Gait Dysfunction in Parkinson Disease: The Role of the Cholinergic System

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Cure Connections®
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Serotonin Receptor Agonism in Dravet Syndrome

BY JENNIFER S. SUN, PHD

CLINICAL VIEWPOINT
The Impact of Telehealth on Patient Experiences in Sleep Medicine

WITH LUCAS M. DONOVAN, MD, MS
SPINRAZA—Strong history, powerful evidence

SPINRAZA has been studied in infants and children in the longest clinical trial program in SMA to date.1,7 SPINRAZA also has the most published real-world evidence in adults up to age 72 with SMA.8-10

Explore the history below.

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

**INDICATION**

SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

**IMPORTANT SAFETY INFORMATION**

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.
IMPORTANT SAFETY INFORMATION (cont’d)
The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.

Please see the brief summary of Prescribing Information on the following pages.


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225 Binney Street, Cambridge, MA 02142
Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells.

Preparation

2.2 Important Preparation and Administration Instructions

SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

Preparation

- Store SPINRAZA in the carton in a refrigerator until time of use.
- Allow the SPINRAZA vial to warm to room temperature (25°C/77°F) prior to administration. Do not use external heat sources.
- Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored. The use of external filters is not required.
- Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
- Administer SPINRAZA within 4 hours of removal from vial.

Administration

- Consider sedation as indicated by the clinical condition of the patient.
- Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.
- Prior to administration, remove 5 mL of cerebrospinal fluid.
- Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle [see Dosage and Administration (2.1)]. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation [see Adverse Reactions (6.3)].

2.3 Laboratory Testing and Monitoring to Assess Safety

Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed [see Warnings and Precautions (5.1, 5.2)]:

- Platelet count
- Prothrombin time; activated partial thromboplastin time
- Quantitative spot urine protein testing

3 DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/5 mL (2.4 mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia and Coagulation Abnormalities

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with a lowest level of 10,000 cells per microliter recorded on study day 28.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.

Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.
5.2 Renal Toxicity
Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney [see Clinical Pharmacology (12.3)]. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of SPINRAZA-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS
The following serious adverse reactions are described in detail in other sections of the labeling:
- Thrombocytopenia and Coagulation Abnormalities [see Warnings and Precautions (5.1)]
- Renal Toxicity [see Warnings and Precautions (5.2)]

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

In clinical studies, 346 patients (47% male, 76% Caucasian) were treated with SPINRAZA, including 314 exposed for at least 6 months, 258 exposed for at least 1 year, and 138 exposed for at least 2 years. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 days to 16 years of age at first dose) with symptomatic SMA; in a sham-controlled trial in infants with symptomatic SMA (Study 1; n=80 for SPINRAZA, n=41 for control); in a sham-controlled trial in children with symptomatic SMA (Study 2; n=84 for SPINRAZA, n=42 for control); an open-label study in presymptomatic infants (Study 3, n=25) and other studies in symptomatic infants (n=54) and later-onset patients (n=103). In Study 1, 58 patients were exposed for at least 6 months and 28 patients were exposed for at least 12 months. In Study 2, 84 patients were exposed for at least 6 months and 82 patients were exposed for at least 12 months.

Clinical Trial in Infantile-Onset SMA (Study 1)
In Study 1, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except that SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%), and requirement for respiratory support (26% vs 15%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in Study 1 were infants, adverse reactions that are verbally reported could not be assessed in this study.

Table 1. Adverse Reactions That Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Infantile-Onset SMA (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg&lt;sup&gt;1&lt;/sup&gt; N=80 %</th>
<th>Sham-Procedure Control N=41 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory infection&lt;sup&gt;2&lt;/sup&gt;</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>1</sup> Loading doses followed by 12 mg (5 mL) once every 4 months
<sup>2</sup> Includes adenovirus infection, bronchiolitis, bronchitis, bronchitis viral, corona virus infection, Influenza, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, parainfluenzae virus infection, pneumonia, pneumonia bacterial, pneumonia influenzal, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral, and respiratory syncytial virus bronchiolitis.
In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

**Clinical Trial in Later-Onset SMA (Study 2)**

In Study 2, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except for the proportion of SPINRAZA-treated patients who had ever achieved the ability to stand without support (13% vs 29%) or walk with support (24% vs 33%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain.

**Table 2. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times As Frequently Than in Control Patients with Later-Onset SMA (Study 2)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg¹ N=84 %</th>
<th>Sham-Procedure Control N=42 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Loading doses followed by 12 mg (5 mL) once every 6 months

Post-lumbar puncture syndrome has also been observed after administration of SPINRAZA.

**6.2 Immunogenicity**

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

The immunogenic response to nusinersen was determined in 294 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Seventeen patients (6%) developed treatment-emergent ADAs, of which 5 were transient, 12 were considered to be persistent. Persistent was defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, “persistent” is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient was defined as having one or more positive results and not confirmed to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

**6.3 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of SPINRAZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious infections associated with lumbar puncture, such as meningitis, have been observed. Hydrocephalus, aseptic meningitis, and hypersensitivity reactions (e.g. angioedema, urticaria, rash) have also been reported.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested (see Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

When nusinersen (1.4, 5.8, or 17.2 mg/kg) was administered to pregnant female mice by subcutaneous injection every other day throughout organogenesis and continuing once every six days throughout the lactation period, adverse neurobehavioral effects (alterations in locomotor activity, learning and memory deficits) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established.

8.2 Lactation

Risk Summary
There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Nusinersen was detected in the milk of lactating mice when administered by subcutaneous injection. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established (see Clinical Studies (14.1)).

Juvenile Animal Toxicity Data
In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1 or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use

Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Thrombocytopenia and Coagulation Abnormalities
Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs [see Warnings and Precautions (5.1)].

Renal Toxicity
Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity [see Warnings and Precautions (5.2)].
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Looking Back While Pushing Forward

The field of neurologic medicine has, as every field has, been faced with and overcome unforeseeable challenges since the start of the COVID-19 pandemic. The ability of clinicians to both rapidly and effectively adapt has been put on full display and has resulted in continued advancement in the face of great adversity.

Medical societies have continued to hold their annual meetings, with novel hybrid approaches offering both live and virtual components that have increased access and provided safe ways for clinicians and researchers to maintain vital connections and share data on a wide scale.

These challenges have also led to a shift in focus for neurologists, somewhat forcing a reimagining of the role of patients in the disease management process, and the benefits of this inclusive and comprehensive approach. It has led to a focus on the aspects of care that are important to those with these diseases, and this focus is highlighted by W. Alex Dalrymple, MD, on page 34, in a feature story that assesses the state of management for gait dysfunction in Parkinson disease—a symptom of major interest to many individuals with the disease.

Novel therapies and reformulations in the pipeline have also continued to move through clinical trials. In 2021, there were more than 20 new approvals for neurologic diseases—and in the background of it all, investigators around the globe pressed on by conducting crucial studies. On page 56 of this issue of NeurologyLive®, Jessica Yi, MD, and Ericka Wong, MD, offer a look into the advances made in just one area of neurology this year: neuromuscular disorders. A field consisting of varying complex diseases, it has seen accelerated progress in the past 5 years, from introductions of novel agents to improved understanding of these disorders, and this feature emphasizes just some of that forward momentum. Similar updates are provided on page 59 by Suzan Khoromi, MD, MHS, in the realm of cluster headache, a condition that has long challenged the treatment attempts of headache and migraine specialists.

Another area of the care paradigm that has propelled itself forward has been stroke and cerebrovascular disease. Despite the effectiveness of tissue plasminogen activator in treating stroke, investigators have refused to be satisfied, continuing on and opening the window of care for patients wider each year. One portion of this effort is present in the ongoing TIMELESS trial (NCT03785678) of tenecteplase (TNKase; Genentech) in acute ischemic stroke, the details of which are explored on page 51 of this issue.

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

Thank you for reading.

Mike Hennessy Jr
President and CEO, MJH Life Sciences™
An Emerging Framework for Parkinson Disease Therapeutics

By Jeffrey Ratliff, MD

FOR CENTURIES, the diagnosis of Parkinson disease (PD) has relied on clinicians’ ability to recognize the clinical manifestations of the disease, both motoric and nonmotoric. The diagnosis may seem straightforward at first, requiring neurologists to rely on their eyes and hands to detect the cardinal motor features of bradykinesia, resting tremor, and rigidity. In 1912, the neuropathological finding of what would come to be called Lewy bodies in the neurons of brains of patients with PD helped shape the clinicopathologic model of the disease. Decades later, key research identified the presence of α-synuclein in Lewy bodies and its potential pathogenic role in PD. This model that Lewy bodies, comprised primarily of α-synuclein, are the pathogenic hallmark of PD has been instrumental in driving understanding of PD and its underlying mechanisms. The discovery of α-synuclein in extracerebral tissues such as the gut or the peripheral nervous system has increased excitement about possible biomarkers and their potential utility in making the diagnosis of PD earlier on. With potentially earlier diagnosis comes increased hope for early interventions with yet-to-be developed disease-modifying drugs and compounds.

Despite increased knowledge about the role of α-synuclein and Lewy bodies in PD, the challenges in making more progress toward disease-modifying therapies has become a sticking point for many in the scientific and clinical Parkinson communities. Although not a new idea, the call to question the prevailing clinicopathologic model of PD has been increasing in its intensity. Emerging now is the idea that the quest for disease-modifying therapies should not rely solely on defining PD by aggregates of α-synuclein but instead consider that the underlying mechanisms for what clinicians define as PD may be myriad. Thus, the future of therapeutic offerings in PD may be similarly varied and tailored to patients’ individual Parkinson syndromes, which are defined molecularly rather than clinically.

In this issue we feature emerging information about the role of acetylcholine in gait and gait dysfunction by Alex Dalrymple, MD. One need not treat many patients with PD before encountering the disability and frustration that can come with the difficulties inherent to gait instability and dysfunction. This frustration is compounded by the often overwhelming or downright inexcusable impact of levodopa and other dopaminergic therapies for this disabling issue. Dalrymple’s article builds upon a larger body of research that has demonstrated that degeneration in cholinergic nuclei and dysfunction of cholinergic systems may underlie many of the disabling clinical features of PD that fail to respond to standing dopaminergic therapies.

The work to build a more complete and effective armamentarium of therapies for PD will be complex. With increased understanding of the nondopaminergic neurophysiologic mechanisms that result in the constellation of clinical manifestations in PD, there is hope that we can develop more therapies that target the non–dopamine-responsive symptoms that have frustrated patients, families, and clinicians alike. In addition, with evolution in the conceptual framework of the underlying molecular mechanisms in PD, perhaps there will follow more ready development of disease-modifying therapeutics for individuals with PD. These therapeutics may rely less on our eyes and hands in defining someone’s clinical syndrome and more on an individualized molecular profile that guides selection of therapeutic options. Ultimately, with an open mind as well as expanding innovation in clinical trial design, there is a reason for optimism in the Parkinson community.

REFERENCES

FROM THE EDITOR


With hereditary transthyretin-mediated (hATTR) amyloidosis...

Patients and their families face a future of functional decline¹-³

**Important Safety Information**

**Infusion-Related Reactions (IRRs)**

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

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

**Reduced Serum Vitamin A Levels and Recommended Supplementation**

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

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

**Adverse Reactions**

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

Please see brief summary of full Prescribing Information following this ad.

References:
4. ONPATTRO Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease\(^4\)

An RNAi-based approach that may transform the future for your patients\(^1,4-6\)

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

Study Design

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

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

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

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

At 18 months, ONPATTRO demonstrated:

**Reversal in neuropathy impairment**\(^4\)

- LS mean change from baseline in mNIS+7 of -6.0 points vs 28.0 with placebo, a treatment difference of -34 points (95% CI: -39.9, -28.1; p<0.001)

**Improvement in quality of life**\(^4\)

- LS mean change from baseline in Norfolk QoL-DN score of -6.7 points vs 14.4 with placebo, a treatment difference of -21.1 points (95% CI: -27.2, -15.0; p<0.001)

**Reduction in autonomic symptoms**\(^6,7\)

- LS mean change from baseline in COMPASS 31 of -5.3 points vs 2.2 with placebo, a treatment difference of -7.5 points (95% CI: -11.9, -3.2; p<0.001)

Visit [www.onpattrohcp.com](http://www.onpattrohcp.com) to get your patients started.
ONPATTRO® (patisiran) lipid complex injection, for intravenous use

Initial U.S. Approval: 2018

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

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

DOSEAGE AND ADMINISTRATION
Dosing Information
ONPATTRO should be administered by a healthcare professional. ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight. For patients weighing less than 110 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks. For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

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

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

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

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRs [see Warnings and Precautions (5.1) in the full Prescribing Information].

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache [see Adverse Reactions (6.1) in the full Prescribing Information]. Severe hypotension and syncope have been reported as symptoms of IRs in the expanded access program and postmarketing setting. Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion [see Dosing and Administration (2.2) in the full Prescribing Information]. Monitor patients during the infusion for signs and symptoms of IRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

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

Reduced Serum Vitamin A Levels and Recommended Supplementation
ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum vitamin A levels do not reflect the total vitamin A in the body.

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

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

A total of 224 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received ONPATTRO in the placebo-controlled and open-label clinical studies, including 186 patients exposed for at least 1 year, 137 patients exposed for at least 2 years, and 52 patients exposed for at least 3 years. In the placebo-controlled study, 148 patients received ONPATTRO for up to 18 months (mean exposure 11.7 months).

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

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

Table 1: Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of ONPATTRO-Treated Patients and at Least 3% More Frequently than in Placebo-Treated Patients

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

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

Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or muscleskeletal pain); flushing (including erythema of face or skin warm); nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

Not part of an infusion-related reaction.

Includes dyspnea and exertional dyspnea.

Includes bronchitis, bronchiolitis, bronchitis viral, lower respiratory tract infection, lung infection.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Ocular adverse reactions that occurred in 5% or less of ONPATTRO-treated patients in the postmarketing experience included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of ONPATTRO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
ONPATTRO® (patisiran) lipid complex injection, for intravenous use

Symptoms of infusion-related reactions have included syncope [see Warnings and Precautions (5.1)] and pruritus.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

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

Data

Animal Data

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (15 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

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

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific surrogate (15 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Lactation

Risk Summary

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Hepatic Impairment

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

Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73 m²) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

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

Recommended Vitamin A Supplementation

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

Pregnancy

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

Pregnancy Exposure Registry

Women may register themselves in the program by calling 1-877-256-9526 or by contacting alnylampregnancyprogram@iqvia.com.

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TTI02-USA-00517-V2
Focal Epilepsy Cell Therapy Gets IND Clearance, Set for Phase 1/2 Trial
By Marco Meglio

NRTX-1001 (Neurona Therapeutics), an inhibitory neuronal cell therapy derived from human pluripotent stem cells, has received an investigational new drug (IND) clearance from the FDA and may now proceed with its first-in-human phase 1/2 clinical trial in patients with drug-resistant mesial temporal lobe epilepsy (MTLE).

This multicenter trial will evaluate the safety, tolerability, and efficacy of single-administration NRTX-1001 in 2 stages. The first is an open-label dose escalation study with up to 10 participants with MTLE, whereas the second stage is a randomized, blinded investigation comparing the safety and efficacy of the cell therapy with a control group in a cohort of 30 participants with MTLE. Delivered as a 1-time dose, NRTX-1001 is designed to secrete the inhibitory neurotransmitter γ-aminobutyric acid (GABA), providing long-term GABAergic inhibition to repair hyperexcitable neural networks that underlie epilepsy and other central nervous system disorders. Neurona indicated that it intends to focus on NRTX-1001 as a restorative treatment for MTLE.

The only data on NRTX-1001 have come from preclinical models, in which treatment with the cell therapy resulted in seizure-freedom for more than two-thirds of the population compared with 5% of the control group. Additionally, investigators observed signs of reduced mesial temporal sclerosis, or tissue damage in the affected seizure-onset area of the brain, with treatment from NRTX-1001.

In November, the company presented preclinical data at Neuroscience 2021, the annual meeting of the Society for Neuroscience. In an intrahippocampal kainate epilepsy mode, investigators were able to establish a baseline progression of hippocampal damage that is important to the characterization of NRTX-1001. Furthermore, in the same model, treatment with NRTX-1001 was found to be well-tolerated and maintained efficient interneuron cell engraftment and disease-modifying activity when combined with anti-seizure medications levetiracetam (Keppra; UCB Pharma) and diazepam (Libervant; Aquestive Therapeutics).

The final abstract showed that NRTX-1001 transplantation into the hippocampus stably suppressed focal seizures and significantly reduced hippocampal pathology in the mouse model of MTLE over a 7-month period. No unwanted behavioral effects were observed as a result of treatment. Additionally, the interneuron cells from NRTX-1001 persisted and distributed in the hippocampus throughout the course of the study and were not proliferative.

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

Device Gets Breakthrough Designation in MCI
By Matt Hoffman

The FDA has granted breakthrough device designation to Renew Biosciences’ Cerezen Device for the treatment of mild cognitive impairment (MCI) due to Alzheimer disease (AD) and mild AD dementia, according to a company announcement.

The nonpharmacologic and noninvasive technology is designed to improve cerebrovascular health through the enhancement of circulation and the simulation of vigorous exercise’s physiological effects and endothelial cell function. The pathology of AD has long been associated with cerebrovascular risk factors, with Renew citing the role that cerebral blood flow and endothelial function are believed to play.

The device’s process begins with securing the inflatable cuffs to the patient’s hips, thighs, and calves; followed by inflating the cuffs to

Phase 3 PHOENIX Study in ALS Starts
By Marco Meglio

The first patients have been dosed in the phase 3 PHOENIX study (NCT05021536), a global study evaluating the safety and efficacy of AMX0035 (Amylyx Pharmaceuticals), an investigational agent for patients with amyotrophic lateral sclerosis (ALS), according to a company news release.

PHOENIX will span across approximately 65 sites in Europe and the US and will enroll 600 participants with clinically definite or clinically probable ALS within 24 months from symptom onset. This differs from the previously completed phase 2/3 CENTAUR trial (NCT03127514), which included those who received a definite ALS diagnosis within 18 months of symptom onset.

