NeurologyLive® Insights series, Alireza Atri, MD, PhD, discusses the methods of testing and diagnosing patients with Alzheimer disease, highlighting the recent FDA approval of aducanumab and its impact.

View video: neurologylive.com/insights-alzheimer
Endoplasmic Reticulum and/or Mitochondrial-Dependent Neuronal Degeneration in ALS

By Jennifer S. Sun, PhD

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is an aggressive neurodegenerative disease with an average age of onset between 40 and 60 years.1,2 ALS presents with progressive degeneration of upper and lower motor neurons, which eventually culminates in lethal respiratory failure within 2 to 5 years of diagnosis.1,2 ALS can result from genetic and nongenetic factors, although there is currently no clear biological link between ALS-associated gene mutations and neural defects.1,2 In fact, only 10% of cases are familial; the remaining 90% are sporadic with unknown etiology.1,2 The leading hypothesis is that aberrant protein expression and aggregation impacts mitochondrial function, which in turn reduces calcium metabolism and triggers reactive oxygen species (ROS) overproduction that underlies motor neuron demise.1,3,4 Dysregulation of other proteostasis-associated pathways—axonal transport, autophagy, nucleocytoplasmic transport, endoplasmic reticulum (ER) stress—also contributes to ALS initiation and progression as part of a vicious feed-forward cycle.1,5

The maintenance of ionic gradients, particularly for intracellular calcium signaling, is essential to fulfill the energetic requirements of motor neurons.3 The ER is the primary site of protein and lipid biosynthesis and intracellular calcium storage, whereby the ER controls calcium concentration, which powers oxidative phosphorylation in the mitochondria.5 Calcium uptake by mitochondria is, in turn, dependent on the mitochondrial membrane potential, which is initially generated by calcium flux and is maintained by the electron transport chain in respiration.1,3,4 Communication between the ER and the mitochondria is essential to coordinate protein and lipid biosynthesis, calcium storage, and adenosine triphosphate (ATP) synthesis.1,5 Aberrant formation of phospholipids by the ER, and protein aggregate–triggered pore formation, can alter ER and/or mitochondrial function.1,3,5 For example, TAR DNA-binding protein 43 (TDP43) and fused in sarcoma (FUS) aggregates alter the mitochondrial proteome and impair buffering against oxidative stress in the cytoplasm.1 Moreover, required membrane interactions may become lost because of protein aggregation.1

In fact, the suspected underlying mechanism of familial ALS appears to mirror that of central nervous system disorders: accumulation of unfolded protein aggregates, which leads to oxidative stress that compromises organelle function and results in motor neuron degeneration.1,3,6 Of the 20 genes that have been associated with ALS to date, the major gene attributed to familial ALS, unsurprisingly, encodes superoxide dismutase 1 (SOD1), which normally scavenges mitochondrial ROS to reduce cellular toxicity; however, accumulated mutations in SOD1 result in gain of function effects which cause SOD1 aggregates to form within mitochondria of motor neurons to create oxidative stress.1 Mutant SOD1 and TDP43 genes have also been identified in patients with sporadic ALS and have been connected to the observed dysregulation of oxidative phosphorylation, overall mitochondrial respiration, and ATP production.1,4 Another prominent mutation associated with familial ALS is a noncoding GGGGCC repeat in the chromosome 9 open reading frame 72 (C9orf72) gene, which encodes a chaperone in the electron transport chain, suggesting a role of RNA processing and nucleocytoplasmic transport in evoking toxicity.1,4 Overall, a disrupted redox environment increases the risk of 1) insufficient mitochondrial ATP production, which is an essential energetic requirement for motor neurons; and 2) shutdown of ER-driven protein synthesis, which impairs the production of phospholipids required for neuronal function.1,2,4,5

Given the importance of mitochondrial and ER function in ALS, disruption of intracellular mitochondria-ER contacts (MERCs, FIGURE) presents yet another avenue for neuronal degeneration,
which could perhaps be the primary point of dysfunction underlying ALS. MERCs are generated, in part, by a tether formed between the outer membrane vesicle-associated membrane protein–associated protein B (VAPB) and protein tyrosine phosphatase–interacting protein 51 (PTPIP51), and maintained by regulatory proteins including the ubiquitin-specific chaperone valosin-containing protein (VCP). Importantly, synaptic activity is directly correlated with the presence of MERCs; increased synaptic activity increases MERC formation, whereas the loss of MERCs reduces synaptic transmission. Loss of MERCs is therefore detrimental to calcium communication and ATP production and can ultimately lead to neuronal death. It is estimated that 15% to 20% of the mitochondrial surface is connected to the ER. Studying the ER and mitochondria as a functional unit could thus reveal more about the underlying genetic disease mechanism in ALS. Indeed, calcium miscommunication between the ER and mitochondria has recently emerged as a major factor in the loss of calcium homeostasis in ALS.

The regions of close physical contact between the 2 organelles (mitochondria-associated membranes; MAMs) facilitate molecular signaling and physical exchange that underlie processes such as calcium signaling, phospholipid metabolism, and autophagy. Altogether, MAMs control mitochondrial metabolism, buffer oxidative stress, and contribute to regulation of inflammation and cell death. A primary function of VAPB-PTPIP51 tethers is to facilitate inositol triphosphate receptor (IP3R)–mediated delivery of calcium from ER stores to mitochondria. The MAM-associated chaperone protein sigma 1 receptor (Sigma1R) is also involved in lipid export and calcium signaling through IP3R regulation. Accordingly, Sigma1R levels are significantly lower in patients with ALS than in healthy populations. Loss of VAPB-PTPIP51 has been correlated with reduction of synaptic transmission as a result of impaired calcium flux and reduced ATP production, which in turn cause myopathy.

