Pressing Gaps in Care Exist for Patients With Parkinson Disease

BY INDU SUBRAMANIAN, MD

COVID-19 Shutdowns and the Disruption to Deep Brain Stimulation Treatment
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CAP-1002 Builds Momentum in DMD With Phase 3 HOPE-3 Study

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Shifting the Paradigm to Address Gaps in Care

The paths that patients with chronic neurologic diseases take in their care journeys can vary significantly. As data on the patient experience continue to be collected, understanding the gaps in access and challenges for various patient groups is at the forefront of discussions about the care paradigm. This has helped identify areas of need for patient populations and highlighted the disparities they face. As we approach the era of personalized treatment and management, the need to understand these individualized challenges is of vital importance.

In Parkinson disease (PD), where challenges in addressing the therapeutic needs of patients have been prioritized, these disparities are particularly apparent for several patient groups. Women with PD have historically been an underserved population and desperately need care that addresses their unique needs, as Indu Subramanian, MD, highlights on page 16 in the cover story of this issue of NeurologyLive®. She points to 2 other major care gaps for the PD population, mental health and loneliness, both of which have been shown to affect not only patient quality of life but potentially also disease progression.

The COVID-19 pandemic exacerbated some of these challenges as well. On page 30, Mustafa Saad Siddiqui, MD, explores how the pandemic shutdown delayed procedures related to deep brain stimulation (DBS) for patients with PD, including initial implantation procedures and replacements of implantable pulse generators for those already with DBS devices. However, not every downstream influence of the pandemic has been negative. The lack of ability to conduct in-person visits ushered in a long-desired era of telemedicine that has helped address access challenges for some patients, a shift widely welcomed by many physicians, including Siddiqui.

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®
AWARENESS EMPOWERS CARE FOR PATIENTS WITH PARKINSON DISEASE

Benjamin L. Walter, MD, MBA

THIS MONTH’S ISSUE OF NeurologyLive® focuses on Parkinson disease (PD). James Parkinson, who first described the essential clinical phenomenology of PD in his 1817 paper “An Essay on the Shaking Palsy” and for whom the condition was named, was born on April 11, 1755.1 Thus, April was chosen as Parkinson’s Awareness Month to remind us of the importance of supporting progress in treating and caring for individuals with this condition and working toward a cure.

After Alzheimer disease, PD is the most common neurodegenerative disease. It affects approximately 10 million individuals worldwide and is expected to affect 12 million to 17 million individuals by 2040, spurred by an increasingly aging population and risk factors associated with industrialization products such as pesticides and solvents.2

As with many other chronic diseases, PD is not imminently fatal nor transient but is incurable. The lifelong search for effective treatments and quality of life intersects with different phases of life as PD affects individuals young and old. It is a heterogenous disorder with motor and significant nonmotor symptoms, and it affects individuals differently based on their unique identities, culture, access to health care, and social support.

In this issue, Indu Subramanian, MD, writes about her work unveiling the disparities in care for underrepresented populations with PD. Although nonmotor symptoms, particularly those affecting mental health, are a significant problem for individuals with PD, they are even more poorly addressed in vulnerable and underserved populations. Subramanian discusses the significant gaps in care facing women with PD.3 Although women are less likely to get PD, much of the common understanding of how individuals are affected is more specific to men and does not adequately address critical issues for women with PD. We need to increase our awareness of these differences to provide individualized care appropriately. Women and minorities are underrepresented in PD research, and our knowledge of treatment strategies and responses to therapies is also lacking in these populations.

The past few years and the enduring COVID-19 pandemic have highlighted how vulnerable individuals with PD can be as their lives intersect with acute care medical issues and hospitalization. As PD progresses, treatment regimens become more complex and there is diminishing flexibility to balance therapeutic efficacy while minimizing adverse effects. Both efficacy and complications of therapy are worsened by concomitant illness and infection. Unfortunately, studies show that as much as 89% of all admissions and 17.4% of all medication dispensing for hospitalized patients with PD are fraught with errors in dose, timing, or concomitant administration of contraindicated medications.4 These errors result in increases in complications, including falls, aspiration pneumonia, and psychosis or delirium, leading to increases in morbidity, mortality, increased length and cost of care, and negative patient experiences.5-7

It is critical to spotlight these issues so we can readily address them in the professional neurological community. The Parkinson’s Foundation has helped empower patients and families with their Aware-in-Care Kits for hospitalization. But more needs to be done proactively by the medical community so that the hard work to optimize patients’ treatment isn’t undone during hospitalization.