Over a 48-week period, investigators will assess the primary outcome of change on ALS Functional Rating Scale-Revised (ALSFRS-R) scale and survival. This randomized, placebo-controlled trial also will assess secondary efficacy outcomes such as change in slow vital capacity, measured both at home with a self-administered spirometer to support virtual data collection and at clinical sites; serial assessments of patient-reported outcomes; ventilation-free survival rates; and more.

The news comes less than a week after the company submitted a new drug application (NDA) to the FDA for AMX0035 for ALS. Amylyx’s hope is that the findings from PHOENIX will build upon the compelling findings from CENTAUR, which were the basis for the NDA.

In CENTAUR, participants were randomized 2:1 to AMX0035 (3 g of sodium phenylbutyrate and 1 g of taurursodiol per sachet) or matching placebo, administered twice daily by mouth or feeding tube for a planned duration of 24 weeks. During the placebo-controlled phase, investigators documented a 44% lower risk of death for those on study drug compared with placebo (HR, 0.56; 95% CI, 0.34-0.92).

Additional data from CENTAUR indicated that AMX0035 met its primary efficacy end point, with a reported ALSFRS-R score of 2.32 points higher than placebo (P = .03) over 24 weeks. There was also a 2.92-point higher mean ALSFRS-R score for the AMX0035 group (P = .01) and a –1.24 points per month change in total ALSFRS-R score compared with –1.66 points per month with placebo (difference, 0.42 points per month [95% CI, 0.03-0.81]; P = .03).

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

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The difference between donanemab and placebo in the change from baseline in Clinical Dementia Rating Scale—Sum of Boxes score was –0.36 (95% CI, –0.83 to 0.12). Additionally, the difference among groups was –1.86 (95% CI, –3.63 to –0.09) on Alzheimer’s Disease Assessment Scale–Cognitive subscale, 1.21 (95% CI, –0.77 to 3.20) for Alzheimer’s Disease Cooperative Study–Instrumental Activities of Daily Living, and 0.64 (95% CI, –0.40 to 1.67) for Mini-Mental State Examination score.

Lilly seeks to have donanemab approved under the same accelerated pathway as Biogen’s aducanumab (Aduhelm). Aducanumab’s approval in June represented a major step for the AD community, as it became the first novel DMT approved for the treatment of this disease since 2003. Under the accelerated approval pathway, Biogen is required to conduct postapproval phase 4 studies to confirm the benefit of the drug, for which some have already been announced.

Enrollment for TRAILBLAZER-ALZ 4, which will compare donanemab’s ability to clear brain amyloid plaque with aducanumab, is expected to begin this year. The company has not released any information on the specifics of the trial, including target enrollment and when updates may become available. Patients assessed in TRAILBLAZER-ALZ are still participating in the ongoing follow-up trial, TRAILBLAZER-EXT (NCT04640077). The safety, tolerability, and efficacy of donanemab are also being evaluated in the ongoing, randomized, placebo-controlled, double-blind, multicenter phase 3 TRAILBLAZER-ALZ 2 study (NCT04437511).

Eli Lilly Initiates Rolling Submission in Therapy for Early Alzheimer Disease

By Marco Meglio

Eli Lilly has announced that it has initiated rolling submission of a biologics license application (BLA) for donanemab, an investigational antibody therapy, to the FDA for accelerated approval in early Alzheimer disease (AD). Additionally, the company announced plans to conduct TRAILBLAZER-ALZ 4 (NCT05108922), a phase 3 head-to-head trial comparing donanemab with aducanumab (Aduhelm; Biogen), the most recently approved disease-modifying therapy (DMT) for patients with early AD.

In June, the company announced that the FDA had granted breakthrough therapy designation for donanemab, along with announcing the plan to submit a BLA. The basis for the decision was data from the phase 2 TRAILBLAZER-ALZ study (NCT03367403), which showed that when compared with placebo, donanemab slowed the progression of AD.

At the time of the original data announcement, Daniel Skovronsky, MD, PhD, chief scientific officer and president of Lilly Research Laboratories, expressed his confidence in the results in a company statement. “The constellation of clinical and biomarker results indicates the potential for long-term disease modification,” Skovronsky said.

The phase 2 trial, which evaluated the efficacy and safety of the investigational agent in 272 patients with early-stage, symptomatic AD, showed a 32% slower decline on the Integrated Alzheimer’s Disease Rating Scale compared with placebo from baseline to 76 weeks. Furthermore, investigators found that donanemab, by targeting N3pG β-amyloid, reduced amyloid plaque by an average of 78%, or an 84-centiloid reduction at 76 weeks compared with a baseline of 108 centiloids.

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

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JOURNAL ROUNDUP

Voice Quality May Be Characteristic in Patients With Cluster Headache

By Marco Meglio

Using a digital voice analysis, investigators found patients with cluster headache (CH) to have significantly lower second harmonic values compared with healthy controls (HC), suggesting they can be characterized by a creaky voice phonation. This type of creaky voice was associated with vocal cord edema underlined by laryngopharyngeal reflux.

The cross-sectional study evaluated whether it was possible to identify typical voice quality in male patients with CH (n = 20) by matching them with HCs (n = 13). Clinical experiences with patients with CH who have demonstrated this low voice quality also factored in the reasoning behind the study.

Patients had voice quality examined using traditional measures of fundamental frequency, calculations of jitter and shimmer, and noise-to-harmonics ratios as well as quantities related to the spectral tilt (ie, H1–H2, H1–A1, H1–A2, and H1–A3). These measures were calculated based on the production of stressed vowels extracted from digitally recorded reading tasks done inside a soundproof insulated cabin in the laboratory of the Audiology Department at the University of Campania in Italy.
At the conclusion of the study, patients with CH showed a significantly lower difference between the amplitude of the first harmonic (H1) and the amplitude of the second harmonic (H2) compared with HC (~6.9 ± 7.6; P = .002). Even after using age and smoking status as covariates, Quade rank analysis confirmed the pattern seen in these patients (Quade test = 7.84; P ≤ .01).

After undergoing videolaryngostroboscopy, 100% of patients with CH had chordal edema, compared with 15% of HC (P < .001). Furthermore, all patients with CH showed marked signs of laryngopharyngeal reflux, 14 of the 15 patients with CH showed a marked bilateral chordal edema, and 6 showed a mild bilateral chordal edema.

Of note, 1 patient had signs of asymmetrical chordal vibration and insufficient chordal adduction. In contrast, 10 of the 13 HCs demonstrated a normal laryngeal picture, whereas 2 had mild bilateral chordal edema, and 1 was excluded due to the poor quality of the laryngoscopy examination. Moderate signs of laryngopharyngeal reflux were observed in just 2 HCs.

CNM-Au8 Shows Efficacy in ALS Despite Failing to Reach End Points
By Marco Meglio

Newly announced topline results from RESCUE-ALS (NCT04098406), a phase 2 clinical trial evaluating CNM-Au8 (Clene Nanomedicine) in patients with amyotrophic lateral sclerosis (ALS), showed that the investigational agent did not meet its primary or secondary end points in change of motor unit number index (MUNIX) biomarker and forced vital capacity (FVC), but did show a MUNIX efficacy signal after 12 weeks of treatment.1

Clene noted that it expects to report results from the HEALEY ALS Platform Trial (NCT04297683), which involves several different investigational agents, including CNM-Au8, in the second half of 2022. RESCUE-ALS, a 36-week, placebo-controlled trial, included 45 patients with ALS who were randomized 1:1 to either 30 mg daily of CNM-Au8 or matching placebo on top of standard of care. As a catalytically active gold nanotherapeutic that drives cellular energy, CNM-Au8 represents a unique approach to ALS care. The agent is designed to produce reactions in the brain that enable neuroprotection and remyelination through increasing neuronal and glial resilience to disease-relevant stressors.

Change in MUNIX, a neurophysiological biomarker that estimates the number of functioning lower motor neurons serving selected muscles, was found to be nonsignificant at the end of the treatment period; however, investigators noted an efficacy signal observed at week 12 (P = .057). In a subset of patients with limb onset ALS, which accounts for approximately 70% of the ALS population, CNM-Au8 showed a significant treatment effect in MUNIX at week 12 (P = .057), with a trend for improvement at week 36 (P = .0741).

At week 36, patients treated with CNM-Au8 demonstrated significant benefits in several exploratory end points, including slowing ALS disease progression (P = .0125), decreasing the proportion of participants with an ALS Functional Rating Scale Revised 6-point decline (P = .035), and improving quality of life as measured by the ALS Specific Quality of Life (P = .018).

The oral treatment was found to be well-tolerated in RESCUE-ALS, with no serious adverse events (SAEs) related to study drug occurring. Aspiration pneumonia (n = 3) and transient gastrointestinal distress (n = 2) were among the most frequently reported AEs associated with CNM-Au8 treatment.

This news comes on the heels of a September 2021 announcement from Clene that it had launched its second FDA expanded access program (CNM-Au8.EAP02) with CNM-Au8 for patients with ALS. This was launched in conjunction with the Healey ALS Platform Trial, after the first expanded access program (CNM-Au8.EAP01), also launched in partnership with the Sean M. Healy & AMG Center for ALS in Boston, Massachusetts. The first program supports access to the investigational agent for 40 individuals with ALS, with enrollment that began in September 2019 and long-term participants now treated for more than 100 weeks.2

CNM-Au8 is also being evaluated for several other neurological disorders, including multiple sclerosis and Parkinson disease. The phase 2 REPAIR clinical trials showed that the treatment can significantly improve brain energetic metabolism in both of these patient groups. REPAIR, which includes REPAIR-MS (NCT03993171) and REPAIR-PD (NCT03815916), resulted in statistically significant increases by an average of 0.589 units (10.4%) in the mean change in the brain ratio of oxidized nicotinamide adenine dinucleotide to reduced nicotinamide adenine dinucleotide after 12 weeks of treatment.3

Dose-Dependent Link Between Parkinson Disease and Physical Activity Is Identified
By Marco Meglio

An analysis featuring more than 10,000 individuals with Parkinson disease (PD) found an inverse association between physical activity (PA) and all-cause mortality as well as an inverse dose-response association between the total PA amount and mortality.

In this nationwide population-based cohort study, 10,699 individuals with PD who were aged 40 years or older were asked to self-report on PA levels using structured questionnaires. Patients were included from January 1, 2010, to December 31, 2013, and were followed up until December 31, 2017. The investigators calculated the total metabolic equivalent of task (MET) minutes per week to quantify the total PA amount. The MET ratings of 3, 5, and 8 were assigned to light-intensity, moderate-intensity, and vigorous-intensity activities.

Among the total cohort followed up for 8 years, there were 1823 deaths (mortality rate, 17%). For individuals who were physically active, investigators observed a significantly reduced mortality risk. After adjusting for confounding variables, Cox proportional hazard regression models for mortality showed HRs of 0.80 (95% CI, 0.69-0.93) for vigorous-intensity PA.
PA, 0.66 (95% CI, 0.55-0.78) for moderate-intensity PA, and 0.81 (95% CI, 0.73-0.90) for light-intensity PA.

From those in the first MET quartile (< 90 MET minutes per week) to the fourth quartile (≥ 820 MET minutes per week), multivariate Cox proportional hazards regression analysis identified a progressively decreasing risk of mortality (HR, 0.61 [95% CI, 0.53-0.70]; P < .001). Furthermore, log-rank test revealed a significant inverse association between mortality rate and total amount of PA in individuals with PD (P < .001).

Physically active participants who continued their PA after receiving a diagnosis of PD showed the greatest reduction in mortality rate for all PA intensities (vigorous: HR, 0.66 [95% CI, 0.50-0.88]; moderate: HR, 0.49 [95% CI, 0.32-0.75]; light: HR, 0.76 [95% CI, 0.66-0.89]). Individuals who started PA after receiving their diagnosis showed a lower mortality rate (vigorous: HR, 0.82 [95% CI, 0.70-0.97]; moderate: HR, 0.69 [95% CI, 0.57-0.83]; light: HR, 0.86 [95% CI, 0.78-0.98]).

A subgroup that looked at variables such as age, sex, alcohol consumption, smoking, and body mass index (BMI) on associations between PA and mortality were all nonsignificant, and the inverse association between PA and mortality remained consistent. Increased mortality was associated with age (HR, 1.07 [95% CI, 1.06-1.07]; P < .001), disability registration (HR, 1.92 [95% CI, 1.66-2.23]; P < .001), and Charlson Comorbidity Index (HR, 1.13 [95% CI, 1.11-1.16]; P < .001), whereas female sex (HR, 0.53 [95% CI, 0.48-0.58]; P < .001) and BMI (HR, 0.94 [95% CI, 0.92-0.95]; P < .001) were associated with reduced mortality.

There were several limitations, including the fact that study only included those who underwent health checkups within 2 years before and after receiving a diagnosis, making it possible that only individuals with PD who were relatively healthy or had health-seeking behaviors were enrolled in the analysis. Additionally, there could be recall bias, as all collected PA information was from self-reported questionnaires. Lastly, the analysis did not include caffeine consumption and dietary habits, nor did it include antiparkinsonian medication use.

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

Cenobamate Continues to Show Durable Efficacy in Reducing Seizure Frequency
By Marco Meglio

Two newly published post hoc analyses from the phase 3 open-label safety study C021 (NCT02535091) showed that long-term treatment with cenobamate (Xcopri; SK Life Sciences) provided safe and effective reduction of seizure frequency and was associated with concomitant antiseizure medication (ASM) dose reductions.1,3

Study C021 was a multicenter study assessing the safety of cenobamate as adjunctive therapy in 1340 adults, aged 18 to 70 years, with uncontrolled focal seizures and taking 1 to 3 ASMs. Cenobamate, an FDA-approved medication for partial-onset seizures, was initiated at 12.5 mg per day and increased at 2-week intervals to 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg per day for at least 6 months.

The first study included 255 patients, 240 of whom had focal aware motor, focal impaired awareness, or focal to bilateral tonic-clonic seizure data available during treatment. In total, 74% (n = 177) of patients remained on the study drug throughout the entire analysis period (media exposure, 2.7 years). During the entire maintenance treatment period, which included 214 patients, 13.1% (n = 28) of those achieved 100% seizure reduction whereas 40.2% (n = 86) achieved at least a 90% reduction. Additionally, 36.3% (n = 87) of patients had 100% reduction for at least 12 consecutive months during the study.2

For the total treatment duration, 71.7% (n = 172) of patients experienced at least 50% response rate to treatment. During titration, these rates were 48.1% during weeks 1 to 4 (12.5-25 mg/day cenobamate) and 61.7% during weeks 5 to 8 (50-100 mg/day cenobamate). Common treatment-emergent adverse events (AEs), which included fatigue (34.6%), dizziness (32.1%), and somnolence (29.6%), were consistent with those in patients from the primary study.

The second post hoc analysis reported on how patients adjusted baseline ASMs while taking cenobamate. The most commonly reported baseline concomitant ASMs were lacosamide (Vimpat; UCB), levetiracetam (Keppra; UCB), lamotrigine (Lamictal; GSK), zonisamide (Zonegran; Eisai), and clobazam (Onfi; Lundbeck). For these ASMs, mean dose reductions and percentage change in dose from baseline to last dose were greater in patients continuing cenobamate vs those who discontinued.3

The greater retention rate for these ASMs—ranging from 71.9% to 78.9% for patients who continued cenobamate and from 21.1% to 28.1% for those who discontinued the study drug—were observed for those who had larger concomitant ASM dose reductions. The percent dose change ranged from −65.8% to −23.4% for those continuing the study drug compared with −7.8% to −25.0% for those who discontinued. The findings suggest that “the cenobamate efficacy was not impaired by decreasing the dose of concomitant ASMs, and that cenobamate tolerability may have improved with greater concomitant ASM dose reductions,” according to investigators.

Among patients continuing cenobamate, 24.6% (97 of 395) completely discontinued 1 or more of their concomitant ASMs. Lacosamide, levetiracetam, and perampanel (Pycompa; Eisai) were the ASMs discontinued in the greatest number of patients overall, with 18, 13, and 11 patients, respectively, discontinuing these concomitant ASMs completely.

Percentages of responders by concomitant ASM in the maintenance population (n = 214) ranged from approximately 75% of patients with at least 50% response to approximately 13% for 100% response. For those who continued the study drug at cutoff with concomitant ASM, approximately 81% were at least 50% responders and approximately 12% achieved 100% reduction in seizures for the entire maintenance phase. Investigators wrote that “the duration …was much longer than what is typically reported in open-label long-term extension studies that provide 100% seizure reduction rates.”3

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

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CLINICIANS’ ROLE IN ADDRESSING THE NEUROLOGIST SHORTAGE: JENNIFER MAJERSIK, MD, MS

The division chief of vascular neurology at the University of Utah discussed the impact that clinicians and neurologists can have, individually, in increasing interest in the field of neurology.

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TREATING THE ROOT OF MULTIPLE SCLEROSIS WITH ATA188: BRIDGET A. BAGERT, MD, MPH

After ATA188 showed potential remyelination effects, the director of the Multiple Sclerosis Center at Ochsner Health offered her perspective on the latest data for this agent in progressive multiple sclerosis.

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RAPID AI’S EFFECT ON STROKE IMAGING

Gregory W. Albers, MD, director, Stanford Stroke Center, and Coyote Foundation Professor of Neurology and Neurological Sciences, Stanford Medical Center, shared insights into the development and clinical use of RapidAI, which he founded. It is a platform that leverages artificial intelligence to create enhanced, high-quality images from noncontrast CT, CT angiography, CT perfusion, and MRI diffusion and perfusion data, aiming to expedite diagnoses, treatment, and transfer decisions.

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ALTERING THE VIEW OF MULTIPLE SCLEROSIS WITH A TOPOGRAPHICAL MODEL

Stephen Krieger, MD, professor of neurology, Icahn School of Medicine, and staff neurologist, Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai, discussed the development of his topographical model of multiple sclerosis and how it had been leveraged to this point, also offering insight into a recently initiated effort with it that he presented recently.
Learn from distinguished experts in multiple sclerosis care with our clinical mentorship series, *The Ever-Changing Face of MS*. The first 4 episodes are now available on-demand, including:

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INDICATION

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

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

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

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

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

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

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

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

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.