The formation of ROS, potentially due to malfunctioning SOD1, can also damage these MAMs by forming pores that then alter MAM function and interaction. In mutant SOD1 (mutSOD1) mice, mutSOD1 aggregates have been shown to localize to the MAM and inhibit MERCs. When Sigma1R was also ablated, further impairment of mitochondrial function was recorded, suggesting a functional interplay among SOD1, Sigma1R, and MAMs in ALS. It is therefore no surprise that ER ultrastructure is altered and MERCs are lost in mouse ALS populations. C9ORF72 is also enriched in MERCs, whereby mutant C9ORF72 containing expanded repeats can cause damage prior to disease onset by specifically disrupting VAPB-PTPIP51 tethers and impairing IP3R-mediated calcium delivery, although no overt differences in these organelles were observed in C9ORF72-mutant mice. The causative relationship between protein aggregates and ALS remains to be comprehensively investigated.

Currently, no cure exists for ALS, partially because of its complex etiology and the inability to prioritize cell functions for drug discovery. Understanding the time line of disease development, particularly the events that lead up to ER-mitochondria dysfunction, can further the development of antioxidant strategies that can promote healthy ER-mitochondria interactions to possibly prevent ALS altogether. Effective targets for ALS therapeutics could include components of MAMs, particularly for the purpose of correcting defects in calcium homeostasis, which is a prominent feature of ALS. For instance, compensating for mutations that disrupt ER-mitochondrial signaling (such as VAPB) has been effective in repairing VAPB-PTPIP51 tethering and ER-mitochondria signaling in rodent models and promises to be a broadly therapeutic strategy for neurodegenerative diseases. Agonists of Sigma1R have also been successful in protecting motor neurons and muscle activity in presymptomatic ALS mutSOD1 mice and in mice with spontaneous neurodegeneration, suggesting that Sigma1R agonists can improve calcium homeostasis regardless of comorbidities. ER stress modulators such as Salubrinal have also been shown to restore calcium homeostasis in SOD1-mutant mice with defective Sigma1R. Activating or blocking IP3R could also modulate calcium homeostasis. Further downstream, correcting mitochondrial NAD+ levels could improve neuronal health. However, something to consider is that dysregulation of ER-mitochondrial signaling could be a secondary effect to other damaged features, in which case it is important to define the primary driver of ALS. Moreover, studies in human subjects, rather than rodent ALS models, will reveal whether MERCs are indeed perturbed in ALS and whether MERC damage can be used not only as an early diagnostic feature, but as a potential drug target.

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REFERENCES
FOR DECADES, CLINICIANS HAVE increased research to elucidate the onset processes for neurological diseases such as Alzheimer disease, Parkinson disease, multiple sclerosis, stroke, and epilepsy but have found little success. The recently launched, first-of-its-kind Cleveland Clinic Brain Study aims to help investigators understand why some individuals develop these diseases by examining biomarker changes that occur before clinical symptoms present.¹

The study, considered to be the largest ever in brain disease, will include up to 200,000 neurologically healthy individuals assessed over a 20-year period. For the first 5 years—the initial phase—10,000 volunteers will undergo yearly assessments including neurological examinations, blood work, eye retina scans, brain MRIs, electroencephalograms (EEGs), sleep studies, and other cognitive function tests. This longitudinal multiyear study hopefully will uncover more about the mechanisms of brain diseases and ultimately lead to the design of preventive treatments for them.

One of the study’s leaders, Imad Najm, MD, director of The Charles Shor Epilepsy Center at Cleveland Clinic’s Neurological Institute in Ohio, sat down with NeurologyLive® to provide some background on the study and how it will be conducted. He also discussed overlap and similarities of certain neurological disorders and how those might play from a preventative perspective.

Q: What was the basis for this study? The Cleveland Clinic Brain Study is designed to address a very important question that everybody, both in the medical field and in the community, faces. And that is, why do we have neurological disorder—in particular, neurodegenerative disorders such as Alzheimer disease, multiple sclerosis, stroke, Parkinson disease, and epilepsy—in our late stages of life? Secondly, what happens before neurological disorders occur? And lastly, what can we do to stop it or cure the neurological disorder?

Q: Can you discuss the main goals of the study? How will this expand on what we previously know? What we’re trying to achieve is an understanding of what happens during what we call the silent period that precedes the clinical onset of neurological problems in patients affected by these various neurological disorders. We are trying to identify
Q: There has been documented overlap between specific neurological diseases—what similarities do we currently know exist?

There is quite a bit that’s known. We know that there are similarities in the silent period for Alzheimer disease, Parkinson disease, and epilepsy. This is what we call the de novo onset of endogenous depression in individuals in their 50s and within 5 years of the onset of the first symptom or sign of epilepsy, Parkinson disease, or dementia. It’s here where there may be some things happening in the brain or the networks in the brain that might be telling us that something will happen later on.

When predicting one of these neurodegenerative disorders, depression is potentially an expression of that network problem that we see. Later on, after the onset of the disease, there are some similarities that are probably the result of the neurodegeneration rather than the causes of these disorders. These include problems with speech, gait, unsteadiness, and probably motor movements in general. In addition to that, there are some cognitive changes—for example, decrease in memory, decrease in responses, decrease in speech, and maybe a little bit more paucity of words that [when] forming sentences may be similar to what is occurring in Parkinson disease and Alzheimer disease. Maybe memory problems are occurring more in Alzheimer disease and epilepsy.

There are some similarities, but we think these similarities are due to the process of neurodegeneration rather than the cause of what leads to Alzheimer disease, Parkinson disease, epilepsy, stroke, and other neurodegenerative disorders.