**IMPORTANT SAFETY INFORMATION (CONT)**

**Infections**

MAYZENT may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred. Before starting MAYZENT, review a recent complete blood count (CBC) (ie, within 6 months or after discontinuation of prior therapy). Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy. Consider discontinuing treatment if patient develops a serious infection. Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with MAYZENT. If CM is suspected, MAYZENT should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

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

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

**Macular Edema:** In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.
FOR PATIENTS WITH FIRST SIGNS OF PROGRESSION IN RMS AND ACTIVE SPMS

STAY AHEAD OF PROGRESSION WITH MAYZENT®
(siponimod)

MAYZENT IS THE FIRST AND ONLY oral DMT studied and proven to delay disability progression in a more progressed RMS population, including active SPMS.*†

THE DUAL MOA OF MAYZENT targets S1P1,5—2 key receptors thought to play a role in RMS inflammation and neurodegeneration.13,6

WITH INTERIM EXPLORATORY DATA UP TO 5 YEARS from an open-label extension study aiming to evaluate long-term safety and tolerability, as well as efficacy measurements, respectively, in the EXPAND extension study.8

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

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

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

IMPORTANT SAFETY INFORMATION (CONT)

Bradyarrhythmia and Atrioventricular Conduction Delays:
Prior to initiation of MAYZENT, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects. MAYZENT was not studied in patients who had:
• In the last 6 months, experienced myocardial infarction,
• Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
• New York Heart Association Class II-IV heart failure

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

Bradycardia and Atrioventricular Conduction Delays (cont):
- History of or observed at screening, unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class la or Class III anti-arrhythmic drugs

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

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

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

Cutaneous Malignancies: Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended. Monitor for suspicious skin lesions and promptly evaluate any that are observed. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended.

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

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

References:

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NOVARTIS

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East Hanover, New Jersey 07936-1080
©2021 Novartis 2/21 MZT-1400690
MAYZENT® (siponimod) tablets, for oral use
Initial U.S. Approval: 2019

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

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

4 CONTRAINDICATIONS
MAYZENT® is contraindicated in patients who have:
- A CYP2C9/3’/3’ genotype [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5) in the full prescribing information].
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, uncompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS
5.1 Infections
Risk of Infections
MAYZENT® causes a dose-dependent reduction in peripheral lymphocyte count to 20% to 30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT may therefore increase the risk of infections, some serious in nature [see Clinical Pharmacology (12.2) in the full prescribing information]. Life-threatening and severe fetal infections have occurred in association with MAYZENT.

In Study 1 [see Clinical Studies (14) in the full prescribing information], the overall rate of infections was comparable between the MAYZENT-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infection were more common in MAYZENT-treated patients. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT-treated patients compared to 2.5% of patients receiving placebo.

Before initiating treatment with MAYZENT, results from a recent CBC (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

Initiation of treatment with MAYZENT should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period [see Warnings and Precautions (5.12)].

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT should be considered if a patient develops a serious infection.

Cryptococcal Infections
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have also occurred with MAYZENT. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. MAYZENT treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Herpes Viral Infections
Cases of herpes viral infection, including one case of reactivation of VZV infection leading to varicella zoster meningitis, have been reported in the development program of MAYZENT. In Study 1, the rate of herpetic infections was 4.6% in MAYZENT-treated patients compared to 3.0% of patients receiving placebo. In Study 1, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT-treated patients compared to 0.7% of patients receiving placebo.

Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT [see Vaccinations below].

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

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

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

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

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT and for 4 weeks after stopping treatment [see Drug Interactions (7.1)].

Vaccinations may be less effective if administered during MAYZENT treatment. MAYZENT treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema
Macular edema was reported in 1.8% of MAYZENT-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT.

Continuation of MAYZENT therapy in patients with macular edema has not been evaluated. A decision on whether or not MAYZENT should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus
Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during MAYZENT therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT, the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

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

MAYZENT was not studied in patients who had:
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), or uncompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Congenital or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second degree AV-block or higher grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)].

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

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

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

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

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

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

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

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

- For patients taking other drugs that decrease heart rate, treatment with MAYZENT should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate [see Dosage and Administration (2.4) in the full prescribing information and Drug Interactions (7.4)].

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

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

5.4 Respiratory Effects

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

5.5 Liver Injury

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

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

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

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

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking MAYZENT, caution should be exercised when using MAYZENT in patients with a history of significant liver disease.

5.6 Cutaneous Malignancies

Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). In Study 1, the incidence of BCC was 1.0% in MAYZENT-treated patients. Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended in patients taking MAYZENT.

5.7 Increased Blood Pressure

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

5.8 Fetal Risk

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

5.9 Posterior Reversible Encephalopathy Syndrome

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

5.10 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating MAYZENT.

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

5.11 Severe Increase in Disability After Stopping MAYZENT

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

5.12 Immune System Effects After Stopping MAYZENT

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

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy [see Clinical Pharmacology (12.2) in the full prescribing information]. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 3 to 4 weeks after the last dose of MAYZENT [see Drug Interactions (7.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

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

6.1 Clinical Trials Experience

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

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

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate of at least 1% higher than in patients receiving placebo.
Table 3: Adverse Reactions Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate of At Least 1% Higher Than in Patients Receiving Placebo)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MAYZENT 2 mg (N = 1099)</th>
<th>Placebo (N = 546)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Transaminase increased</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Falls</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Terms were combined as follows:
- Headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache
- Hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased
- Alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased
- Edema peripheral, joint swelling, fluid retention, swelling face
- Bradycardia, sinus bradycardia, heart rate decreased
- Pain in extremity and limb discomfort

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

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

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

Vascular Events
Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.0% of MAYZENT-treated patients compared to 2.8% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

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

7. Drug Interactions
7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies
MAYZENT has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration [see Warnings and Precautions (5.1)].

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects [see Warnings and Precautions (5.10)].

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

7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate
MAYZENT has not been studied in patients taking QT prolonging drugs.

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

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., vabradine, digoxin) [see Warnings and Precautions (5.3) and Drug Interactions (7.3)]. If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

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

7.4 Vaccination
During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination [see Warnings and Precautions (5.1)]. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT [see Warnings and Precautions (5.1)].

7.5 CYP2C9 and CYP3A4 Inhibitors
Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., ritonavir/ritonavir) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor.

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

7.6 CYP2C9 and CYP3A4 Inducers
Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause strong CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer.

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

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended in patients with CYP2C9*1/3 and *2/3/*5 genotype [see Clinical Pharmacology (12.3) in the full prescribing information].

8. Use in Specific Populations
8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman [see Data]. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital, and skeletal) in rats and in embryofetal death, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

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

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

Data
Animal Data
When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post-implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, the only dose with fetuses available for evaluation. A no-effect dose for adverse effects on embryo-fetal development in rats was not identified. Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose of 0.6 mg/day.

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

When siponimod (0, 0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual maturation were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m² basis.

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

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

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

8.5 Geriatric Use
Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 CYP2C9 Genotype
Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4% to 0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod [see Dosage and Administration (2.3) and Clinical Pharmacology (12.5) in the full prescribing information].

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

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

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Swank, Wahls Diets May Reduce Fatigue and Cognitive Dysfunction in MS

By Matt Hoffman

IN THE RECENT RANDOMIZED, parallel-arm WAVES study (NCT02914964), the utilization of either the Wahls or Swank elimination diets for individuals with multiple sclerosis (MS) led to significant reductions in fatigue and cognitive dysfunction for both groups.1

At 12 weeks, the Swank diet group (n = 38) reported total Perceived Deficits Questionnaire (PDQ) scores of 25.1 (± 2.00) compared with 32.4 (± 2.36) at baseline, whereas the Wahls group (n = 39) reported total scores of 29.1 (± 2.71) compared with 35.9 (± 2.16) at baseline, both being a significant improvement (P ≤ .05). At 24 weeks, those scores remained significant at 26.1 (± 2.14) and 25.1 (± 3.03), respectively (P ≤ .05).

Tyler Titcomb, PhD, RDN, IFMCP, postdoctoral scholar at Wahls UIHC Clinical Research Lab at University of Iowa in Iowa City, presented the data at the 2021 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting. He explained that plans to further assess these diets are ongoing, with an expected follow-up study in the coming months that will include both a control group and MRI measures.

Titcomb noted that the improvements reported by both the Wahls diet and Swank diet groups may be driven by a similar mechanistic action brought on by each diet, and he emphasized the urgent need to identify this mechanism.

"Studies are ongoing right now to try to tackle this," Titcomb said in his presentation. "Possible mechanisms of these [diets] include modulation of the microbiome, inflammation, the immune system, or micronutrient optimization. The key thing to note about dietary intervention studies in multiple sclerosis is that we do not know if diet [affects] disease activity or not."

Although these data were not presented at CMSC 2021, body mass index also was significantly reduced for both groups—from 27.6 (± 0.94) for the Swank group and 30.2 (± 1.3) for the Wahls group at baseline—which Titcomb noted may also be a mechanistic driver of the improvements reported by each group. "There is plenty of evidence to show that weight loss can be beneficial [to patient-reported outcomes]," he said.

Titcomb also noted that a reduction in sodium intake, likely driven by the avoidance of processed foods, may have helped influence these reductions, and that data on both of these facets were submitted to be presented at the Americas Committee for Treatment and Research in Multiple Sclerosis 2022 Forum.

The planning, prospective memory, retrospective memory, and attention portions of the PDQ scores for both groups were also significantly changed. The Swank group reported 12-week scores of 6.81 (± 0.66), 5.03 (± 0.46), 6.16 (± 0.58), 7.08 (± 0.54), respectively, compared with 8.50 (± 0.65), 6.63 (± 0.57), 8.11 (± 0.71), and 9.20 (± 0.64) at baseline (P ≤ .05 for all). For the Wahls group, 12-week scores of 7.24 (± 0.79) on planning, 6.37 (± 0.57) on prospective memory, 7.63 (± 0.80) on retrospective memory, and 7.87 (± 0.71) on attention were reported, compared with 9.46 (± 0.67), 7.33 (± 0.52), 9.33 (± 0.60), and 9.79 (± 0.57), respectively, at baseline (P ≤ .05 for all).

“One thing to note about these figures is that if you look in the literature, the typical [patient] with MS has a PDQ score of [approximately] 46, so participants in both groups tended to be lower than what you would see in the general MS population,” Titcomb said.
In addition to their baseline values of 32.4 and 35.9 for the Swank and Wahls groups, respectively, scores after the 12-week run-in prior to baseline were similar, at 33.1 (± 2.50) and 35.1 (± 2.24). In recent years, additional literature has suggested that the Mediterranean diet may be an effective dietary intervention for patients with MS.2, 3 With this in mind, Titcomb noted that the choice to assess these 2 diets was driven by their key differences but also their similarities—the recommendations of fruit and vegetable consumption and avoidance of processed food, which Titcomb called their “most important” aspects.

“If you look at the whole of dietary intervention studies, they all have significant improvements because they all recommend those 2 things,” he explained in the question-and-answer portion of the session. “One of the key things [in the WAVES study] is the principle of Wahls elimination diet is based on paleo diet principles, which recommend the avoidance of grains, whereas the Swank diet recommends quite a bit of consumption of grains, so they’re drastically different in that regard.”

The Swank diet focuses on low saturated-fat intake, with all vegetable consumption and avoidance of processed food, which Titcomb called their “most important” aspects.

“If you look at the whole of dietary intervention studies, they all have significant improvements because they all recommend those 2 things,” he explained in the question-and-answer portion of the session. “One of the key things [in the WAVES study] is the principle of Wahls elimination diet is based on paleo diet principles, which recommend the avoidance of grains, whereas the Swank diet recommends quite a bit of consumption of grains, so they’re drastically different in that regard.”

The Swank diet focuses on low saturated-fat intake, with all vegetable consumption and avoidance of processed food, which Titcomb called their “most important” aspects.

REFERENCES


MS Wellness Programs Significantly Improve Quality of Life

By Abby Reinhard

DATA PRESENTED AT THE 2021 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting showed that patients with multiple sclerosis (MS) who participated in weekly wellness programs had significant improvements in quality of life (QOL).

At baseline, investigators, led by Brian Hutchinson, PT, MSCS, director of the Multiple Sclerosis Achievement Center (MSAC), Dignity Health, in Sacramento, California, included a total of 110 patients with MS who participated in weekly wellness sessions via the MSAC. Patient-reported outcome (PRO) measures were used to determine improvements in self-reported disease impact and QOL over a 3-year period. A total of 86 patients were included in the 2-year data, collected in January 2019, and 62 patients were included in 3-year data, collected in January 2020.

When comparing the initial analysis with 3-year data, results showed that some effects emerged at the 1-year mark and were sustained through the 3-year period. Others did not emerge until the 2-year follow-up mark; these also were maintained at 3 years.

The programs, conducted weekly by the MSAC, included group exercise, education, cognitive stimulation, and socializing and community outings. The Multiple Sclerosis Impact Scale (MSIS-29), Multiple Sclerosis Self-Efficacy Scale-10 item (MSSE), and Godin Leisure-Time Exercise Questionnaire were included as outcome measures, with the Neuro-QoL used for questions about anxiety, depression, emotion and behavior, positive affect, cognition, ability to participate, and social roles.

Investigators found statistically significant improvement in several Neuro-QoL sections, including ability to participate at year 2 (P = .02) and at year 3 (P = .004), as well as social roles at year 2 (P = .001) and at year 3 (P = .004). Significant changes were also seen in the MSSE (P = .02) and the MSIS (P = .03), according to 3-year data analyses. It was noted that depression and emotional behavioral dyscontrol were statistically significant when compared with scores at the 1-year mark, but scores were not significant when compared with baseline measures. At both the 1-year and 2-year analyses, investigators found correlations between PRO measures of self-efficacy, ability to participate, and positive affect.

REFERENCE
Ocrelizumab Has Long-Term, Positive Effects on MS Symptoms, Productivity

By Alicia Bigica

SWITCHING TO OCRELIZUMAB from other disease-modifying treatments (DMTs) for multiple sclerosis is associated with improvements in work productivity and a decrease in overall symptom burden, according to an analysis from the phase 3b CASTING trial (NCT02861014).

The findings were presented by Gary Cutter, PhD, professor emeritus of biostatistics at the University of Alabama at Birmingham, at the 2021 Consortium of Multiple Sclerosis Centers Annual Meeting.

Cutter and colleagues set out to quantify the effects on work productivity and activity impairment that switching to ocrelizumab (Ocrevus, Genentech) had on patients with MS over a 2-year period. In this analysis, 680 patients with MS with a suboptimal response to 1 or 2 prior DMTs received 600 mg intravenous ocrelizumab every 24 weeks for 96 weeks, during which changes in the Work Productivity and Activity Impairment (WPAI) questionnaire, 29-item Multiple Sclerosis Impact Scale (MSIS-29), and SymptoMScreen (self-reported symptom burden) were assessed at baseline, week 24, year 1, and year 2.

Of note, patients had an Expanded Disability Status Scale score of 4 or less. From baseline to year 3, significant reductions in overall work impairment and activity impairment were recorded as improvements in WPAI (Δ−3.08, P = .020; Δ−5.69, P < .001), with consistent trends noted in work time missed (Δ−2.54, P = .102) and impairment while working (Δ−1.66, P = .129). As such, improvements in WPAI correlated with improvements in total SymptoMScreen score, including work time missed (r_s = 0.196), impairment while working (r_s = 0.387), overall work impairment (r_s = 0.362), and activity impairment (r_s = 0.421) over 2 years (all P < .01).

Additional correlations were observed between improved in MSIS-29 physical and psychological subscores and reductions in work time missed (physical: r_s = 0.181; psychological: r_s = 0.198), impairment while working (physical: r_s = 0.457; psychological: r_s = 0.361), overall work impairment (physical: r_s = 0.386; psychological: r_s = 0.343), and activity impairment (physical: r_s = 0.524; psychological: r_s = 0.384) over 2 years (all P < .01). Overall, the findings demonstrate ocrelizumab’s association with improvements in physical and psychological aspects of MS over the long term.

REFERENCE

Optimized Conversations May Improve Outcomes in Patients With MS

By Abby Reinhard

CONVERSATIONS BETWEEN health care providers (HCPs) and patients with multiple sclerosis (MS) should be open and optimized to best suit the patient’s needs while also building trust and an understanding of a shared decision-making process, findings from a new study suggest.

Cortnee Román, FNP-C, of the Rocky Mountain Multiple Sclerosis Clinic and Research Group in Salt Lake City, Utah, and Bryan Walker, MHS, PA-C, of the Department of Neurology at Duke University School of Medicine in Durham, North Carolina, presented these findings at the 2021 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting.

Four practical strategies to be adopted and implemented by HCPs were proposed: (1) utilize plain-language techniques, (2) implement teach-back, a communication method to ensure patients understand the information being provided to them, (3) use open-ended questions, and (4) practice active listening/paraphrasing. These suggestions were developed following the discovery that better conversations were supported by patient resources outlining the basics of health care.

When discussing previous conversations with patients, the group of advanced practice provider investigators found that there were several recurring themes, including specific information to look for and where, reliable and unreliable sources, and overpromising language. Investigators noted that when patients were misinformed, it was often fueled by information found online or information that came from social media.

“Robust health literacy, defined by the Centers for Disease Control and Prevention as the degree to which an individual…”
Inadequate Data Are Available Regarding Cannabis Use in MS

By Marco Meglio

ALTHOUGH MOST PATIENTS WITH multiple sclerosis (MS) have discussed cannabis with their physician, only 12% of patients consider their physician their primary source for medical guidance on the matter, suggesting that inadequate medical and clinical information sources are available to these patients and their health care providers, according to results of a recent survey. There currently are no tetrahydrocannabinol-containing FDA-approved medications for physicians to prescribe for patients with MS.

Lead author Robert Fox, MD, a neurologist at the Mellen Center for Multiple Sclerosis and vice chairman for research at the Cleveland Clinic Neurological Institute in Ohio, and colleagues conducted a supplemental survey on cannabis use in 1012 North American Research Committee on Multiple Sclerosis Registry participants, in which 9019 patients with MS completed a questionnaire regarding health

and by current users (45%). After dispensaries, dealer/friend (29%), product label (24%), and certificate of analysis (13%) were the most used sources from the entire cohort. Health care provider was reported by 9% of ever users.

Among current users, 62% reported that they typically get the cannabis they use from dispensaries, whereas 18% said family/friend, 13% said acquaintance, and 7% said someone grows it for them. Growing it on their own (6%), dealer (5%), online (4%), and other (3%) rounded out the methods of acquiring cannabis.

Investigators also questioned patients on what the most important factors were when selecting a source from which to purchase cannabis. The most common answers were perceived quality and safety (70%), access to preferred potency or formulation (40%), and location (39%), among others.

In the survey, cannabis/marijuana referred to products from the cannabis/marijuana plant, which included smoking, vaping, eating, ingesting, or any other form of use. The study also excluded hemp cannabidiol (CBD) or products marketed as CBD only.

REFERENCE


FOLLOW US ON SOCIAL MEDIA for more clinical practice resources
North American, European Registry Data Show Impact of COVID-19 on Patients With MS

By Abby Reinhard

AT THE 2021 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting, Anne H. Cross, MD, a professor of neurology and the Manny and Rosalyn Rosenthal – Dr. John Trotter MS Chair in Neuroimmunology at Washington University in St. Louis, Missouri, presented registry data on the effect of COVID-19 on patients with multiple sclerosis (MS), as well as the impact of individual disease-modifying therapies (DMTs) on the severity of COVID-19 outcomes.

Registry data from a multitude of sources, including the COVID-19 Infections in MS & Related Diseases (COViMS) registry in North America (n = 3452) and European registries (n = 1787), suggest that patients with MS who are older, are male, have greater disabilities, or have comorbidities are likely to develop more-serious cases of COVID-19 if they contract the infection.

In North America, with every 10 years of age, risk of death increased by 87.5% (P < .0001), whereas being male increased the risk of death by 2.2 times (P < .0077). Black patients in North America also had risk increased by 2.5 times for hospitalization, admission to the intensive care unit (ICU), and use of a ventilator, but not an increased risk of death, when compared with White and Hispanic patients.

Data further suggested that worse COVID-19 outcomes were associated with B-cell depleting agents, as well as treatment with methylprednisolone in the prior month to contracting the virus. According to electronic medical record data, those taking glatiramer acetate (Copaxone) and β-interferons had a reduced incidence of the virus. Those taking β-interferons also had better COVID-19 outcomes if they contracted the virus.

Combined registry data suggest that although worsening of preexisting symptoms is commonly reported, this is not universal and there is no evidence that COVID-19 causes true exacerbations or the onset of MS itself. Cross commented on this in her presentation, stating, “My conclusion after looking through the literature is that we need more studies—that would be the first one—and we need better studies.”

A question about COVID-19 vaccination was added to the COViMS registry on April 27, 2021. According to data through October 5, 2021, 240 patients who had COVID-19 in 2021 addressed the question: 100 (42%) had not been vaccinated, 99 (41%) had been vaccinated, and 41 (17%) had unknown vaccination status.

While addressing the potential for bias, Cross noted that patients who were taking ocrelizumab (Ocrevus; Genentech) had no significant reduction in hospitalization after vaccination. As of November 11, 2021, 95 deaths from COVID-19 have been reported in the COViMS registry, all in the United States. Of those, 8 patients were vaccinated, with most (n = 6) receiving the Pfizer/BioNTech COVID-19 mRNA vaccine. Of those 8 patients, 5 were on a B-cell depleting agent.

Cross also discussed recommendations for treating high-risk patients with MS who contract COVID-19, highlighting the use of anti–SARS-CoV-2 monoclonal antibodies. She called attention to the use of casirivimab/imdevimab (REGEN-COV; Regeneron), which decreased patients’ risk of being hospitalized by more than 80%.

Cross also presented data from an Italian MS registry of patients with suspected or confirmed COVID-19 infection (n = 844), prior to vaccination, which reported an overall mortality rate of 1.5% (13 deaths). Of the patients who died, 11 had progressive MS and 5 were being treated with DMTs.

This registry found that anti-CD20s, including rituximab (Rituxan; Genentech/Biogen) and ocrelizumab, were associated with a more severe course of COVID-19, and recent use of methylprednisolone was associated with worse outcomes, both conclusions that also were drawn from the North American registry. More recent pooled data from Italy and France of confirmed COVID-19 cases found that those patients on anti-CD20s had higher rates of hospitalization, ventilation, stay in the ICU, and death, when compared with those on β-interferons.

In North America, the COViMS registry was developed to address the gap in information on COVID-19 infections in patients with MS. Health care providers enter patient data for those with confirmed or suspected COVID-19 infection after a minimum of 7 days. Data collection began on April 1, 2020, and data presented at CMSC 2021 spanned through October 15, 2021.

Certain limitations of registry data were highlighted by Cross, including the possibility of ascertainment bias, as patients information was voluntarily submitted, as well as differences in behavior across populations over time and geographical region. There also have been alterations in treatment of COVID-19 since the onset of the pandemic and the emergence of new virus variants. Data may have been skewed by patients taking DMTs receiving the vaccine at difference rates, Cross said.

With new COVID-19 virus strains and additional waves of disease, Cross further stressed the importance to log data in the registry, as well as to monitor outcomes and DMT interactions for this patient population.

REFERENCE

Ocrelizumab Shows Safety for Treating MS in Older Patients and Individuals With Disabilities

By Matt Hoffman

**FOR PATIENTS WITH** multiple sclerosis (MS) who have higher baseline levels of disability and those who are older, treatment with ocrelizumab (Ocrevus; Genentech) does not appear to be associated with a higher rate of adverse events (AEs), according to the real-world results of ACAPELLA, a single-center, prospective study.

Presented in a poster at the 2021 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting, the data show that patients with an Expanded Disability Status Scale (EDSS) score of 6 or higher (n = 82) had a slightly higher rate of urinary tract infections (UTI), but no increased incidence of infections (45%; n = 37) or herpes simplex virus (HSV) 1 or 2 (5%; n = 4) compared with the overall population of 354 patients (Infections: 36% [n = 126]; HSV-1 or HSV-2: 8% [n = 28]). Similar results were observed for the group 55 years and older (n = 134) for rates of both HSV-1 and HSV-2 (7%; n = 28) and overall moderate infections (37%; n = 49).

All told, 5% (n = 17) of the cohort experienced serious infection that required hospitalization, though no correlations with age or disability were observed in this group. Patients who were older and had greater disability reported serious infection at a rate of 6% (n = 3), whereas those with only more disability and those who were older reported rates of 7% (n = 6) and 2% (n = 8), respectively.

“Ocrelizumab and other anti-CD20 antibodies generally have an excellent safety profile. Concerns have been raised about the potential for increased risk of infection, hypogammaglobulinemia, and malignancy with long-term use,” Ellen S. Lathi, MD, codirector of The Elliot Lewis Center for Multiple Sclerosis Care in Wellesley, Massachusetts, and colleagues wrote. “Although our hypothesis was that older and/or more disabled patients might have higher rates of AEs, thus far in our cohort of 354 patients treated with [ocrelizumab] for up to 4 years, this was not observed.”

Study coauthor Elizabeth Douglas, MPH, clinical research coordinator at The Elliot Lewis Center, told NeurologyLive® that “in older and/or more disabled patients, there was a trend toward higher risk for UTI but no increased risk for other infections or malignancy.”

For the combined group of those 55 years and older with an EDSS score of 6 or greater, rates of moderate infection and HSV-1/2 were 44% (n = 21) and 8% (n = 4), respectively. Herpes zoster was not present in any individuals in the EDSS of 6 or greater group nor the combined group of those 55 years and older with an EDSS of 6 or greater, though the group 55 years and older experienced a similarly low rate (2%; n = 3) compared with the overall group (3%; n = 9).

Overall, the majority of patients (53%; n = 188) in the study were on at least their fifth cycle of ocrelizumab treatment, equating to 24 months of therapy. Additionally, 41% (n = 144) had completed their sixth cycle, or 30 months, and 5% (n = 30) were on their seventh cycle, or 36 months of therapy.

Of the total patient population, 64.1% (n = 227) had relapsing MS and 35.8% (n = 127) had progressive disease, with respective mean ages of 44 years and 56 years and respective mean EDSS scores of 2.5 and 5.0. The total cohort had a mean age of 48 years, with a mean EDSS score of 3.5.

“Six patients developed malignancies of different types,” Lathi et al wrote, adding that “in our study, malignancies occurred at a rate similar to that observed in the general MS population. These incidences were reported as grade II estrogen/progesterone receptor-positive ductal carcinoma in situ (n = 1), stage T2b adenocarcinoma of the prostate (n = 1), stage IIIb colon cancer (n = 2), colorectal cancer met to the liver (n = 1), and squamous cell carcinoma of the neck (n = 1). The majority of these patients—save for 1 with stage IIIb colon cancer—were at least 3 months past their most recent dose.

Incidences of breakthrough disease, defined as clinical relapse and/or new MRI activity, were also low (3%; n = 12), as were rates of mild to moderate postinfusion symptoms or prolonged malaise (6%; n = 22). None of the postinfusion symptoms were deemed related to early B-cell reconstitution.

“The ACAPELLA trial is a prospective, observational study that includes those patients who would fall outside of the parameters specified in clinical trials,” Lathi and colleagues wrote. “In addition to AEs, ACAPELLA substudies are evaluating the impact of [ocrelizumab] on immunoglobulin levels, CD19 reconstitution, and JC virus antibody titers. Interim data analyses occur on a biennial basis and findings will be reported annually.”

**REFERENCE**

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**Gait Dysfunction in Parkinson Disease: The Role of the Cholinergic System**

By W. Alex Dalrymple, MD
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**PARKINSON DISEASE (PD) IS THE** most common neurodegenerative movement disorder, affecting approximately 0.1% to 0.2% of the population and approximately 1% of individuals 60 years or older. PD manifests through a multitude of symptoms, including the classic quartet of bradykinesia, cogwheel rigidity, resting tremor, and impairment of gait and balance. Other nonmotor symptoms include cognitive dysfunction, psychosis, hallucinations, and constipation. Although there are a handful of definitive genetic causes of PD, most patients with PD have an idiopathic form of the disease. As a chronic, progressive, and degenerative condition, PD leads to a significant burden on health care resources and society as a whole, one that is expected to increase in the future as the nation’s percentage of elderly patients increases.

By the early 1960s, PD pathophysiology was determined to be due to dopamine deficiency in the striatum, which was a direct result of neuronal loss in the substantia nigra. Combination carbidopa-levodopa, in various formulations, remains the gold standard treatment of many of the motor features of PD to this day, and it is especially effective in treating bradykinesia, rigidity, and tremor. Gait dysfunction, on the other hand, remains more difficult to treat.

**More Than Just Dopamine**
Although dopaminergic deficiency is seen as the primary driver of most of the motor symptoms of PD, gait dysfunction often responds poorly to dopaminergic therapies. This prompted investigators to look for other potential underlying mechanisms of symptom development in PD, including investigations of cholinergic degeneration. In 2003, Bohnen et al used positron emission tomography (PET) to show that there is actually greater in vivo cortical cholinergic dysfunction in PD dementia than in Alzheimer dementia. Subsequent studies revealed that cholinergic degeneration is also closely associated with gait dysfunction, balance impairment, and falls. Dopaminergic degeneration in PD seems to lead to a loss of gait automaticity, thus requiring more sustained attention from individuals and placing a greater burden on the neocortical cholinergic system. When there is concurrent cholinergic degeneration, significant gait dysfunction occurs.

There are 3 main sources of acetylcholine within the brain. The first is the basal forebrain, including the nucleus basalis of Meynert, which has widespread projections to the neocortex, thalamus, and striatum. The second is the pedunculopontine nucleus (PPN) within the brainstem, which projects mainly to the cerebellum, thalamus, and basal forebrain. Third, cholinergic interneurons are present within the striatum and help to regulate dopaminergic pathways. In general, degeneration of the basal forebrain leads to cortical cholinergic denervation, whereas degeneration of the brainstem (especially the PPN) leads to thalamic cholinergic denervation.

Unfortunately, it can be difficult to quantify cholinergic degeneration because the major nuclei (basal forebrain, PPN) lack clear borders on standard imaging techniques. Until recently, most studies investigating cholinergic degeneration in PD have relied on PET or short latency afferent inhibition (SAI; a transcranial magnetic stimulation-based measure of motor cortex function dependent on thalamocortical cholinergic input) to quantify the degree of degeneration of the cholinergic nuclei. Results of a 2009 study showed that patients with PD who fall frequently had similar rates of striatal dopaminergic degeneration compared...
with nonfallers, but that they had significantly worsened thalamic cholinergic degeneration compared with nonfallers.\(^9\) Thalamic acetylcholine, as mentioned above, largely arises from the PPN in the brainstem, thus it was surmised that this finding represents degeneration of the PPN in patients with PD and frequent falls. These results were replicated in a similar study in 2010.\(^8\)

Although degeneration of the PPN and subsequent thalamic cholinergic denervation have been implicated in increased fall risk in PD, degeneration of the basal forebrain and subsequent cholinergic denervation of the neocortex have been implicated in reduced gait speed in PD.\(^10\)-\(^12\) Investigators in a study in 2013 used PET imaging to show that patients with PD and reduced cortical cholinergic innervation had slower gait speeds compared with those with PD without evidence of cholinergic degeneration and compared with healthy controls.\(^10\) Of note, there was no difference in nigrostriatal dopaminergic degeneration between the 2 PD groups, thus clarifying that cortical cholinergic degeneration is a large driver of the difference. In another study, SAI was used as a surrogate marker of cholinergic activity. The results showed that loss of SAI is associated with reduced gait speed, stride length, and stride time deviation in patients with PD.\(^11\) Recently, an MRI-based method has been described to quantify degeneration of cholinergic nucleus 4, one of the major cholinergic nuclei within the basal forebrain.\(^12\) This method also confirmed an association between cholinergic degeneration and reduced gait speed in a retrospective cohort of patients with PD undergoing work-up for deep brain stimulation.

Given this evidence, the cholinergic system becomes an obvious therapeutic target for improving gait dysfunction in PD.

**Treatment Implications**

Three studies have investigated the effect of cholinesterase inhibitors on falls in PD.\(^18\)-\(^20\) All 3 were phase 2, randomized, double-blind, and placebo controlled. The first, published by Chung et al in 2010, enrolled 23 patients with PD who were falling at least 2 times per week. Utilizing a crossover design, the participants received either donepezil or placebo for 6 weeks, followed by a 3-week washout and then a crossover. The primary outcomes of the study were self-reported falls and near-falls. Fall frequency was 0.25 (± 0.08) per day on placebo versus 0.13 (± 0.03) on donepezil \((P = .049)\), whereas the frequency of near-falls did not significantly differ across the treatment and placebo phases. That said, the statistical significance of this study was driven in large part by those participants who fell most often at baseline having rather dramatic improvements in their number of falls, whereas the majority of participants did not show a significant improvement.\(^18\)

The second, published by Li et al in 2015, enrolled 176 patients with PD (with and without cognitive dysfunction) and randomized the patients with evidence of cognitive dysfunction to either receive rivastigmine or placebo for 1 year. At baseline, the number and incidence of falls increased with worsening cognition. After 1 year of either rivastigmine or placebo treatments, patients in the rivastigmine group had both higher Montreal Cognitive Assessment scores \((P = .002)\) and fewer falls \((P < .01)\).
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Why Gait Matters

**PATIENTS WITH PD OFTEN** experience postural instability, reduced gait speed, reduced stride length, slower turns, freezing of gait, and falls.\(^5^,\(^2^2\) These various forms of gait dysfunction are often quite disabling, and can be a primary driver of accumulation of disability for many patients. Results of a 2008 study showed that axial impairment, defined as the combination of postural instability and gait dysfunction, was the primary contributor to disability as measured through 3 different scales. Gait dysfunction and postural instability accounted for 31% to 37% of the variance in these metrics. Additionally, gait dysfunction and postural instability were major drivers of decreased quality of life, accounting for 44% of the variance in measures of social functioning, and 55% of the variance in overall quality of life.\(^2^3\) Falls, which often arise as a consequence of postural instability and gait dysfunction, are a major contributor to injury and comorbidity as well as to caregiver burden.\(^2^4\) Results of a separate study indicated that decline in gait function was closely associated with worsening quality of life,\(^2^5\) whereas results of another study revealed that gait dysfunction was a predictor of cognitive decline in early PD.\(^2^6\)

Results of a recent review showed that up to 25% of patients will experience a hip fracture within 10 years of receiving a diagnosis of PD due to gait dysfunction. In addition, the results showed that minor injuries such as bruises, joint dislocations, and skin lacerations are common. Fear of future falls often restricts daily activities, leading to a loss of independence and worsened social isolation. Falls and immobility are closely associated with admission to nursing homes, thus increasing the socioeconomic burden of disease. Most worrisome is that patients with significant gait and balance impairment have increased mortality risk. Average survival is reduced to 7 years once recurrent falls are present.\(^2^7\)

Current treatments for gait dysfunction are few and far between. Levodopa, dopamine agonists, catechol-O-methyl transferase inhibitors, monoamine oxidase type B inhibitors, and adenosine antagonists do not have data supporting their use for gait.\(^2^8\) Amantadine may be associated with improvement in freezing of gait,\(^2^9\) but more evidence is needed. Anticholinergic agents, although useful for tremor, can actually worsen freezing of gait.\(^2^3\) Deep brain stimulation (regardless of target) has shown mild benefit in some gait metrics, mainly related to improvement in bradykinesia, but has not shown efficacy in improving freezing of gait,\(^3^0\) and in some instances can worsen gait dysfunction.\(^3^1\) A dedicated physical therapy regimen seems to be the current treatment with the best evidence in improving gait and reducing falls.\(^3^2\)

**Next Steps**

Determining evidence-based treatments to help gait and balance and to reduce falls in PD is of utmost importance. If the above results can be replicated on a larger scale in phase 3 trials, then cholinesterase inhibitors would likely be adopted as standard of care for the treatment of gait dysfunction in PD. Determining consistent, validated, and clinically relevant outcome measures will be necessary for the adoption of cholinesterase inhibitors in standard practice.\(^1^7\) Many studies investigating falls have relied on the retrospective reporting of patients and family members. Perhaps as wearable devices become more mainstream, it will be easier to gather objective data on falls and near-falls in this patient population.