Q: If this study is successful, are there specific preventive measures or tactics that may be implemented?

This study, if successful, will achieve a couple of very important goals. In the short term, within the next 5 years, we may be able to identify surrogate biomarkers of some of these diseases. These surrogate biomarkers will hopefully serve us in making an early diagnosis before the onset of the clinical symptoms. That should be, I think, the first result of the study. Second, the main objective of the study is to identify causative biomarkers for various neurodegenerative disorders. The identification of these biomarkers should get us to the final and most important goal, which is to target these biomarkers with new therapies to shut down the disease, reverse the disease, but more importantly, the ultimate goal would be to prevent the disease from happening. We do not want to run after the disease like we do now. We want to stop it before it does happen and preserve these brain cells without being subjected to the destruction or deaths that happen from many of these devastating neurodegenerative disorders.

Q: Is there a reason to test patients for neurological disease even earlier than what is currently done?

Yes, I think this is one of the most important goals that we’re looking at in the study. That is, we want to find out what are the targets we need to look for in the phase that precedes the clinical phase….Any individual over 50 years old may be considered at risk for the occurrence of Alzheimer disease, Parkinson disease, stroke, epilepsy, and other neurodegenerative disorders. But we don’t know how to screen for these risks.

Let’s compare this with what happened in the 1940s and 1950s. We used to see individuals in their 40s suddenly drop dead from a heart attack. Nobody knew why this was happening, but even more importantly [we didn’t know why this person was at higher risk or how] to mitigate these risks and prevent cardiovascular disorders from happening. This was the first time a study, maybe similar to what we’re doing, looked at the precursors and risk factors that we don’t know.

This was the Framingham study, which looked over 30, 40, 50, and 60 years of data of risk factors. Everything we know about risk factors for coronary artery disease and heart diseases—high cholesterol, high blood pressure, diabetes, high obesity—were all recognized because of this study, which is the same type of design we have now.

We are trying to do the same type of study but with the technology of the 2020s. We are looking at clinical biomarkers—but much more sophisticated biomarkers that will include genetic, genomic, molecular microbiome myoma biomarkers. And then we are looking for biomarkers based on imaging such as high-resolution MRIs, retina scans, as well as neurophysiological biomarkers with post processing, using signal processing analysis that looks for things that clinicians would not know.

Our main goal is to find good biomarkers in the blood, body, and via MRI that will tell us, “Hey, the risk is very high for a disease.” And then maybe some of them could be the target for our intervention. Our end goal is to make sure that the brain will keep up with the heart. Over the past 16 years, we’ve kept this pump beating in a healthier way, healthier than it’s ever been over the past 100 years. But we’re now discovering that the brain is not able to keep up with the heart after the age of 50, 60, 70, 80, and 90. Our goal is to make sure the pump is pumping and the brain is functioning to a satisfaction of every one of us with our cognitive and motor abilities to enjoy our later stages of life with our loved ones.

This type of study, we hope, will be the precursor of many studies later on, and we will use some of the data we’ve collected to recognize the risk factors for neurodegenerative disorders, find ways to target these devastating and crippling disorders, try to prevent them from happening, and improve the quality of life for humans of multiple generations in the future.
AGITATION IS AMONG THE most common symptoms reported by the more than 6 million Americans impacted by Alzheimer disease (AD). Drug development, however, has focused on reversing the cause of the disease, leaving few therapies to treat less-pronounced symptoms like agitation.

The investigational BXCL501 (Igalmi; BioXcel Therapeutics, Inc) is an orally dissolving thin-film formulation of dexmedetomidine that received FDA approval in April 2022 for agitation associated with schizophrenia and bipolar I or II disorder.1 It will now be assessed in a phase 3 program for AD-related agitation.

This program, called TRANQUILITY, consists of 2 randomized, placebo-controlled, adaptive, parallel group pivotal trials—TRANQUILITY II (NCT05271552) and TRANQUILITY III (NCT05276830)—that will enroll 150 and 75 patients with dementia 65 years and older, respectively. BXCL501 will be self-administered in doses of 40 mcg or 60 mcg during a 3-month period. Patients will be randomized to study drug or placebo and will be assessed on changes in agitation based on the Positive and Negative Syndrome Scale, Excitatory Component (PEC) and Pittsburgh Agitation Scale (PAS) total scores (TABLE).2

TRANQUILITY II will enroll those in assisted living or residential facilities requiring minimal assistance with activities of daily living (the first patient was dosed in May 2022),3 whereas TRANQUILITY III will include patients in nursing homes with moderate to severe dementia requiring moderate or greater assistance with activities of daily living.

Robert Risinger, MD, chief medical officer of BioXcel Therapeutics, said in a statement that it is “expanding TRANQUILITY II to more than 10 clinical trial sites in the US and [that] with no current FDA-approved treatments for agitation associated with this disease, we are making strong and swift efforts to potentially bring BXCL501 and its proven ability to address agitation to this large market.”

The primary efficacy end point for both studies will be change in PEC score from baseline at 2 hours after the initial dose and subsequent doses. The PEC rating evaluates 5 elements associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement. Those who complete either study will be eligible to enter an open-label extension, in which investigators will assess efficacy and safety of the study drug during a 52-week period.

BXCL501 was granted breakthrough therapy designation by the FDA based on data from the phase 1b/2 TRANQUILITY ascending-dose finding study (NCT04251910). That trial included 54 patients in assisted living facilities with agitation related to dementia, 87% of whom had AD. The participants were treated with either BXCL501 30 mcg (n = 16), 60 mcg (n = 20), 90 mcg (n = 4), or placebo (n = 14).

The study’s primary end points were met, with no severe or serious adverse events (AEs) reported. The AEs observed included hypotension (60 mcg, 10%; 30 mcg and placebo, 0%), orthostatic hypotension (60 mcg, 5%; 30 mcg, 6.3%; placebo, 0%), and dizziness (60 mcg, 5%; 30 mcg, 6.3%; and placebo, 0%). Higher exposure levels of BXCL501 were observed in the older patient population compared with earlier trials, so the company focused on studying the 30- and 60-mcg doses.4

The group receiving BXCL501 60 mcg met the secondary efficacy end points on all 3 primary agitation scales—PEC, PAS, and the Modified Cohen-Mansfield Agitation Inventory—demonstrating statistically significant and clinically meaningful reductions in total scores at 2 hours post dosing. Investigators observed the rapid and sustained reductions in PEC total as early as 30 minutes following dosing and in both PEC and PAS total scores at 60 minutes, lasting through 8 hours post dosing.

The FDA’s decision to approve the medication for agitation associated with schizophrenia or bipolar I or II disorder in adults was based on data from 2 pivotal randomized, double-blind, placebo-controlled parallel group phase 3 trials—SERENITY I (NCT04268303) and SERENITY 2 (NCT04276883)—that evaluated the drug for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder, respectively.

In both trials, BXCL501 in 120-mcg and 180-mcg doses met its primary end point in change from baseline in PEC total score assessed at 2 hours. The mean changes from baseline in PEC total score were –10.4 (SD, 4.4) for sublingual BXCL501 180 mcg and –9.0 (SD, 5.3) for 120 mcg compared with –4.9 (SD, 4.7) for placebo. On the key secondary end point, statistically significant treatment effects were evident 20 minutes after initial treatment for both doses (180 mcg, P = .007; 120 mcg, P = .009) compared with placebo.5 The company said it expects to launch BXCL501 the second quarter of 2022.1

For a full list of references, see the article on NeurologyLive.com.
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New Treatments in Migraine: An In-Depth Review

By Arathi Nandyala MD*, and Jessica Ailani, MD**

* Resident, Department of Neurology, Medstar Georgetown University Hospital
** Director, MedStar Georgetown Headache Center; Associate Professor, Department of Neurology, Medstar Georgetown University Hospital

MIGRAINE IS A CHRONIC and often debilitating disease affecting 1 in 7 individuals globally and one of the top 20 causes of disability worldwide. Thus, the importance of effective strategies for managing this disease could not be more paramount. During the past 5 years, several new treatments, both preventive and acute, have become available.

Although clinicians now have plenty of options, it can be difficult to choose between them and understand how novel treatments compare with traditional therapies.

Traditional migraine treatments are most often discontinued by patients and clinicians due to lack of efficacy and poor tolerability.¹,² The new wave of therapeutics have a targeted mechanism of action (MOA) based on migraine pathophysiology. This targeted MOA comes with a reduction in adverse effects, resulting in greater tolerability, increased ability for patients to remain on treatment, and improved long-term results. Newer acute treatments can address unmet patient needs by providing nonoral formulations, reduced adverse effects, eliminated risk of medication-overuse headache, different modes and mechanisms of action, and reduced contraindications.

Newer preventive treatments bring the first migraine-specific pharmacologic preventives to the field.

Although new treatments and innovations are a sign of growth in the field, it is important to realize that growth comes with a certain amount of pain. In clinical practice, choosing the right treatment option for patients in a time-limited visit is often a dilemma. Add to that the complexity of constant insurance hurdles and the fact that excitement about innovative products can wane as the fatigue associated with prior authorizations mounts—resulting in delays in getting your patient appropriate care becoming standard. Recognizing that new treatments require some general agreement around their use vs what was considered standard of care, the American Headache Society published an updated consensus statement in 2021 focused on assisting clinicians in when to consider new acute and preventative medications or neuromodulation for patients with migraine.³

In this article, we will highlight new therapeutic options for both acute and preventive treatment of migraine and discuss their use versus traditional therapies.

Updates in Acute Migraine Medications
Gepants and ditans
Since 2019, 2 new classes of medications have become available with
CGRP monoclonal antibodies

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<th>Derivation</th>
<th>Half-life</th>
<th>Dosing interval</th>
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<td>Eptinezumab-jjmr</td>
<td>IgG1</td>
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**Dihydroergotamine POD**

Dihydroergotamine (DHE) is an effective treatment for migraine, but due to poor gastrointestinal (GI) absorption, it is usually administered via injection or nasal spray. A recent phase 3 trial evaluated the use of DHE mesylate (Migranal; Bausch Health Companies Inc) via precision olfactory delivery (POD) technology directed to the upper nasal cavity. In the initial phase 1 trial, 1.45 mg of DHE POD was equivalent to 1.0 mg of intravenous DHE mesylate and 2.0 mg of DHE mesylate. Thirty-eight percent of patients achieved pain relief within 2 hours of administration vs 30.1% with usual care. Commonly reported adverse effects included nasal congestion (15%), nausea (6.8%), and nasal discomfort (5.1%). DHE via the POD device offers patients a more convenient way to self-administer.

**Celecoxib**

Nonsteroidal anti-inflammatory drugs are a class of medication that represents a mainstay in acute treatment. However, GI adverse effects are a common limiting factor. A recent randomized, double-blind, placebo-controlled trial found the liquid formulation of celecoxib capsules (Celebrex; Viatris), called DFN-15, at 120 mg to be an effective treatment for migraine attacks. DFN-15 has a shorter time to maximum effect and greater bioavailability than oral formulations, with a higher percentage of patients reporting 2-hour pain freedom with treatment of a single migraine attack of any pain intensity comparatively (46.2% vs 31.1%; P < .001). The most common adverse effects reported were nausea and dysgeusia.