It is also possible that patient selection has been imperfect. In the study by Chung et al in 2010, the statistically significant results were largely driven by only a handful of super-responders, which begs the question of exactly why those particular patients responded so robustly and others not at all.\(^1^8\) None of the above studies used quantified measures of cholinergic degeneration at baseline, which could potentially serve as a biomarker of sorts to determine if cholinesterase inhibition would be useful in any given patient.

Alternatively, it is conceivable that cholinesterase inhibition is not adequate. In treating the other motor symptoms of PD, true dopaminergic supplementation (levodopa, dopamine agonists) provides a much more robust symptom response than medications that inhibit metabolizing enzymes (catechol-O-methyl transferase inhibitors, monoamine oxidase type B inhibitors).\(^3^3\) Similarly, perhaps the degree of cholinergic degeneration needed to significantly impair gait would itself hinder the effect of cholinesterase inhibitors, as there simply could be little to no acetylcholine produced in the brains of affected patients. Since acetylcholine is a ubiquitous neurotransmitter throughout the body, it may be a challenge to develop targeted therapies that act solely on the brain.

Finally, future studies should seek to better understand the underlying mechanism of cholinergic degeneration and its relationship with dopaminergic degeneration in PD. It is likely that cholinergic degeneration, although clearly associated with gait dysfunction and falls, is but another piece of the complex pathophysiological puzzle that is PD.
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MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.
DRAVET SYNDROME (DS) IS A rare form of childhood-onset epilepsy that affects approximately 1 in 30,000 people worldwide.1-5 DS significantly impacts individuals throughout their lifetime and increases the risk of Sudden Unexpected Death in Epilepsy.1-3 DS seizures are often febrile and prolonged, generalized or unilateral, and clonic or tonic-clonic.4,6 These prolonged seizures, which begin in infancy,4,6 eventually contribute to developmental delays, cognitive and behavioral impairments, impaired quality of life, and increased mortality.2-3 DS is particularly difficult to treat because it is often drug resistant (refractory).2,7 DS is often nonresponsive to currently approved antiepileptic drugs (AEDs).1,2 There is thus a need for novel, innovative, and safe AEDs for DS.7

DS is a heterogeneous disease that can arise from de novo mutations of genes involved in neurotransmission.1,6 Approximately 70% to 80% of patients with DS carry de novo mutations in SCN1A, which encodes a neural voltage-gated sodium channel and is the most clinically relevant epilepsy gene.1,4,8 The underlying etiology of epilepsy is an imbalance of central inhibitory (eg, γ-aminobutyric acid; GABA) vs excitatory (eg, glutamate) neurotransmission in the forebrain (Figure).4,8 Prolonged seizures that manifest during childhood are associated with a decrease in GABAA receptor activity and a resulting increase in glutamatergic N-methyl-D-aspartate (NMDA) receptor activity.4,8 In refractory forms of epilepsy such as DS, this NMDA receptor stimulation is deregulated and causes aberrant, unchecked excitatory activity leading to seizures.8 In clinical trials, NMDA receptor antagonists have shown activity in mitigating epilepsy in children and adults; however, their significant adverse effects (AEs) have severely limited their continued use.8

FIGURE. Underlying Etiology of Epilepsy*4,8

Many drugs that elevate brain extracellular 5-HT levels, such as serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors, exhibit antiepileptic effects.9 Specifically, an increase in 5-HT tone is associated with an increased seizure threshold and/or antiepileptic activity, whereas a decrease in 5-HT is associated with a reduced seizure threshold.8 Found in the central and peripheral nervous systems, 5-HT receptors (5-HTRs) are G protein-coupled receptors and ligand-gated ion channels.1 Fourteen subtypes of 5-HTRs are currently known, with strong evidence that the 5-HT2C subtype is involved in seizures.1,9 Among the 5-HTRs, 5-HT2C is a particularly attractive therapeutic target because its expression is restricted to the central nervous system (CNS).7

Preclinical investigations in animal models have validated the efficacy of proprietary 5-HT2CR–targeting therapeutic compounds for DS.10 Animal models are fast, cost-efficient tools for AED screening.11 Important for this approach, all 14 known human 5-HTR subtypes have orthologues in zebrafish, an important model organism for DS research.11 Mutant mice lacking 5-HT2CR experience spontaneous tonic-clonic seizures and a decreased seizure threshold.2,4 Conversely, agonists (stimulants) of 5-HT2CR provide protection against convulsive seizures.8 In humans, reduced levels of 5-HT in the brain similarly result in spontaneous seizures, premature death, and greater sensitivity to convulsants.1

As a result of their global effects on 5-HTRs and other signaling proteins, 5-HTR–targeting AEDs exhibit overwhelmingly harmful off-target effects, which preclude their use in treating DS.8 5-HT2CR and 5-HT2C heteroreceptor complexes are targets for novel anti-absence drugs.9 Agonists of 5-HT2CR, it should be noted, may be hallucinogenic in humans.9 Moreover, some 5-HT2C agonists have been shown to increase seizure length, rather than prevent seizures.9 Some studies suggest that 5-HT2CR is the primary target of DS therapeutics currently in clinical development.1 Overall, there is controversy regarding whether modifying signaling through 5-HTRs (either through agonism or antagonism) can achieve anticonvulsant activity.1,4,8 Investigators are endeavoring to resolve the precise mechanism through which 5-HT is associated with seizure susceptibility; identification of the specific receptors that mediate the effects of 5-HTR-targeting therapies would help guide drug development in this area.1 Of particular importance is understanding which receptors are targeted by each therapeutic because modulating certain receptors’ function (ie, 5-HT2CR) can cause severe AEs.1,3

One 5-HTR–activating drug under investigation is fenfluramine (Fintepla;
Zogenix.\(^1\)\(^3\) Fenfluramine is a racemic mixture of 2 enantiomers, which are metabolized in vivo into compounds with different degrees of affinity for fenfluramine's targets in the 5-HT family: 5-HT\(_{2A}\)R, 5-HT\(_{2C}\)R, and 5-HT\(_{3C}\)R.\(^4\) Fenfluramine functions by stimulating 5-HT release in the brain.\(^3\)\(^4\) Coadministration of fenfluramine with phentermine was once commonly prescribed to promote weight loss in obese patients, but this was found to have significant cardiac AEs—valvulopathy and pulmonary hypertension—possibly due to its effects on 5-HT\(_{2C}\)R.\(^6\)\(^12\)

Fenfluramine exhibits antiepileptic properties and thus diminishes epileptiform discharges in experimental animal models of DS.\(^8\) Fenfluramine is a selective agonist of the receptors—5-HT\(_{1D}\)R, 5-HT\(_{2A}\)R, 5-HT\(_{2C}\)R, and 5-HT\(_{3C}\)R—that mediate seizure risk in animal models.\(^2\)\(^4\)\(^6\)\(^6\) In a preclinical zebrafish study, prolonged use of fenfluramine correlated with increased neurogenesis and stabilized interneuron activity (FIGURE).\(^4\)\(^6\)\(^8\) In a small, open-label trial (add-on treatment), fenfluramine demonstrated a significant reduction in seizures in children with DS; 70% of the patients remained seizure free for more than 1 year.\(^7\) ZK008, a low-dose fenfluramine, has been granted orphan drug designation for DS by the FDA.\(^8\) Phase 3 clinical trials (NCT03355209)\(^13\) with ZK008 are currently ongoing worldwide, with expected completion in March 2024.\(^8\)\(^13\)

Lorcaserin (Belviq; Eisai)\(^14\) is another 5-HT-agonist that is being tested for use as a DS treatment.\(^7\)\(^12\) Lorcaserin was previously marketed as an appetite suppressant.\(^12\) In February 2020, Eisai voluntarily withdrew this drug and discontinued sales in the United States due to findings from a safety clinical trial that showed possible increased occurrence of cancer.\(^15\) Lorcaserin is selective for 5-HT\(_{2C}\)R, which may minimize its safety liabilities compared with drugs, such as fenfluramine, that more broadly target the serotonergic system.\(^7\) In a preclinical zebrafish model, lorcaserin reduced seizures.\(^7\) In a small-scale study in humans, lorcaserin was used to treat 5 patients with medically intractable DS.\(^16\) Seizure frequency was successfully reduced by 65% during the first 3-month treatment period.\(^16\)

The phase 3 MOMENTUM 1 clinical study (NCT04572243), which is expected to be completed by May 2023, is evaluating lorcaserin in patients with DS.\(^17\) MOMENTUM 1 has a target enrollment of 58 patients with DS at 25 sites in the United States and 5 in Canada.\(^17\) Subjects must be 2 years or older, have a diagnosis of epilepsy with DS, and have at least 4 convulsive seizures during the 4-week period before baseline, and currently be on an AED treatment regimen that is stable for at least 4 weeks before screening and is expected to remain stable throughout the study.\(^17\) Exclusion criteria include patients who received lorcaserin or fenfluramine within 4 weeks or 2 months before screening, respectively, have recent or concomitant use of serotonergic medications or monoamine oxidase inhibitors, or currently have progressive CNS disease other than DS.\(^17\) Patients receive oral lorcaserin or placebo twice daily for 14 weeks at 1 of 3 dosages according to body weight.\(^17\) The primary end point, the percent change from baseline in the number of convulsive seizures per 28 days, will be compared between the lorcaserin and placebo groups.\(^17\)

A secondary end point is the percentage of patients with a 50% or greater reduction in the frequency of convulsive seizures per 28 days in the core treatment period compared with baseline.\(^17\) A major goal of MOMENTUM 1 is to characterize the pharmacodynamics of lorcaserin and the relationships between lorcaserin plasma concentrations and efficacy and safety.\(^15\)\(^18\) MOMENTUM 2 (NCT04457687)\(^19\) is an ongoing lorcaserin expanded access program for patients who have completed the MOMENTUM 1 trial or who have refractory epilepsy currently treated with lorcaserin, which was initiated prior to its market withdrawal in February 2020.\(^18\)\(^19\) Patients must experience clinical benefit from lorcaserin use, as determined by their treating physician.\(^19\)

Novel 5-HT\(_{2C}\)R agonists for DS are under development to improve selectivity for 5-HT\(_{2C}\)R over other 5-HTR subtypes.\(^4\)\(^9\)\(^10\) Bright Minds Biosciences released preclinical data in August 2021 on their proprietary 5-HT\(_{2C}\)R agonist BMB-101.\(^10\) BMB-101 showed efficacy against DS-like symptoms in 2 preclinical rodent models (mouse 6-Hz psychomotor seizure model and rat maximum electroshock seizure model) and a zebrafish model (scn1Lab). Lower seizure duration and frequency was observed in the mice, and the zebrafish had reductions in locomotor activity and cumulative duration of epileptiform events in the brain.\(^10\) In the zebrafish model, BMB-101 diminished abnormal brain activity to prevent seizures.\(^4\)\(^10\) The rat model demonstrated meaningful protection against generalized seizures in a dose-dependent manner.\(^10\) BMB-101 exhibited effects similar to those of other AEDs, such as fenfluramine.\(^10\)

Large-scale drug discovery and development should continue leading to improved seizure control outcomes and potentially even reversal of neurodevelopmental defects in patients with DS.\(^2\)\(^12\) For instance, fenfluramine has been determined to do more than just promote 5-HT release.\(^2\) Fenfluramine can also positively modulate activity at sigma-1 receptors (Sigma1Rs), which may play a secondary role in this drug’s antiseizure activity (FIGURE).\(^2\)\(^4\)\(^6\)\(^8\) Additionally, Sigma1Rs may mediate nonseizure comorbidities in the pathophysiology of developmental and epileptic encephalopathies such as DS.\(^2\) Sigma1R is a chaperone protein with diverse functions in maintaining calcium homeostasis in the cell.\(^2\) Similar to 5-HTRs, Sigma1Rs in the brain function to regulate neuronal responses by maintaining the balance between excitatory and inhibitory circuits in neurons and glial cells.\(^2\) The excitatory/inhibitory neuronal imbalance that leads to seizures can trigger Sigma1R activation. Sigma1R is thus a potential novel target for treating seizure-related disorders such as DS.\(^2\) Fenfluramine may positively impact cognition through a Sigma1R-related mechanism.\(^2\) The combined effect of fenfluramine on 5-HTRs and Sigma1Rs may thus be effective in promoting antiseizure activity while improving cognitive function in patients with DS.\(^2\)

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For a full list of references, see the article on NeurologyLive.com.
NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) is an inflammatory autoimmune condition of the central nervous system (CNS) that affects the optic nerves and spinal cord. For many years it was not understood to be a standalone disorder and often was misdiagnosed as multiple sclerosis (MS). But over the past 2 decades, advances in the field of demyelinating disease have led to historically fast progress in the care of patients with NMOSD, and in the past 5 years those advances have resulted in 3 FDA-approved treatments.

NMOSD is distinct from MS mainly in the severity of its associated attacks and its somewhat selective nature of target as well as its prevalence. Although MS affects between 1 in 500 and 1 in 1000 individuals, NMOSD affects approximately 1 in 20,000 individuals. NMOSD usually is diagnosed with the identification of an immunoglobulin antibody directed against aquaporin-4. In the recent NeurologyLive® CURE Connections® series “Managing Neuromyelitis Optica Spectrum Disorders (NMOSD),” a group of individuals from assorted backgrounds—including a physician, an advocacy director, and a pair of patients with the disorder—were brought together in conversation with June Halper, MSN, APN-C, MSCN, FAAN, a certified adult nurse practitioner specializing in MS and CEO of the Consortium of Multiple Sclerosis Centers. Halper inquired about the current state of care for NMOSD and moderated the discussion of varying aspects of treatment, with the patients offering their perspective and sharing their experiences with the disease.

TREATING NMOSD DURING COVID-19
The COVID-19 pandemic has affected the care of patients across the spectrum of disease. Halper asked Brian G. Weinshenker, MD, a consultant neurologist and a professor of neurology at Mayo Clinic, in Rochester, Minnesota, how COVID-19 has changed NMOSD care.

“The question is, what does NMO do to COVID-19, and [what does] the treatment for NMO do to COVID-19, and also does COVID-19 have any effects directly on NMO?” Weinshenker asked. “We generally would suggest [patients get] any COVID-19 vaccines or other vaccines because some of these drugs, such as inebilizumab [Uplizna; Horizon Therapeutics], can make patients very prone to another bacterial infection called meningococcus. We generally want vaccines to be administered before patients start on these treatments. Drugs such as inebilizumab, because it blocks the antibody response, likely would cause some impairment in the vaccine response if given afterward, although it’s likely there would be significant immunity. We encourage all patients with neuromyelitis optica to get the COVID-19 vaccine.”

Weinshenker noted that in recent months, data from studies in Italy and France have suggested that these patients do not face an increased risk of severe COVID-19 infection or mortality from COVID-19. This, he noted, was good news, as many patients take rituximab (Rituxan; Genentech/Biogen) or other therapies that deplete B cells.

“The evidence suggests that there’s minimal, if any, increased risk of getting severe COVID-19 or dying by virtue of being on these therapies,” Weinshenker said. “We’ve not seen any significant increased risk of severe COVID-19 in these patients.”

Halper then asked patient Jacinta M. Behne, MA, the executive director of the Guthy-Jackson Charitable Foundation, how she feels about the data being released on COVID-19 and its impact on patients.

“I think that there’s a lot of important questions that have yet to be answered,” Behne said. “For example, it’s really important that we understand if there’s any increased risk of serious complications from COVID-19 in patients taking the medications that have been approved by the FDA for treating NMO. It’s also important to understand how the pandemic has affected the way we think about how to treat NMO and how we think about how to deliver care to patients.”

Managing and Treating Neuromyelitis Optica Spectrum Disorder

An expert neurologist, advocacy director, and a pair of patients with NMOSD discuss the current landscape of the demyelinating disorder.

By Matt Hoffman
treatments. Generally, we recommend that patients with NMO continue on their NMO treatments and don’t stop them because of fears that they may make COVID-19 worse,” Weinshenker said.

Kim, a patient who had received a diagnosis of NMOSD fairly recently, explained to the group that COVID-19 has certainly influenced her conversations with her doctor. She explained that after getting her first vaccination dose, there was hesitancy about her getting the second and final dose over concerns it might trigger disease activity or relapse.

“We’re going to revisit that this week with my doctor because of everything that’s coming out,” she explained. “I have been especially careful, double masking and everything, and watching my little circle and keeping within my circle of people and knowing that they’re vaccinated. We do what we can to stay safe.”

Navigating NMOSD Infusion-Based Treatment
For patients who have just received a diagnosis of NMOSD, the treatment process can be challenging. Although NMOSD has been differentiated from MS, there can be misdiagnoses and confusion over the complexity of the disease and its treatments. Kim told the group that her journey has been packed with information.

“I’d felt something in my chest like a sharp pain as well as some other burning here. I had gone to an urgent care, and I had also had a stomachache,” she said of her experience at disease onset. “I was sent home [after being told], ‘Oh, just take some medication for constipation.’ That doctor dismissed my symptoms. Within 1 more day, I went to [a different] urgent care, and I’m so happy that I was able to go to [one at] the best hospital. Right away they ran tests and eventually, when I received the diagnosis of NMO, I first received the plasma exchange, which was nerve-wracking.”

Kim explained that she is taking rituximab, and in her first 5 months there has been no recurrence or relapse. “I do feel pain every day because of the spasms, but as far as the relapses—none. I’m due next month in September to have another infusion. I didn’t have any problems before, so it’s just a little bit of a longer time. It does take sometimes between 4 and 6 hours,” she said.

For Doug, another patient with NMOSD, the treatment process was also a little daunting. He explained that he was treated with rituximab and concurrent corticosteroids while undergoing inpatient physical therapy. “Honestly, one of the scariest things of this whole process was when they had to put a jugular device in my neck. That’s a little uncomfortable to have that happen, and I actually had to have it done twice. The actual plex, or the plasmapheresis, for me was not too bad,” he said.

Doug explained that although his experience on rituximab was good because it prevented relapse, he was hospitalized every 4 to 6 weeks with an opportunistic infection, though he now undergoes monthly doses of immunoglobulins to prevent them. Overall, though, his patient journey has been a difficult one.

“I had to learn to walk all over again. I still don’t walk very well. The left side of my body is still pretty numb,” he explained. “I used to play the guitar and the piano, and I just don’t have the dexterity to do that. The plasmapheresis made a difference for me. The steroids didn’t seem to affect me at all, so I’m grateful that Dr Weinshenker developed that process because it made a difference in my life. I likely would be in much worse shape now without that.”