**Remote electrical neuromodulation**

Neuromodulation devices offer a noninvasive option that may avoid several issues with medications, including adverse effect intolerance, medication-overuse headache, and medication contraindication. The remote electrical neuromodulation (REN) device (Nerivio; Theranica) activates peripheral nerves in the upper arm but below the perceived pain perception, which leads to conditioned pain modulation. In episodic migraine, pain relief at 2 hours was achieved by a significant proportion of patients compared with sham in a randomized, double blind, placebo-controlled trial (66.7% vs 38.8%; P < .0001). When compared with usual care (either migraine specific or nonspecific or no pharmacological treatment) in post hoc analyses, REN was more effective for pain relief 2 hours post treatment with 66.7% of patients on treatment reporting relief vs 52.5% of those on usual care (P = .034). Regarding adverse events, 13.5% of patients experienced at least 1, most commonly warmth sensation, temporary arm/hand numbness, or redness.

**External concurrent occipital and trigeminal stimulation**

External concurrent occipital and trigeminal neurostimulation (eCOT-NS; Relivion MG; Neurolief Inc) is another neuromodulation device that was recently cleared by the FDA. Previously, evidence showed that surgically implanted concomitant occipital and supraorbital nerve stimulation was effective but had significant adverse effects and was cost prohibitive. eCOT-NS uses transcutaneous, noninvasive peripheral nerve stimulation of both the occipital and trigeminal nerve. eCOT-NS was assessed for treatment of acute migraine in a randomized, blinded, placebo-controlled trial in adult patients with chronic or episodic migraine. In the treatment group, 76.2% experienced headache improvement at 2 hours vs 36.1% in the control group (P = .0100). Commonly reported adverse effects included headache, numbness/paresthesia, and skin irritation.

**Updates in Preventive Migraine Medications**

CGRP monoclonal antibodies

CGRP monoclonal antibodies (mAbs) have been on the market since before 2020. These include erenumab-aooe (Aimovig; Amgen Inc), galcanezumab-gnlm (Emgality; Eli Lilly and Company), fremanezumab-vfrm (Ajovy; Teva Pharmaceuticals USA, Inc), and eptinezumab-jjmr (Vyepti; Lundbeck Seattle BioPharmaceuticals). In a recent meta-analysis, all 4 CGRP mAbs were compared and found to have similar efficacy and tolerability. They vary by binding site, antibody, and mode of administration (TABLE 1).

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**TABLE 1. CGRP Monoclonal Antibodies**

<table>
<thead>
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CGRP, calcitonin gene-related peptide; Ig, immunoglobulin.
**Newer Treatments vs Traditional Treatments**

With the emergence of several new treatment options, studies comparing these new agents with traditional therapeutics are imperative to make decisions in patient care, such as timing of treatment initiation (TABLE 2 and TABLE 3). A recent head-to-head study compared the efficacy and tolerability of erenumab vs topiramate. This was one of the first studies to directly compare a CGRP receptor antibody with an older preventative medication. The findings showed that 55% of participants on erenumab had at least a 50% reduction in migraine days per month compared with 31.2% of patients on topiramate ($P < .001$). Overall, fewer adverse effects were reported in the erenumab group, with 10.6% of patients discontinuing erenumab due to adverse effects compared with 38.9% of those taking topiramate ($P < .001$).21 Because many medication choices are made based on tolerability, this may change the hierarchy of various classes.

In another comparison study, a meta-analysis of phase 3 randomized controlled trials assessed absolute differences in benefit-risk ratios between CGRP mAbs topiramate and propranolol. OnabotulinumtoxinA injections (Botox; Allergan Inc) were also included for the treatment of chronic migraine. Overall, all CGRP mAbs had a higher likelihood of being beneficial than harmful compared with other medications, including onabotulinumtoxinA, topiramate, and propranolol, suggestive of improved efficacy and tolerability. This further supports a more favorable benefit-risk ratio with CGRP mAbs.22

For chronic pain conditions, there is often an associated placebo effect, which is important to consider and can be effective for many patients. A recent systematic review and meta-analysis of CGRP mAbs showed pooled proportion contextual effect to be 0.66 for episodic migraine and 0.68 for chronic migraine, suggesting a large portion of benefit is due to contextual effects.23 These factors are important to think about when considering which medications to start and what may benefit patients most.

**Conclusion**

With a new wave of medications, many providers are faced with the dilemma of choosing between traditional and new therapies for patients with migraine. Historically, traditional therapies may be limited by lack of efficacy or poor tolerability, but newer options are uniquely targeted toward migraine pathophysiology. 

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**TABLE 2. When to Initiate Newly Approved Acute Treatment Options**

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td>Ditans/gepasts</td>
<td>• At least 18 years &lt;br&gt; • ICHD-3 diagnosis of migraine with aura, migraine without aura, or chronic migraine&lt;br&gt; • One of the following: &lt;br&gt; - Vascular contraindication to triptans/ergots &lt;br&gt; - Poor response to at least 2 triptans&lt;br&gt; • Forditans: ability to avoid driving for 8 hours after administration</td>
</tr>
<tr>
<td>DHE POD</td>
<td>• At least 18 years &lt;br&gt; • ICHD-3 diagnosis of migraine with aura, migraine without aura, or chronic migraine&lt;br&gt; • Individuals preferring noninvasive alternative to DHE &lt;br&gt; • Nonoral option needed or preferred &lt;br&gt; • Migraine longer lasting &lt;br&gt; • Inefficacy to other treatment(s)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>• At least 18 years &lt;br&gt; • ICHD-3 diagnosis of migraine with aura, migraine without aura, or chronic migraine&lt;br&gt; • Individuals with NSAID intolerance &lt;br&gt; • Individuals preferring potential for faster onset efficacy</td>
</tr>
<tr>
<td>Neuromodulation devices</td>
<td>• ICHD-3 diagnosis of migraine with aura, migraine without aura, or chronic migraine &lt;br&gt; • 1 of the following: &lt;br&gt; - Vascular contraindication to triptans/ergots &lt;br&gt; - Poor response to at least 2 triptans &lt;br&gt; - Patient preference &lt;br&gt; • Individuals preferring nonpharmacological options &lt;br&gt; • Patients with MOH &lt;br&gt; • Pregnant patients</td>
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**TABLE 3. When to Initiate Newly Approved Preventive Treatment Options**

<table>
<thead>
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<th>Criteria</th>
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<tr>
<td>CGRP monoclonal antibodies</td>
<td>• At least 18 years or older &lt;br&gt; • Diagnosis of migraine with or without aura or chronic migraine* &lt;br&gt; • Inability to tolerate or inadequate response to at least 2 traditional treatments&lt;br&gt; • If patient has 4-7 MMD, patient should have at least moderate disability:</td>
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<td>CGRP receptor antagonents</td>
<td>• At least 18 years or older &lt;br&gt; • Diagnosis of migraine with or without aura or chronic migraine* &lt;br&gt; • Inability to tolerate or inadequate response to at least 2 traditional treatments&lt;br&gt; • If patient has 4-7 MMD, patient should have at least moderate disability.</td>
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CGRP, calcitonin gene-related peptide; MMD, monthly migraine days.

DHE, dihydroergotamine; ICHD-3, International Classification of Headache Disorders (3rd edition); MOH, medication-overuse headache; NSAID, nonsteroidal anti-inflammatory drug; POD, precision olfactory delivery.
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Updates in Dravet Syndrome: Entering a New Era

Progress in therapeutics and diagnosis over the past decade has dramatically shifted the treatment landscape for this genetic epilepsy and rapidly advanced patient care.

By Joseph Sullivan, MD
Professor of Neurology, University of California, San Francisco Weill Institute for Neurosciences

THE PAST 10 YEARS have brought incredible advances in the diagnosis and treatment of Dravet syndrome (DS). What was once considered a rare epilepsy syndrome with limited treatment options is now being increasingly diagnosed, and diagnoses seem to be occurring at an earlier age.

This progress is largely due to increased awareness on the part of clinicians as well as caregivers, who may rely on the internet and/or social media to arrive at the most accurate diagnosis they can for their child. These earlier diagnoses are also being driven by the more widespread availability and access to genetic testing, which allows clinicians to obtain an expanded epilepsy gene panel in a young child with a newly presenting epilepsy who may or may not have declared themselves with the “classic” presenting DS phenotype.

In parallel with this increased awareness has come unprecedented interest of pharmaceutical companies to test novel therapies, with the goal of reducing seizures and ultimately improving overall quality of life. This interest has led to a host of clinical trials, resulting in the FDA approval of 3 new medications in just the past 4 years and many other therapies in various stages of clinical development. Despite these additional safe and effective treatment options, there continues to be a large unmet need because, unfortunately, most patients still do not experience prolonged periods of seizure freedom; in addition, the coexistence of the various comorbidities has a significant negative impact on overall quality of life.

Thankfully, as we move more in a direction of disease-modifying therapy, some potential interventions are well positioned to start addressing these comorbidities.

Looking Back 5 Years

In one of the largest surveys of caregivers of patients with DS, a European study of 584 unique responses highlighted the state of DS in 2016, with less than 10% of patients being free of seizures in the preceding 3 months. Furthermore, trends toward earlier diagnosis were seen: More than 50% of those younger than 5 years had a time to diagnosis of less than 6 months compared with only 2% of those 12 years and older, with more than 70% of this older age group...
taking 3 or more years from initial symptoms to receive a diagnosis of DS.\(^1\) At the time of this survey, no medications were specifically approved for DS in the United States.

Making an accurate and early diagnosis not only impacts the specific medications to consider but, and equally as important, informs us as to which medications to avoid. A 2018 study showed the impact that duration of contraindicated medication (CIM) use has on subsequent cognitive outcomes, with those who had been exposed to a CIM longer than 11 months having significantly lower developmental quotient/IQ scores compared with those who had not received a CIM or had received a CIM for less than 11 months.\(^2\)

**DS-Specific Clinical Trials**

In 2000, stiripentol (Diacomit; Biocodex, Inc) was the first medication to be specifically studied in a small cohort of DS patients, in which 71% of patients receiving stiripentol had a 50% or greater reduction in generalized tonic-clonic or clonic seizures compared with only 5% of those who received placebo. Impressively, 9 of the 21 patients who received stiripentol were seizure free during the 2-month treatment period compared with none of the patients who received placebo.\(^2\) All patients in this study were also on concomitant valproate and clobazam. Due to limited follow-up studies, the FDA did not approval stiripentol until 2018, despite many US physicians being able to obtain the agent for their patients through individual compassionate-use investigational new drug applications.

It was not until 2014 that the next trial specifically focusing on patients with DS opened to enrollment. This initial double-blind, placebo-controlled study of cannabidiol (Epidiolex; GW Pharmaceuticals) met its primary end point, with a 39% median reduction in seizures compared with a 13% reduction in those receiving placebo;\(^1\) a second study exploring 2 different doses also met its primary end point, with percentage reductions from placebo of 29.8% and 25.7% in the 20 mg/kg/day and 10 mg/kg/group, respectively.\(^1\) The treatment was well tolerated, and the most common adverse effects were diarrhea, vomiting, decreased appetite, and somnolence. In 2018, the FDA approved cannabidiol for seizures associated with DS.