NMOSD Research Programs
The first FDA-approved therapy for NMOSD was a terminal complement inhibitor, eculizumab (Soliris; Alexion), which received approval in 2019. Since, 2 others have joined the treatment paradigm: inebilizumab, a B-cell depleting antibody therapy, and satralizumab (Enspryng; Genentech), an interleukin-6 receptor blocker. Before then, however, patients faced perhaps an even tougher journey with the disease, although advocacy groups pushed for more research. One such group, the Guthy-Jackson Charitable Foundation in Beverly Hills, California, has worked tirelessly to improve the lives of patients.

“We have funded a tremendous body of research, which has resulted in a body of high-impact papers in leading journals. Why? Because we knew that the research had to happen to best help our patient community,” Jacinta M. Behne, MA, executive director of the Guthy-Jackson Charitable Foundation, said. “When I say we’re a research foundation, we’re really a patient-centric foundation learning that we had to help these patients when there were no therapeutics on the shelf.”

Behne described the years of effort to get the pharmaceutical industry involved in the development of therapies for NMOSD, after watching as therapies with potential that could have been repurposed for the condition sat untouched on the shelf. All they needed, Behne said, was to convince 1 company to conduct a clinical trial.

“We made the argument that NMO could be a steppingstone to learning more about MS and other autoimmune diseases. Fortunately, at that time, we began working with the FDA. We knew that they were going to want to support clinical trials,” Behne said. CIRCLES, the first major study from the group, started in 2013 and ended in 2020 after collecting 7 years of patient data and blood specimens from 850 individuals with NMOSD. Now, she added, the group is embarking on a new study, SPHERES (NCT04886492).

“The thing about SPHERES is that we’re working with an organization called CorEvitas. It’s a registry that is accustomed to working with regulatory studies. The end of the trials that have just happened and the therapeutics that just went on the shelf need to pass another phase from the FDA of scrutiny. How safe are they? That’s what SPHERES is all about,” she said.

Although the research is important to Behne and the foundation, she explained that they are also interested in investing in patient quality of life. The Relapse Navigator tool helps patients identify and track their disease activity or relapse.

“Then it’s finally rolled out for all, it’s a tool that will help clinicians adjudicate a relapse. It’s a tremendous instrument, and we’re very grateful for our neurologists for helping this along,” Behne said.
The Impact of Telehealth on Patient Experiences in Sleep Medicine

By Abby Reinhard

WITH THE ONSET OF the COVID-19 pandemic, health care providers initiated the use of telehealth to continue to deliver medical services to patients when stay-at-home and quarantine orders prevented in-person clinical visits. In the field of sleep medicine, the use of telehealth was also employed, and it continues to be developed and adapted as the pandemic persists.

Lucas M. Donovan, MD, MS, spoke with NeurologyLive® about a recent study, which evaluated patients’ experiences using telehealth to receive sleep care, recruiting participants between June 2019 and May 2020. He is an assistant professor in the Division of Pulmonary, Critical Care, and Sleep Medicine at the University of Washington, and core investigator at the Seattle-Denver Health Services Research & Development Center of Innovation, Veterans Affairs Puget Sound Health Care System, Seattle Division. Donovan discussed key findings, with participants reporting both positive and negative experiences with in-clinic video, home-based-video, and telephone telehealth encounters.

Further, Donovan provided insight on the role of telehealth in overcoming barriers to care, particularly geographic divisions for patients in rural areas and avoidance of crowds, which could be anxiety-inducing for this patient population. He also noted that telehealth is not a panacea, and in-person treatment will still be necessary for physical exams and other evaluations, depending on patients’ needs and preferences. Looking forward, Donovan emphasized the need to establish equitable access to care via telehealth, while also striking a balance between in-person settings and developing innovative methods to administer care remotely.

Q: Can you provide an overview of the study? What were the key findings?

The aim of the study was to ascertain a spectrum of patients’ experiences with sleep medicine telehealth encounters and their perceptions of how these telehealth encounters impacted their care. We conducted interviews among 35 VA patients with recent sleep medicine telehealth encounters. These encounters occurred either through in-person clinical visits, where they were in a clinic and with a specialist from another facility, or remote visits where the veteran patient was home and having a teleconference or telephone encounter with a provider.

Through these interviews, we identified 5 overall themes. One was improved access to care. Patients appreciated that telehealth is providing access to sleep care in a timely and convenient manner. Two, security and privacy—patients describe how home health/telehealth afforded them greater feelings of safety and security, due to the avoidance of anxiety-provoking triggers such as crowds. Some patients also noted a potential loss of privacy with telehealth. Third was personalization of care. Patients described experiences with telehealth that either improved or hindered their ability to communicate their needs. Fourth was patient empowerment: Patients described how telehealth empowered them to actually manage their own sleep disorders. And then fifth was unmet needs. Patients recognized specific areas where telehealth did not meet their needs, including the need for tangible services, such as mask fittings for CPAP [continuous positive airway pressure].

Q: Were any of the findings surprising in any way?

Going into these interviews, I expected the patients would discuss how telehealth encounters were either just the same or perhaps slightly worse than in-person [encounters]. And while many patients did find that telehealth encounters mimicked in-person care, or had slight technical downsides, other veterans

LUCAS M. DONOVAN, MD, MS
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expressed how telehealth was actually superior in facilitating good communication with providers. They felt that their providers had fewer distractions over telehealth and were able to answer their questions in a way that felt like it was less pressure with their health, and they could speak their mind more freely, particularly when the encounter was over the telephone.

Q: What was the importance of telehealth following the COVID-19 pandemic? What is going well, and what might need improvement?

I think telehealth is playing an enormous role in helping us overcome barriers to communication between patients and providers. Telehealth helps patients overcome geographic as well as scheduling barriers. Patients don’t need to drive a long distance and spend all that time in the car, or a waiting room, for a 30-minute appointment. In that way, telehealth has played a huge role in helping us reach rural veterans, rural patients, and those with busy schedules due to work or family obligations.

It’s clear that telehealth by itself is not a panacea. Patients in our study highlighted that they still needed tangible services that could not be delivered by telehealth—some patients noted that they had all their questions answered by the provider over telehealth, but even though their questions were answered, they still had difficulty accessing the services that were typically needed, particularly those that were delivered in person, such as mask fittings of CPAP devices. Patients also felt concerned about the lack of a physical exam, and they were wondering what information could be missed.

We also know need to make sure that we have equitable delivery of telehealth. There has been some concern over a digital divide and that we are missing those who do not have access to technology. This includes those who may have lower incomes and resources and may not be able to afford a smartphone or a computer to do a telehealth encounter at home. Also, it could include those who are older or have less experience with technology. The VA is starting to approach this issue directly through home-based clinical video telehealth where the VA will send veterans tablets and provide training if they do not have the equipment. Long term, we need to make sure that these efforts are effective and that we deliver telehealth equitably.

Q: How did telehealth impact patient care during the pandemic? Do you foresee its continued use in years to come?

In sleep medicine, I honestly did not see a major impact to care during the pandemic. From my perspective, as a sleep physician, I have not seen a change in the care that I’m able to deliver through telehealth, vs that which I was able to deliver in-person. The only changes are that I’m able to see more patients through telehealth, I have fewer no-shows in my clinic, and virtually all the visits are able to start on time.

The only negative issues related to the pandemic that I’ve experienced were related to a lack of in-person sleep testing, as we had to avoid in laboratory testing for a while, particularly at the beginning of the pandemic. Since then, we’ve been able to safely reopen our sleep labs. However, the majority of patients with suspected obstructive sleep apnea can be effectively managed at home [with] home sleep apnea tests and auto-titrating CPAP.

In the years to come, I see us continuing to utilize telehealth for most of our patients in sleep medicine, but we should maintain at least a proportion of our clinic grids available for in-person consultation based on patients’ needs and preferences. At our center, we currently maintain about a third of our clinic grids for in-person care, and that seems to be working well. Over time, I anticipate that the proportion of in-person visits will need to be fine-tuned for different centers, based on their capabilities and the patients’ needs.

Q: What does the clinical community need to know about these findings, both in sleep medicine and in general neurology?

Our main takeaway from this study is that patients who experienced telehealth encounters in sleep medicine really tended to appreciate it. I think the main action item that we appreciate from this study is that we do need to pay attention to the areas where telehealth does not meet patients’ needs. For instance, we need to understand where the physical exam is absolutely necessary and identify those patients who need who need to be seen in person. What we can do is we can consider the ways to accomplish the tasks that we typically do in person, such as CPAP mask-fittings, and find ways to do those remotely, and so I would like to see innovation in that field.

With regard to general neurology, I’m a pulmonologist, not a neurologist, so I’m hesitant to make any comments that would be relevant to the wider field of neurology. I do think that adaptations will be necessary for the neurologic exam, in particular, and that will be a really important consideration as to how to do the neurologic exam remotely, but I will leave the specifics to the card-carrying neurologists.

REFERENCE
**ZEPOSIA—FOCUSED ON WHAT COUNTS**

ZEPOSIA was studied in the largest number of patients with RMS in 2 pivotal head-to-head trials against an active comparator (N=2659).¹²³

**POWERFUL Efficacy**
- Proven superior in reducing relapses vs Avonex
- Proven superior in reducing GdE and T2 lesions vs Avonex

**COMPARABLE Safety Profile vs Avonex**
- Consistently low discontinuation rates vs Avonex
- Comparable rates of serious infections and malignancies vs Avonex

**The FIRST AND ONLY S1P With No First-Dose Observation Required**
- Full Prescribing Information for ZEPOSIA has NO FIRST-DOSE OBSERVATION required
- NO genetic testing required
- NO ophthalmic testing required for most patients

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² Study designs: SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (Interferon beta-1a), 30-µg intramuscular injection. Primary endpoint: ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, respectively). Secondary endpoints: ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.²³

³ Adverse reactions: Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. Serious infections: The rate of serious infections at 1 year for ZEPOSIA was 1.1% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. Malignancy rates: The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0.0% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.¹³

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

**IMPORTANT SAFETY INFORMATION**

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

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

**Indication**

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.

**Adverse reactions:**

Overall incidence of adverse reactions for ZEPOSIA reduced the number of new or enlarging T2 lesions vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and 2 years was 74.7% and 83.0%, respectively. Across 2 double-dummy, active treatment-controlled studies of daily (2 years; N=1313) were multicenter, randomized, double-blind, SUNBEAM (1 year; N=1346) and RADIANCE dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-/uni03BCg oral ozanimod 0.46 mg (not approved for maintenance double-dummy, active treatment-controlled studies of daily dose).

**What counts**

**What counts**

**Patient selection**

**Important safety information (continued)***

ZePOSIA was studied in the largest number of patients with RMS with no first-dose observation required.

**Safety profile vs Avonex**

Consistently low discontinuation rates vs Avonex: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, respectively, and at 2 years were 3.0% and 4.1%, respectively. For patients with a history of uveitis or macular edema, an ophthalmic assessment is required. An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.

ZePOSIA did not increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZePOSIA.

**Progressive Multifocal Leukoencephalopathy (PML):**

An opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. No cases of PML were identified in active-controlled MS clinical trials with ZePOSIA. PML has been reported in patients treated with S1P receptor modulators and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZePOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZePOSIA should be discontinued.

**Herpes zoster:**

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 (S1P) receptor modulators. Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation. For patients with a history of uveitis or macular edema, an ophthalmic assessment is required. An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.

**Diabetes mellitus and uveitis:**

Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZePOSIA.

**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:**

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 (S1P) receptor modulators. Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies to VZV before initiating ZePOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZePOSIA.

**Cases of fatal cryptococcal meningitis (CM):**

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:**

Live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZePOSIA.
IMPORTANT SAFETY INFORMATION (CONTINUED)

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

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

Liver Injury: Elevations ofaminotransferases 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 symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

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

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

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

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

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

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

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

**Herpes Viral Infection**

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

**Cryptococcal Infection**

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

**Progressive Multifocal Leuкоencephalopathy**

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

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

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

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

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

**Vaccinations**

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

Vaccinations may be less effective if administered during ZEPOSIA treatment.

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

**Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA.**

**5.2 Bradyarrhythmia and Atrialventricular Conduction Delays**

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

ZEPOSIA was not studied in patients who had:

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

**Reduction in Heart Rate**

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

Initiation of ZEPOSIA without titration may result in greater decreases in heart rate [see Dosage and Administration (2.2)].
In Study 1 and Study 2, bradycardia was reported on the day of treatment initiation in 0.6% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.6% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

5.4 Fetal Risk

Initiation of ZEPOSIA may result in transient atrioventricular conduction delays. At ZEPOSIA exposures higher than the recommended dosage without dose titration, first- and second-degree type 1 atrioventricular blocks were observed in healthy volunteers; however, in Study 1 and Study 2 with dose titration, second- or third-degree atrioventricular blocks were not reported in patients treated with ZEPOSIA.

If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- With significant QT prolongation (QTc > 450 msec in males, > 470 msec in females)
- With arrhythmias requiring treatment with Class 1a or Class 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 with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block [see Contraindications (4)]

5.5 Increased Blood Pressure

In clinical trials, ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked, and ZEPOSIA should be discontinued if significant liver injury is confirmed. Individuals with an AST or ALT greater than 1.5 times ULN were excluded from Study 1 and Study 2. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA, caution should be exercised when using ZEPOSIA in patients with a history of significant liver disease.

5.6 Respiratory Effects

In Study 1 and Study 2, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients who received IFN beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ZEPOSIA and 3.1% of patients who received IFN beta-1a. The median time to an elevation of 3-fold the ULN was 6 months. The majority (79%) of patients continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2-4 weeks.

In clinical trials, ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked, and ZEPOSIA should be discontinued if significant liver injury is confirmed. Individuals with an AST or ALT greater than 1.5 times ULN were excluded from Study 1 and Study 2. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA, caution should be exercised when using ZEPOSIA in patients with a history of significant liver disease.

5.7 Macular Edema

In Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA.

Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus

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

Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a (Pooled Study 1 and Study 2)

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

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

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

ZEPOSIA has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive drugs. Caution should be used when co-administering ZEPOSIA with drugs that have additive effects on immune modulation. Serotonin release from co-administration is not recommended. Monitor patients for hypertension with concomitant use.

### Opioid Drugs

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

### Serotonin Drugs

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

### Symptomimetic Medications

Concomitant use of ZEPOSIA with pseudoephedrine did not potentiate the effects on blood pressure [see Clinical Pharmacology (12.3)]. However, hypertensive crisis has occurred with administration of ZEPOSIA alone [see Warnings and Precautions (5.5)] and hypertensive crisis has been reported with co-administration of serotoninergic medications, including selective and nonselective MAO inhibitors (e.g., rasagiline) and symptomimetic medications.

7.9 Tyramine

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

### Data

**Animal Data**

Oral administration of ozanimod (0, 0.2, 1, 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. At the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0, 0.2, 0.6, or 2.0 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality at the highest dose tested and increased fetal malformations (malformed blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, plasma ozanimod exposure (AUC) was approximately 2 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycle) and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day) for adverse effects on pre- and postnatal development, plasma ozanimod exposure (AUC) was 30 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

### 8.2 Lactation

**Risk Summary**

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

Following oral administration of ozanimod, ozanimod and/or metabolites were detected in the milk of lactating rat at levels higher than those in maternal plasma.
8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

Mutagenesis

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

Impairment of Fertility

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

17 PATIENT COUNSELING INFORMATION

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

Risk of Infections

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

After years of research showing that it demonstrates similar benefit to alteplase, tenecteplase’s benefit in a large patient cohort with acute ischemic stroke will be tested in the TIMELESS trial.

By Marco Meglio

THE PHASE 3 TRIAL CALLED Thrombolysis in Imaging-eligible, Late-window Patients to Assess the Efficacy and Safety of Tenecteplase (TNKase; Genentech), or TIMELESS (NCT03785678), will evaluate tenecteplase, an FDA-approved therapy for myocardial infarction, as a treatment for patients with acute ischemic stroke (AIS).

Tenecteplase is a tissue plasminogen activator (tPA) developed from modifications of natural human tPA complementary DNA. It binds to fibrin-rich clots and cleaves the Arg/Val bond in plasminogen to form plasmin, which then degrades the fibrin matrix of the thrombus, thereby exerting its thrombolytic action. For years, evidence has mounted that tenecteplase could offer similar benefit to alteplase, the only FDA-approved thrombolytic medication for AIS; however, large clinical studies confirming this benefit were still needed.

Approximately 456 participants will be included in TIMELESS, with ordinal modified Rankin scale (mRS) score at 90 days as the primary end point. The investigator team—which includes Gregory W. Albers, MD, director of the Stanford Stroke Center as well as Coyote Foundation Professor of Neurology and Neurological Sciences at Stanford Medical Center—will also assess several other secondary end points. These include proportion of patients with functional dependence, defined as an mRS score of 0 to 2; proportion of patients with angiographic reperfusion; and median National Institutes of Health Status Scale score, among others.1

Patients must be aged at least 18 years, have AIS symptom onset that began within 4.5 to 24 hours, signs and symptoms that are consistent with the diagnosis of an anterior circulation ischemic stroke involving occlusion of the internal carotid artery and/or the M1 or M2 segments of the middle cerebral artery, and be functionally independent (mRS, 0-2) prior to stroke onset (FIGURE).

All patients will receive standard-of-care therapy according to the American Heart Association/American Stroke Association clinical guidelines from 2018. In one treatment arm, patients will receive tenecteplase 0.25 mg/kg administered as a single bolus injection over 5 seconds. Patients in the other treatment arm will receive placebo since a thrombectomy is FDA approved in the United States for use only out to 4.5 hours, and the standard-of-care guidelines support use out to 4.5 hours.