In 2015, a double-blind, placebo-controlled study of fenfluramine (Fintepla; Zogenix, Inc) met its primary end point, with the higher dose of 0.7 mg/kg per day showing a 62.3% greater reduction in mean convulsive seizures compared with placebo. All key secondary end points were also met. Most notably, 50% of patients in the high-dose group and 23% of patients in the low-dose group (0.2 mg/kg per day) experienced a 75% reduction or more compared with only 2% in the placebo group.\(^6\) Near seizure freedom, defined as 0 or 1 seizure during the entire 14-week treatment period, was achieved in 25% of the high-dose group and 12.8% of the low-dose group.\(^6\) The treatment was well tolerated, with the most common adverse effects being decreased appetite, diarrhea, fatigue, and decreased weight. Despite the historical concerns regarding cardiac risk and fenfluramine exposure, no instances of cardiac valvulopathy or pulmonary hypertension occurred in any subject at any time.\(^4\) In 2020, based on these findings together with another study with concomitant stiripentol,\(^7\) the FDA approved fenfluramine for seizures associated with DS.

Despite a lack of understanding of the full mechanisms of action for each of these 3 antiseizure medications, it is widely accepted by clinicians that they work in different ways without much mechanistic overlap. This allows for rational polypharmacy with each of these agents to try to achieve the best seizure control with limited and tolerable adverse effects. Today it is not uncommon for many patients to be on combination therapy of 2, or even all 3, of these medications.

Additional mechanisms are also being explored with various agents in different stages of clinical trials, including soticlestat, a cholesterol 24-hydroxylase inhibitor, as well as clemizole, lorcanoserin, BMB-101, and LP352—all of which, like fenfluramine, act via the serotonin pathway, but with different potencies or selectivity to different serotonin receptor subtypes.

With more proven safe and effective treatment options, the treatment landscape for patients living with DS in 2022 has changed dramatically; however, an ongoing unmet need remains for better seizure control and much-needed interventions to improve many of the nonseizure outcomes. A post hoc analysis of patients who enrolled in the various fenfluramine trials and received at least 1 year of treatment in the open-label extension study was done to evaluate for clinically meaningful changes on the Behavior Rating Inventory of Executive Function. In the 58 children included in this analysis, 45 (78%) achieved a greater than 50% reduction in seizures, with clinically meaningful improvement on both the emotional regulation index and the cognitive regulation index.\(^8\) These findings support the notion that nonepileptic outcomes can improve in this patient population and allows for redefining our treatment goals as we strive to treat all aspects of the syndrome.

**Disease-Modifying Therapies**

Our current understanding of the underlying pathophysiology of DS being caused by pathogenic gene variants that lead to Na\(_{\text{1.1}}\) haploinsufficiency sets the stage for possible disease-modifying interventions that would ideally address more than just seizures. Families and caregivers aspire to stop neurodevelopmental stagnation and reduce the impact on their families’ well-being, with a particular desire to improve all aspects of communication, including both expressive and receptive language delays.\(^9\) Although many clinicians believe earlier diagnosis and more targeted syndrome-specific management with both aggressive seizure rescue plans and individualized antiseizure medication management can improve some of these outcomes, the community acknowledges this is not addressing the underlying cause. At present, 2 approaches in the later stages of development serve to address this.

STK-001, an antisense oligonucleotide approach being developed by Stoke Therapeutics, Inc, has been shown in the Scn1a mouse model of DS to increase productive messenger RNA transcript and Na\(_{\text{1.1}}\) levels to that of wild type and, more importantly, reduce seizure frequency and increase long-term survival.\(^10\) This targeted
augmentation of nuclear gene output, or TANGO, approach is delivered intrathecaically via lumbar puncture and is currently being studied in a phase 1/2a first-in-human clinical trial (NCT04442295) evaluating both single and multiple ascending doses given at various intervals. Preliminary results are encouraging: The therapy has been well tolerated, and 70% of patients—including 100% of those in the cohort aged 2 to 12 years—have experienced some reduction in convulsive seizures. Additional outcome data are expected soon for those receiving the higher doses, and prospective cognitive and neurodevelopmental assessments are ongoing.11

Another novel, potential one-time disease-modifying approach to address the underlying Na\textsubscript{v}1.1 haploinsufficiency is being developed by Encoded Therapeutics. Called ETX101, it is an adeno-associated virus serotype 9 SCN1A gene regulation therapy that expresses an engineered transcription factor to upregulate the SCN1A gene from the endogenous genome, along with a cell-selective regulatory element to target transgene expression specifically to GABAergic inhibitory interneurons. A single bilateral intracerebroventricular (ICV) injection of ETX101 in DS mice reduced the frequency of spontaneous and hyperthermia-induced seizures and prolonged survival for up to 470 days post dosing.12 In nonhuman primates, delivery of ETX101 by unilateral ICV injection led to widespread vector biodistribution and transgene expression throughout the brain. The interventional study of ETX101 is planning to enroll the first patient in late 2022. Although each of these approaches have different routes and frequency of dosing and use different mechanisms of achieving upregulation of functional Na\textsubscript{v}1.1 channels, both approaches have the potential to address the full range of symptoms that affect patients with DS by correcting the underlying Na\textsubscript{v}1.1 haploinsufficiency. Further data are needed for each approach to understand the full safety profile and whether there is an optimal age window to achieve maximum benefit. Still, clinicians and caregivers remain excited about this new direction.