Alteplase, an intravenously (IV) administered medication, has practical issues that have forced clinicians to explore the use of tenecteplase in the acute setting. Thus far, research has suggested that tenecteplase is as efficacious as alteplase with regard to neurologic improvement, and its theoretical advantages include greater fibrin specificity and longer half-life.2

A meta-analysis published in 2019 confirmed these thoughts. Using 5 randomized trials, investigators compared the 2 treatments on freedom from disability, measured by scores of 0 to 1 on mRS at 3 months, as the primary end point. In total, 57.9% of those on tenecteplase (standard 0.1 mg/kg dosing) vs 55.4% of those on alteplase (0.9 mg/kg) achieved this goal.3

Tenecteplase has a few advantages over alteplase. First, administration is more practical: single bolus, vs bolus plus 1-hour infusion with alteplase. Additionally, the administration of alteplase drip requires an IV pump. Not all emergency medical technicians are qualified to manage IV pumps, which may, in certain circumstances, delay or complicate a patient’s interfacility transfer. Tenecteplase also lacks the nonnegotiable risk of symptomatic intracranial hemorrhage, and limited efficacy in the rate of vessel recanalization, especially with large vessel occlusion, that is observed with alteplase.

The results of the EXTEND-IA TNK study (NCT02388061), indicated that treatment with tenecteplase prior to thrombectomy is associated with a higher incidence of reperfusion and better functional outcome. The findings showed that 22% of those treated with tenecteplase vs 10% of those treated with alteplase met the primary end point of at least 50% reperfusion of the involved ischemic territory.4 Three randomized trials have also reported on the disparities in major bleeding between the 2 treatments. In the largest, ASSENT-2, patients with acute myocardial infarction randomized to tenecteplase had reduced rates of noncerebral bleeding complications (26.43% vs 28.95%; P = .0003) and less need for blood transfusion (4.25% vs 5.49%; P = .0002) compared with those on alteplase.5

The 2 treatment options have also been compared in a real-world setting. Results of a pilot observational study published earlier this year confirmed the same neurological improvements seen with tenecteplase over alteplase. This real-world observation included 19 patients on tenecteplase and 39 on alteplase, with the authors concluding that larger studies are needed.

For a full list of references, see the article on NeurologyLive.com
Things You Should Know About Reversal of Anticoagulation in Intracranial Hemorrhage

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Learning Objectives
Upon successful completion of this activity, you should be better prepared to:
- Discuss intracranial hemorrhage (ICH) risk and assessment in patients taking direct oral anticoagulant (DOAC) therapy
- Evaluate the safety and efficacy of reversal agents for DOAC-associated bleeds
- Apply current practice guidelines on DOAC reversal therapies for optimal management of ICH and hemorrhagic stroke

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To learn more about this topic, including information on best care practices for hemorrhagic stroke focusing on DOAC reversal, go to gotoper.com/go/ncsichdoac21
Direct oral anticoagulants (DOACs) are an effective anticoagulant therapy recommended by several guidelines for various indications in the prevention and treatment of thromboembolic disease.1,3 DOAC classes include factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (dabigatran). They are associated with lower risks of stroke, embolic events, and death compared to warfarin, have fewer drug–drug interactions, and do not require routine monitoring or dietary restrictions.4,5 However, increased risk for major bleeding, such as intracranial hemorrhage (ICH), is a safety concern that may require the need for anticoagulant reversal. Here are 3 things you should know about the reversal of DOACs in ICH.

**DOAC reversal strategies address an important need in DOAC-associated bleeding.**

Although DOACs have demonstrated favorable safety and efficacy profiles in the absence of a specific reversal agent, DOAC reversal is warranted during overdose, serious bleeding, or the need for immediate surgery. DOACs have become more widely used over the last several years and are now prescribed at least as frequently as warfarin.6,7 DOACs carry an increased risk of serious bleeding. Approximately 3% to 4% of patients using DOACs experience major bleeding, and approximately 13% of these major bleeds are ICHs.8 At least 900 ICHs are estimated to occur monthly in the United States due to factor Xa inhibitors. ICHs can have a 30-day mortality rate of up to 45%.9 Thus, managing DOAC-associated bleeding events appropriately is important in preventing adverse outcomes including death.

**ICH accounts for 13% of major bleeds in patients taking DOACs.**

Currently available strategies for reversing DOACs include nonspecific agents such as prothrombin complex concentrates (PCCs), antifibrinolytic agents, desmopressin, drug removal from the circulation and/or gastrointestinal tract, and specific reversal agents.9

**There are 2 FDA-approved specific DOAC reversal agents.**

Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran.10 The RE-VERSE AD trial was a cohort study of 503 patients who required reversal of dabigatran due to uncontrolled or life-threatening bleeding (group A) or upcoming surgical or invasive procedure (group B).11 The median maximum percentage reversal was 100% (95% CI, 100–100) within 4 hours of administration, measured by diluted thrombin time and ecarin clotting time. No serious adverse safety signals were detected. The median time to cessation of bleeding was 2.5 hours. At 30 days, the rate of thrombotic events was 5.0% in group A and 4.6% in group B. The 30-day mortality rate was 13.5% in group A and 12.6% in group B.

Andexanet alfa is approved as a reversal agent for rivaroxaban and apixaban.12 It is a recombinant modified form of the human factor Xa protein that acts as a decoy to bind factor Xa inhibitors. It was studied in the ANNEXA-4 trial of 352 patients with acute major bleeding.13 In 134 patients who were taking apixaban, the median anti-factor Xa activity decreased 92% after a bolus of andexanet alfa (95% CI, 91–93). In 100 patients who were taking rivaroxaban, the median anti-factor Xa activity also decreased by 92% (95% CI, 88–94). At 12 hours, 82% of patients evaluated had excellent or good hemostatic efficacy (95% CI, 77–87). The 30-day rate of thrombotic events was 10%, and the 30-day mortality rate was 14%. No other serious safety outcomes were reported.

### FDA-Approved Specific Reversal Agents for DOACs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Approved Indication</th>
<th>FDA Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Reversal of anticoagulant effects of dabigatran when needed for emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding10</td>
<td>October 16, 2015</td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>Reversal of anticoagulant effects of rivaroxaban or apixaban when needed for life-threatening or uncontrolled bleeding12</td>
<td>May 3, 2018</td>
</tr>
</tbody>
</table>

### Clinical guidelines direct use of reversal of anticoagulation in ICH.

Guidelines are available to help direct the management of bleeding and the reversal of anticoagulation when needed in ICH.14–16 The 2020 American College of Cardiology (ACC) Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants defines major bleeds as bleeding at a critical site, hemodynamic instability, or bleeding resulting in at least 2 g/dL decrease in hemoglobin or requiring a transfusion of at least 2 units of packed red blood cells.14 For patients with major bleeds, anticoagulant and antiplatelet agents should be discontinued, and supportive care measures should be implemented.

The ACC guidelines (Figure 1, next page) recommend that DOAC reversal agents be used if available in patients with a major bleed. In patients taking dabigatran, idarucizumab should be administered at a dose of 5 g IV; PCC or activated prothrombin complex concentrate (aPCC) may be used if idarucizumab is not available.16 Patients who are taking apixaban or rivaroxaban should preferably be given andexanet alfa as a reversal agent per the ACC guidelines, but PCC or aPCC can be given if andexanet alfa is not available; the comparative efficacy of these agents is still being evaluated.16 Dosing is based on the time and strength of the last DOAC dose. The ACC recommends that patients experiencing major bleeding who are taking edoxaban should be treated off-label with high-dose andexanet alfa, if available, or PCC or aPCC.16 These recommendations can be used to guide management of DOAC-associated major bleeding, and clinical trials are underway to evaluate the use of idarucizumab and andexanet alfa specifically in ICH.17,18
FIGURE 1: ACC ANTICOAGULANT REVERSAL RECOMMENDATIONS

WHICH ANTICOAGULANT THERAPY IS THE PATIENT TAKING?

VKA (warfarin and other coumarins)
- Administer 4F-PCC
  - INR 2 to <4, 25 units/kg
  - INR 4-6, 35 units/kg
  - INR >6, 50 units/kg
- Or low fixed-dose option
  - 1,000 units for any non-intracranial major bleed
  - 1,500 units for ICH
  - If 4F-PCC is not available, use plasma 10–15 mL/kg

DOI (dabigatran)
- Administer 5 g idarucizumab
  - If dabigatran is not available, administer PCC or aPCC
  - Consider activated charcoal for known recent ingestion (within 2-4 h)

FXa Inhibitor (apixaban and rivaroxaban)
- Administer 5 g idarucizumab
  - If dabigatran is not available, administer PCC or aPCC
  - Consider activated charcoal for known recent ingestion (within 2-4 h)

FXa Inhibitor (betrixaban and edoxaban)
- Administer 10 g idarucizumab
  - If dabigatran is not available, administer PCC or aPCC
  - Consider activated charcoal for known recent ingestion (within 2-4 h)

DTI (dabigatran)
- Administer 5 g idarucizumab
  - If dabigatran is not available, administer PCC or aPCC
  - Consider activated charcoal for known recent ingestion (within 2-4 h)

If idarucizumab is not available, administer PCC or aPCC
- Consider activated charcoal for known recent ingestion (within 2-4 h)

If andexanet alfa is not available, administer PCC or aPCC
- Consider activated charcoal for known recent ingestion (within 2-4 h)

If andexanet alfa is not available, administer high-dose andexanet alfa
- If andexanet alfa is not available, administer PCC or aPCC
- Consider activated charcoal for known recent ingestion (within 2-4 h)

Adapted from Tomaselli et al (2020)

KEY REFERENCES


For a full list of references go to gotoper.com/go/ncs21doacr-post

CME POST-TEST QUESTIONS

1. What proportion of all major bleeds in patients on direct oral anticoagulant (DOAC) therapy are intracranial hemorrhage (ICH)?
   - A. 5%
   - B. 13%
   - C. 25%
   - D. 43%

2. In the RE-VERSE AD trial, which evaluated idarucizumab for dabigatran reversal, what was the median time to cessation of bleeding?
   - A. 1.5 hours
   - B. 2.0 hours
   - C. 2.5 hours
   - D. 3.0 hours
   - E. 4.0 hours

3. According to final results of the ANNEXA-4 trial, which evaluated andexanet alfa, what percentage of patients had excellent or good hemostatic efficacy at 12 hours?
   - A. 42%
   - B. 62%
   - C. 82%

4. AJ is a 79-year-old man who was in a motor vehicle accident, resulting in a head injury. Upon evaluation in the emergency department, he is found to have an intracranial hemorrhage. His past medical history is significant for a deep vein thrombosis/pulmonary embolism 1 year ago, for which he is taking rivaroxaban. Which of the following therapies would be best for this patient in accordance with current treatment guidelines?
   - A. Fresh frozen plasma
   - B. Recombinant activated factor VII
   - C. Andexanet alfa
   - D. Idarucizumab

To learn more about this topic, including information on best care practices for hemorrhagic stroke focusing on DOAC reversal, go to gotoper.com/go/ncsichdoac21

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A Practical Approach to Chronic Immunosuppression in Myasthenia Gravis

By Jessica Yi, MD,* and Ericka Wong, MD**

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** Director, Neurology Neuromuscular Residency Program, Thomas Jefferson University.

MYASTHENIA GRAVIS (MG) IS AN autoimmune disorder caused by the presence of autoantibodies against the neuromuscular junction, which results in fatigable weakness. Chronic immunosuppression is among the mainstays of long-term therapy in MG. This article offers a practical approach to initiating and tapering corticosteroids, in addition to reviewing some of the considerations in the selection and monitoring parameters of steroid-sparing agents. We will also briefly introduce some novel therapies for MG.

Corticosteroids

Per international consensus, corticosteroids (specifically prednisone) comprise first-line immunosuppressive therapy for all patients who have not achieved disease control with pyridostigmine. Efficacy trials have shown marked improvement (45%) or remission (30%) in most MG patients initiated on corticosteroids.

There are 2 treatment approaches to the initiation of corticosteroids, and the choice of approach is dependent upon the patient’s level of disability at presentation. The low-dose, slow-titration approach is generally appropriate for patients with mild-to-moderate generalized or ocular disease. This regimen is less likely to produce the paradoxical worsening that can be seen within the first 3 weeks in up to half of patients started on steroids. The high-dose, rapid-induction approach is considered for patients with impending myasthenic crisis or severe disability due to a faster onset of action. In these cases, the risk of paradoxical worsening from steroids is usually offset by simultaneous administration of either intravenous immunoglobulin (Ig) or plasmapheresis.

The high-dose treatment regimen involves initiation of prednisone at a dose of 1.5 mg/kg/day (up to 100 mg per day) for 2 to 4 weeks. After this, the patient can either be transitioned to a high daily dosing or alternate-day dosing routine; for example, the patient can either be started on 50 mg daily or 100 mg every other day. The high daily dosing or alternate-day dosing is maintained until a plateau has been reached in clinical improvement for at least 4 weeks. A slow taper can then be introduced, decreasing by 10 mg every
4 weeks until the patient is on 20 mg daily. Once the patient is on 20 mg daily, tapering is commonly slowed to decrease by increments of 5 mg every month. Below 10 mg daily, an even slower taper (1.0-2.5 mg every 2-4 weeks) is often necessary to prevent relapse of symptoms.

The low-dose, slow-titration schedule starts the patient on 10 to 20 mg of prednisone per day, with an increase of 10 mg every 1 to 2 weeks up to 1 to 1.5 mg/kg/day (no more than 60-100 mg daily).3 Again, the higher dose is maintained until the patient has been stable for at least 4 weeks, and then the patient is slowly tapered as described above. If a patient experiences relapse in symptoms during a taper, the dose of steroids is increased again to the lowest effective dose.

Chronic, continual corticosteroid use is associated with increased susceptibility to infection, diabetes, weight gain, osteoporosis, steroid myopathy and aseptic necrosis of the joints.3 Prior to initiating steroids, patients should be screened for tuberculosis (TB), and those with a history of TB may need to be prophylactically treated. Monitoring of bone density with a dual-energy X-ray absorptiometry (DEXA) scan at baseline and at 6 to 12 months after steroid initiation can be considered, and patients should be prophylactically started on calcium and vitamin D supplements to prevent osteoporosis.3 Bisphosphonates may be initiated for postmenopausal women or for patients who have evidence of osteopenia or osteoporosis on their DEXA scans. Blood glucose should also be monitored carefully while patients are maintained on steroids, particularly when they are on higher doses.

Due to the myriad of complications that result from chronic corticosteroid use, the objective is to taper patients down to the lowest effective steroid dose without causing recurrence of symptoms. Alternate “steroid-sparing” immunosuppressive agents are added with the goal of reducing the daily steroid dose or discontinuing steroids altogether. They may be started simultaneously with prednisone in patients with severe disease due to their delay in onset of action; they can also be started later on if a patient is unable to taper to low-dose prednisone (often accepted to be 10 mg or less daily) without relapsing. Once a patient has remained stable for 6 to 12 months on a steroid-sparing agent, prednisone can be gradually tapered to low-dose prednisone (often accepted to be 10 mg or less daily) without relapsing. Once a patient has remained stable for 6 to 12 months on a steroid-sparing agent, prednisone can be gradually tapered as previously described.1 In patients with diabetes or osteopenia, steroid-sparing agents can be considered as first-line treatment to avoid the adverse effects (AEs) of steroids.

Steroid-Sparing Agents
Various classes of steroid-sparing immunosuppressants are used to treat MG: antimetabolites (eg, azathioprine, mycophenolate mofetil, methotrexate), calcineurin inhibitors (eg, cyclosporine), monoclonal antibodies (eg, rituximab), complement inhibitors (eg, eculizumab, ravulizumab), and the upcoming FcRn antagonists.

Antimetabolites
Azathioprine is the most frequently utilized steroid-sparing immunosuppressant in MG and currently has the best efficacy data. A double-blind, placebo-controlled study randomized patients into groups receiving azathioprine + prednisolone or placebo + prednisolone, and approximately 60% of the azathioprine group did not require retreatment with steroids after 36 months.4 Azathioprine is typically initiated at 50 mg daily and increased by increments of 50 mg every 2 to 4 weeks to a goal of 2 to 3 mg/kg/day. Some patients experience a flu-like illness that can contribute to early intolerance of the medication. Complications can include bone marrow suppression, hepatic toxicity, pancreatitis, and teratogenicity.2 To monitor for these AEs, a complete blood count (CBC) and a hepatic panel should be obtained at baseline and then monitored closely, particularly in the first few months. Screening for deficiency of the enzyme thiopurine methyltransferase, which predisposes patients to bone marrow toxicity in those exposed to azathioprine, is often performed, although the benefit is unclear. Leukopenia is a good indicator of bone marrow suppression, and it can be seen as early as 1 to 2 weeks after initiation.2 The dose should be decreased if the white blood cell (WBC) count is less than 4000/mm3, and azathioprine should be held if the WBC count is less than 2500/mm3 or the absolute neutrophil count is less than 1000 mm3.2 Hepatotoxicity can be observed within the first several months, and azathioprine should be discontinued if transaminases increase by more than 2 to 3 times the initial levels.2 Other practical considerations include the avoidance of allopurinol due to its interference with the metabolism of azathioprine.2 In addition to other AEs, a limitation of the use of azathioprine is the delayed onset of action of approximately 6 months; the full benefit may not be seen until as long as 12 to 18 months after the agent is started.2,3

The use of mycophenolate mofetil (MMF) is not supported by evidence from clinical trials but is used in MG based on clinicians’ observational experience. Its ease of use and tolerability are also attractive. MMF showed reported benefit in a few observational studies and open-label trials, but 2 double-blind placebo-controlled studies did not show a significant difference between MMF + prednisone vs placebo + prednisone.4 Typical dosing for MMF consists of 1000 to 2000 mg per day divided into 2 doses. Clinical improvement is most often observed within the first 3 months but can be delayed up to 1 year after initiation.2 Leukopenia is a significant AE; other common AEs include diarrhea, nausea, and infections. A CBC should be obtained at baseline and then closely monitored. MMF is teratogenic and contraindicated in pregnancy.2

Evidence for the benefit of methotrexate (MTX) in MG is limited, but it may be considered for patients who have not responded to other steroid-sparing agents.5 It also has the advantage of an earlier onset of action compared with azathioprine. It is started at 7.5 mg per week (divided into 3 doses given 12 hours apart) and increased by 2.5 mg every 1 to 2 weeks up to 20 to 25 mg per week.2-5 MTX can cause AEs including stomatitis, bone marrow suppression, interstitial lung disease, pulmonary fibrosis, renal toxicity, and liver toxicity.2 Patients should be started on folic acid to mitigate these AEs. Due to teratogenicity, MTX is contraindicated in women who may become pregnant; it should also be used in caution with patients with lung disease.2 CBC and hepatic panels should be monitored closely.
Calcineurin Inhibitors
Cyclosporine has been shown to be effective in the treatment of MG but is rarely chosen as a first-line agent due to its AE profile and monitoring parameters. Its main advantage over azathioprine is its quicker onset of action, with improvement typically seen within 2 to 3 months of initiation. The most notable AE is nephrotoxicity, which can be seen in approximately a quarter of patients and can occur in both the acute setting and in a delayed fashion. Serum creatinine needs to be monitored monthly after initiation, and the dose should be decreased with any significant elevation in creatinine. Trough cyclosporine levels should also be monitored. Other AEs include hypertension, tremor, liver toxicity, hirsutism, paresthesias, and headache. Cyclosporine is initiated at a dose of 3 mg/kg/day divided into 2 doses and gradually increased to a maximum of 6 mg/kg/day.

Monoclonal Antibodies
Rituximab is a CD20 monoclonal antibody with favorable evidence from case series for its use in both anti-AChR and anti-MuSK MG, and it should be considered early on for anti-MuSK MG that has not responded to initial immunotherapy. A common dosing regimen is 375 mg/m² infusions given weekly for 4 weeks. Another frequently used method is administering 1 g/m² twice, 2 weeks apart. The frequency of redosing is dependent on the patient’s clinical response; response can be seen as early as 4 to 6 months or as late as 24 months after initiation. Before initiating rituximab, patients should obtain a baseline CBC and be screened for hepatitis B due to the risk of reactivation. Possible AEs also include leukopenia, anemia, and thrombocytopenia. An uncommon but potential complication is the development of progressive multifocal encephalopathy.

Complement Inhibitors
Complement inhibitors interfere with the autoimmune pathway, which results in endplate destruction. These medications are not effective in anti-MuSK MG because the MuSK autoantibodies do not activate the complement cascade. Eculizumab is a humanized monoclonal antibody against complement protein C5, and it can be considered for refractory anti-AChR MG. A randomized, placebo-controlled trial demonstrated benefit in refractory MG with a significant reduction in quantitative MG score. In a phase 3 trial, patients were given an induction dose of 900 mg/week for 4 doses, followed by a maintenance dose of 1200 mg every 2 weeks; benefit was demonstrated over the placebo group but it did not reach statistical significance. The most serious AE with administration of this drug is the increased risk of Neisseria meningitidis infection, so patients should be vaccinated prior to treatment.

Zilucoplan is a synthetic peptide that binds to complement protein C5 at a different binding site compared with eculizumab, so it may be considered in the future for patients with C5 mutations who do not respond to eculizumab. A phase 3 trial of zilucoplan is currently ongoing and will include nonrefractory MG patients. Ravulizumab is a monoclonal humanized antibody that also binds to complement protein C5 but has a longer half-life compared with eculizumab and can be administered every 8 weeks. A phase 3 trial of ravulizumab is currently ongoing.

FcRN Antagonists
The FcRN antagonists comprise a novel class of medications in the treatment of MG; they aim to interfere with the recycling of autoantibodies in the process of lysosomal degradation. Efgartigimod is a humanized IgG1-derived Fc fragment that was given in 4 infusions over 3 weeks in a double-blind, placebo-controlled trial to patients with anti-AChR MG. The study showed a decrease in IgG serum concentration by 50% by week 3 and a statistically significant reduction of quantitative MG scores after the first infusion. A multicenter, randomized, placebo-controlled, phase 3 trial was recently completed, finding that efgartigimod was well tolerated and efficacious in patients with generalized MG.

Rozanolixizumab is a humanized IgG4 monoclonal antibody that was given as a subcutaneous infusion once weekly for 6 weeks in a randomized, subject-blind, placebo-controlled trial in patients with anti-AChR MG. The study demonstrated improvement in all clinical scores compared with placebo without reaching statistical significance, but improvement in the MG-Activities of Daily Living score was statistically higher in the treatment arm compared with placebo.

Conclusion
Chronic immunosuppressive therapy in MG can provide long-term stability for many patients. For patients who continue to be refractory or are unable to tolerate current medication options due to AEs, emerging novel therapies with more targeted immunosuppression may offer alternatives in the near future.

REFERENCES
Cluster Headache: A Clinical Overview

By Suzan Khoromi, MD, MHS
Associate clinical professor of neurology, University of California San Diego Health Neurological Institute

Cluster Headache (CH), the most common trigeminal autonomic cephalalgia (TAC), is defined as a unilateral severe headache accompanied by ipsilateral autonomic features such as unilateral ptosis, miosis, conjunctival injection, rhinorrhea, and lacrimation, as well as restlessness.

Two main distinguishing features of CH compared with other TACs is a duration of 15 to 180 minutes per attack and circadian periodicity with headaches recurring typically at the same time each day. Patients may experience between 1 attack every other day to up to 8 attacks a day. As opposed to migraine headaches, in which the affected side may switch from one side to the other during an attack and from one attack to the next, CHs are typically side locked during attacks and affect the same side with most if not all attacks. In some instances, the severity of CH can lead to suicidality.¹

According to the third edition of the International Classification of Headache Disorders, episodic CH is defined as attacks over periods of weeks to months with pain-free intervals of at least 3 months or longer. Chronic CH, on the other hand, is characterized by episodes that last for a year or longer without remission or with pain-free intervals of less than a month.² Identifying CH may be delayed by several years, therefore it is important to include questions addressing autonomic features in questionnaires used to elicit a headache history.³

Epidemiology
The peak prevalence of CH is between 20 to 50 years of age and the lifetime prevalence of the condition is estimated to be approximately 0.1%.⁴ CH can occur in children, although it is rare. Risk factors for CH may include head trauma, smoking, and passive smoke exposure, as well as genetic factors, with 5% to 20% of patients with CH endorsing a positive family history.⁵,⁶ Genome-wide association studies have identified multiple genetic risk loci for CH, but no clear mode of inheritance has been established in the literature.⁷ Previously, the male-to-female ratio of prevalence had been estimated to be 4:1, but findings from more recent epidemiological studies suggest a ratio of 2:1 or 3:1.⁴,⁵

Pathophysiology
In addition to information gleaned from clinical features, animal experiments, and known secondary causes, results from functional imaging studies have contributed to our understanding of the pathophysiology of CH, showing attack-related activation of the posterior ipsilateral hypothalamus.⁸ This most likely contributes to the circadian and seasonal rhythmicity of CH. Orexins, which are primarily synthesized by hypothalamic nuclei, are involved in pain modulation as well and may be implicated in CH.⁹ Data suggest that secondary activation of the trigeminal nerve and the trigeminovascular complex contribute to pain; the trigeminal autonomic pathways including the superior salivatory nucleus centrally and sphenopalatine ganglion peripherally mediate十月
the autonomic features in CH. Implicated mediators include vasoactive intestinal peptide, nitric oxide, and calcitonin gene-related peptide (CGRP). In 1 study of patients with episodic CH, CGRP infusion triggered attacks during a cycle of CH.

**Differential Diagnosis**
The differential diagnosis of CH is divided into secondary causes of vascular type such as cervical arterial dissection, intracavernous carotid artery thrombosis or hemangioma, and cerebral venous sinus thrombosis on one hand, and nonvascular etiologies such as glaucoma, sphenoid sinusitis, nasopharyngeal malignancies, trigeminal nerve root compression, and pituitary tumors on the other. Other primary headaches such as other subtypes of TAC, migraine, trigeminal neuralgia, and primary stabbing headache can also cause unilateral frequent headaches.

**Workup**
Because of possible secondary mimics, the workup of patients presenting with CH usually includes brain imaging, preferably a brain MRI with contrast as well as vascular imaging of the head and neck.

**Treatment**
The management of CH is divided into 3 categories: acute treatment, transitional/bridging treatment, and preventive treatment.

**Acute Treatment**
The structures implicated in the pathophysiology of CH explain some of its unique treatments such as oxygen, which is specific, effective, and safe in the acute management of CH. Randomized controlled trials (RCTs) support the usage of 100% oxygen with a nonrebreather mask, at 10 L/min to 15 L/min for 15 minutes. The type of mask used, such as demand valve oxygen, may also be important in the effectiveness of oxygen therapy. Recently, discussion between patient and physician advocacy groups and the Centers for Medicare & Medicaid Services about reimbursement and coverage for oxygen therapy for patients with CH has led to changes in the national coverage determinations. These allow Medicare administrative contractors to make coverage determinations regarding the use of home oxygen and oxygen equipment for CH, expand patient access to oxygen and oxygen equipment in the home, and permit contractors to cover the use of home oxygen and oxygen equipment to treat CH.

Noninvasive stimulation of the vagus nerve, via an FDA-approved device marketed under the name of gammaCore, has also been shown to be effective as an acute treatment in episodic CH. The device is used to deliver 3, 2-minute stimulations of the ipsilateral cervical branch of the vagus nerve.

**Transitional/Bridging Treatment**
Because of their rapid onset of action, parenteral triptans such as sumatriptan subcutaneous (SC) 4 mg to 6 mg; sumatriptan nasal spray 20 mg; zolmitriptan nasal spray 5 mg; intramuscular, SC, and nasal dihydroergotamine; and lidocaine nasal spray are also commonly used for the acute treatment of CH. Among these treatments the FDA has approved only SC sumatriptan, but usage of the other treatments is evidence-based.

While waiting for a preventive treatment to become effective, bridging/transitional therapies are also often used. These include high-dose oral steroids such as prednisone 60 mg to 80 mg per day tapered over 2 weeks, prednisone 100 mg for 5 days followed by a 20-mg taper every 3 days, or dexamethasone [Decadron] 4 mg twice daily for 1 week followed by 4 mg daily for 1 week. Ipsilateral suboccipital nerve blocks using a combination of an anesthetic such as lidocaine or bupivacaine [Marcaine] and 40 mg to 80 mg triamcinolone or prednisolone can also be effective and obviate the need for systemic steroids.

**Preventive Treatment**
Verapamil in doses ranging from 240 mg to 480 mg daily in 3 divided doses is widely used as a first-line preventive treatment of CH. Because large doses may be needed, clinicians should obtain a baseline electrocardiogram (EKG) and blood pressure recording. Doses should be increased slowly, usually by 80 mg in total daily dose every 2 weeks; an EKG should be obtained prior to each increment to follow the PR interval because the atrioventricular blocking effect of verapamil may be delayed by 10 days. Dosing should not exceed 960 mg per day.

Support also exists for the use of lithium in prophylaxis of both episodic and chronic CH; however, this treatment has a narrow therapeutic window and dosing is based on serum levels and adverse effects. In addition, thyroid and kidney function should be measured at baseline and periodically. Therapeutic doses range from 600 mg to 1200 mg daily. Preventive treatment is usually continued for 2 weeks after the end of a CH cycle.

The SC injection of the CGRP monoclonal antibody galcanezumab 300 mg has also been shown to reduce the number of CH attacks over 3 weeks in patients with episodic CH in an RCT. This FDA-approved treatment has a favorable adverse effect profile and can be used once a month for up to 3 months in patients with episodic CH.

The FDA has also approved neuromodulation with vagal nerve stimulation as an adjunctive treatment for the prevention of episodic CH. Injection of the sphenopalatine ganglion peripherally has anecdotally been reported to be useful as well, but needs to be further studied to establish a standardized technique.

For patients with chronic refractory CH, neuromodulation of the sphenopalatine ganglion via an implanted microstimulator in the pterygopalatine fossa has been shown to be safe and effective but its usage has not yet been cleared by the FDA. Deep brain stimulation of primarily the posterior hypothalamus and the ventral tegmentum is also reported as a treatment in chronic refractory CH but carries a high surgical risk.
Joseph C. Landolfi, DO, CPE, is New CMO of JFK University Medical Center
Joseph C. Landolfi, DO, CPE, was named chief medical officer of the Hackensack Meridian Health’s JFK University Medical Center in Edison, New Jersey, in October. Landolfi serves as vice chairman of the JFK Neuroscience Institute and medical director of oncology. “After a lengthy selection process, we are proud to have Joe Landolfi as our third chief medical officer in JFK’s 54-year history,” Amie Thornton, president and chief hospital executive of JFK University Medical Center, said in a statement. “Dr Landolfi already brings 23 years of dedicated service to JFK in which he has provided invaluable clinical and administrative leadership to our entire team.” Landolfi also is corporate medical director at Hackensack Meridian Health JFK Cancer Care and section chief of neuro-oncology and radiosurgery at JFK Brain Tumor Treatment and Rehabilitation Center. He is a professor of neurology at Hackensack Meridian School of Medicine and a volunteer clinical associate professor of neurology at Rutgers Robert Wood Johnson Medical School.

RESEARCH REWARDS
Fred Lublin, MD, and Aaron Miller, MD, Receive NMSS Hope Award
The prestigious Hope Award from the National Multiple Sclerosis Society (NMSS) was presented to 2 experts in multiple sclerosis (MS) from Mount Sinai at the annual NMSS Dinner of Champions in New York, New York. Fred Lublin, MD, Saunders Professor of Neurology, and director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis; and Aaron Miller, MD, professor of neurology and medical director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis, were honored at the September event, recognizing their research and clinical practice in the MS field. “We are thrilled to honor Drs Aaron Miller and Fred Lublin as the 2021 Hope Honorees. As global MS research leaders, they have made landmark contributions to how we diagnose and treat MS and to the development of disease-modifying treatments that have improved the lives of people with MS,” Tim Coetzee, PhD, chief advocacy, service and research officer at NMSS, said in a statement.

Javits Neuroscience Investigator Award Honors Peter B. Crino, MD, PhD
Peter B. Crino, MD, PhD, has received the Javits Neuroscience Investigator Award, according to an October announcement from E. Albert Reece, MD, PhD, MBA, dean of the University of Maryland School of Medicine (UMSOM) in Baltimore. Crino is a professor and chair of the UMSOM Department of Neurology. Established in 1983, the award honors the late US Senator Jacob Javits, who had amyotrophic lateral sclerosis and became an advocate for research into diseases of the brain and nervous system. The award provides $2.7 million in funding, allocated over 4 years, with administrative review determining an additional 3 years of funding. “I am very humbled, honored, and grateful to be chosen for the Javits Award. I want to share the credit for the award with my laboratory staff, who have helped to drive our research program for the past 2 decades,” Crino said in a statement. “There is still so much work to be done to understand the causes of epilepsy and autism and to hopefully achieve new therapeutic strategies for individuals facing these challenges every day. The Javits Award will greatly augment our lab progress and productivity in these critical areas of research.”

Northwestern University Scientists Receive Awards for Parkinson Disease Research
Scientists at Northwestern University were granted 2 awards from the Aligning Science Across Parkinson’s (ASAP) Collaborative Research Network in November. D. James Surmeier, PhD, MS, Nathan Smith Davis Professor and chair of the Department of Neuroscience at Northwestern University Feinberg School of Medicine in Chicago, Illinois, will utilize $9 million in funding, dispersed over 3 years, to research brain circuit dysfunction when it begins and its evolution to making moving and sleeping difficult for patients. An $8.9 million award was also received by Rajeshwar Awatramani, PhD, professor of neurology at Feinberg School of Medicine, who will study the substantia nigra pars compacta—dopamine-producing neurons in the brain—learning more about how they contribute to movement and are affected in patients with Parkinson disease. The ASAP Collaborative Research Network is a component of the larger ASAP initiative, which was established in partnership with The Michael J. Fox Foundation for Parkinson’s Research.

INSTITUTIONAL INFORMATION
NYU Langone Launches Parekh Center for Interdisciplinary Neurology
Parekh Center for Interdisciplinary Neurology has been launched by NYU Langone Health. The center was made possible by a gift from Deven and Monika Parekh through the Psquared Charitable Foundation. The center aims to advance research and scientific discovery for neurodegenerative conditions, uniting clinicians and investigators across the institution. Un Jung Kang, MD, the Founders Professor of Neurology, professor of neuroscience and physiology, director of translational research at the Marlene and Paolo Fresco Institute for Parkinson’s and Movement Disorders, will be the center’s codirector with Shane A. Liddelow, PhD, an assistant professor in the Department of Neuroscience and Physiology. Research will include 4 projects centered on understanding the underlying mechanisms of neurodegenerative disease and neurodevelopmental disorders. The center also will issue pilot project grants for those in the NYU Langone community to encourage innovative research, with directors and scientific advisory committee members coming from different disciplines, including the Division of Infectious Disease and Immunology, the Neuroscience Institute, the Center for Human Genetics and Genomics, and the neurology and psychiatry departments.
POLARIS
Evaluating safety and efficacy of Mazindol ER in clinical trials for the treatment of narcolepsy.

Now enrolling

NLS-1021: A Four-week, Double-blind, Placebo-controlled, Randomized, Multicenter, Parallel-group Study of the Safety and Efficacy of NLS-2 (Mazindol Extended Release) in Adults for the Treatment of Narcolepsy.

NLS-1022: An Open Label Extension study available the day after completion of patient four-week treatment cycle of NLS-1021, in which the patient will roll in and take Mazindol ER once-daily as an oral tablet for up to 6 months.

POLARIS program

POLARIS is comprised of two concurrent clinical studies, NLS-1021 and NLS-1022.

The NLS-1021 program has a simple, straightforward, patient friendly study design. NLS-1022 is an Open Label Extension study offering patients enrolled in NLS-1021 the possibility to take Mazindol ER once-daily as an oral tablet for up to 6 months.

The drug substance Mazindol, with a long history of clinical use, has a unique dual mechanism of action, acting as an Orexin-2 receptor partial agonist and as inhibitor of reuptake of dopamine, norepinephrine, and serotonin.

Key inclusion criteria

• Males and females between 18 and 65 years of age, inclusive
• Diagnosis of narcolepsy according to ICSD-3 (International Classification of Sleep Disorders, 3rd Edition) or Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria
• Body mass index from 18 to 40 kg/m2, inclusive
• Consent to use a medically acceptable method of contraception
• Willing and able to provide written informed consent

Key exclusion criteria

• Female subjects who are pregnant, nursing, or lactating
• Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness
• History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria
• Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness
• Use of any medications that could affect the evaluation of cataplexy
• Received an investigational drug in the past 30 days or five half-lives (whichever is longer)

To learn more about this study, visit polaris.nlspharma.com