Too Late?
Could it ever be “too late” to intervene with a disease-modifying therapy? Because mouse models of DS develop symptoms around P18-24, a study in a DS mouse model was able to conditionally activate the Scn1a silent allele at various time points during disease progression. When Scn1a expression was reactivated at P30, not only were seizures suppressed, but the hyperactivity and cognitive deficits were also rescued. Furthermore, when reactivated later at P90 (corresponding to a 20-year-old human), rescue of seizures was also achieved.13

Whether this is translatable to humans across the age spectrum remains to be seen. But many clinicians who care for patients with DS agree that it is never too late to pursue syndrome-specific treatments, and it is our hope that this will apply to disease-modifying therapies as well.

Entering a New Era
From the original description of DS by Charlotte Dravet in 1978 to the discovery of the SCN1A gene being the primary cause in 2001, this childhood-onset epilepsy syndrome has attracted more attention than any other. Thankfully, this has led to the availability of more effective treatment options for seizures and, more importantly, to the study of some novel, potentially disease-modifying approaches that, if effective, could not only dramatically improve the lives of those living with DS now, but could change the face of the natural history of the syndrome as we know it.

References
RESEARCH AWARDS

Stantonford Institute Is Awarded Gift From Nike Founder to Study Neurodegeneration

With the help of a $75 million gift from Nike founder Phillip H. Knight and his wife, Penny, Stanford University launched a new campus-wide initiative aimed at understanding why some individuals develop neurodegenerative diseases and some don’t. At the time of the announcement, Tony Wyss-Coray, PhD, the D.H. Chen Distinguished Professor II of Neurology and Neurological Sciences at Stanford, was appointed the inaugural director of the Phil and Penny Knight Initiative for Brain Resilience. The initiative will leverage Stanford’s interdisciplinary expertise in medicine, neurosciences, engineering, human biology, chemistry, psychology, and more to foster first-of-its-kind collaborations among investigators, clinicians, and scholars. The idea behind the donation is to create new innovations and take knowledge to a point where it is possible to promote brain rejuvenation and stave off certain brain disorders, as well as prevent and treat cognitive decline.

Grant from National Institutes of Health Boosts Einstein Aging Study

The National Institutes of Health awarded a 5-year, $32 million grant to support the ongoing Einstein Aging Study (EAS), which focuses on normal aging and the special challenges of Alzheimer disease and other dementias. The funding will be split among researchers at Albert Einstein College of Medicine, faculty at Pennsylvania State University, and other institutions. Also headed by Richard B. Lipton, MD, director of Montefiore’s Headache Center, the renewal is also being led by Carol Derby, PhD, a research professor in the Saul R. Korey Department of Neurology. The new grant will allow EAS investigators to follow more than 700 adults 60 years and older from the Bronx, New York, who live at home. Each study participant will be given a customized smartphone for a 2-week period so they can answer questions about their daily experiences and state of mind, as well as play games that measure their cognition.

EXPERT APPRECIATION

National MS Society Awards Prestigious Honor to Pediatric Program Director

Naila Makhani, MD, MPH, associate professor of pediatrics and director of the Pediatric Multiple Sclerosis (MS) Program at Yale School of Medicine has been named a Harry Weaver Neuroscience Scholar by the National MS Society, starting in July 2022. The 5-year, early-career award provides approximately $600,000 in funding to Makhani to continue her research on biomarkers associated with MS in children with radiological isolated syndrome (RIS).

In a recent published manuscript, Makhani explained that individuals with RIS lack clinical neurological symptoms but are at risk for the subsequent development of a first clinical neurological event consistent with a diagnosis of MS. Makhani’s research will aim to identify markers that identify children at the greatest risk of MS, which may ultimately lead to prevention strategies.

Stephen Hauser, MD, Receives Scientific Breakthrough Award From ABF

The American Brain Foundation (ABF) honored Stephen L. Hauser, MD, professor of neurology and director of the Weill Institute for Neurosciences at the University of California, San Francisco, with its second annual Scientific Breakthrough Award, which is given to an individual or group for their advances in the care of patients with neurological diseases. Hauser was honored for his career-long commitment to advancing the understanding of the genetic basis, immune mechanisms, and treatment of multiple sclerosis. ABF applauded Hauser’s dedication to research that has led to the advancement of B-cell therapies, which have significantly transformed the treatment landscape during the past decade. In addition to the Scientific Breakthrough Award, Hauser has received numerous awards and honors for his work, including the Jacob Javits Neuroscience Investigator Award, the Charcot Award, and the Taubman Prize for Excellence in Translational Medical Research.

INSTITUTION INITIATIVES

Cleveland Clinic Plans to Invest $1.3 Billion in New Facilities

Tomislav Mihaljevic, MD, CEO and president of Cleveland Clinic, announced the institution will be investing $1.3 billion in capital projects, including construction of new buildings and renovation of facilities in Ohio, Florida, and London. As part of the upgrades, Cleveland Clinic will add a 1-million-square-foot Neurological Institute building on the main campus, expand the Cole Eye Institute building, and significantly expand research facilities through its commitment to the Cleveland Innovation District. The Neurological Institute building will include inpatient and outpatient care, along with imaging and surgical services and research laboratories to investigate the function of the human brain and innovation labs to develop future treatments for neurological diseases.
Every day, people with Parkinson’s face a challenging opponent. Yet, members of this amazing community strive to follow their passions undeterred, refusing to let Parkinson’s define them. That fighting spirit inspires our resolve to work towards innovative new therapies. At Supernus, we’re proud to partner with the community, and to share some of the iconic ways people with PD strive to live their best lives today and every day.