Much has been published on the unique vulnerabilities of individuals with neurological conditions, including PD, during the COVID-19 pandemic. In this edition, the works by Subramanian and Mustafa Saad Siddiqui, MD, highlight different aspects of this. Although individuals with PD are not more likely to get COVID-19, they are more likely to have complications from it. Strikingly, the excess mortality in patients with PD during this time has been significant.8 This highlights the likely intersecting vulnerability of having PD with social

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He is a board-certified neurologist and fellowship-trained movement disorders specialist and has practiced in northeast Ohio since 2004. His research focuses on deep brain stimulation, functional MRI, and developing novel healthcare delivery paradigms to optimize care for Parkinson disease.

He graduated summa cum laude from Emory University with a bachelor of science in biology and received his medical degree from MCP-Hahnemann School of Medicine. He completed an internship in internal medicine and residency in neurology at Emory University. He subsequently completed a fellowship in movement disorders with an emphasis on intraoperative mapping and deep brain stimulation at Emory University. He also graduated from the Weatherhead School of Management at Case Western Reserve University’s Executive MBA Program.

FROM THE EDITOR
isolation and more significant difficulties in getting care during a pandemic. This is also likely further compounded in individuals with preexisting poor access to care.

As the weather warms and we progress through April, let us give thoughtful attention to the problem of PD. This diverse, multifaceted condition deserves multidisciplinary care and open discourse on reducing disparities and individualizing care. We need to continue fighting for research funding for better treatments and a cure. Let us be diligent but driven by hopeful optimism and inspire our patients to keep fighting.

REFERENCES


FDA Accepts INDs for Bacterium-Based Parkinson Disease Agents

The FDA has cleared investigational new drug (IND) applications for 4D Pharma’s live biotherapeutic, gut-derived Parkinson disease (PD) agents MRx0005 (*Parabacteroides distasonis*) and MRx0029 (*Megaphera massiliensis*), which will be initiated in a first-in-human phase 1 study beginning in mid-2022, according to a news release from 4D Pharma. These oral, single-strain medicines discovered using 4D Pharma’s MicroRx platform have shown the ability in preclinical settings to reduce inflammation, including inflammation induced by α-synuclein, and to protect neurons from oxidative stress-induced death. In addition to demonstrating a positive impact on PD pathology, MRx0005 and MRx0029 have respectively protected against the loss of dopamine metabolites and dopamine-producing neurons in the brain in animal models of Parkinson’s disease.

**REFERENCE**


COVID-19 Vaccine Booster Increases Effects of Anti-CD20 MS Therapy

Among a cohort of patients with multiple sclerosis (MS) treated with ocrelizumab (Ocrevus; Genentech), an anti-CD20 therapy, COVID-19 messenger RNA (mRNA) vaccination induced robust T-cell responses to both Delta and Omicron variants, suggesting a protective effect against severe COVID-19 infection, according to study results published in *JAMA Neurology*. Furthermore, T-cell response rates increased after the third dose, demonstrating the importance of booster doses for this population.

Previous studies had shown that 2 doses of a COVID-19 mRNA vaccine induced suboptimal antibody responses but robust and functional T-cell responses against the vaccine strain. This prospective study, conducted between March 2021 and November 2021, included 20 patients, 11 (55%) of whom were men, with a total median age of 45.8 years (IQR, 37.8-53.3). Specific T cells were measured using the activation-induced marker assay. Peripheral blood mononuclear cells were stimulated with peptide pools covering the different spike proteins, and specific T cells were identified by the expression of activation surface markers such as 4-1BB, CD69, and OX40.

In total, 16 patients received a third dose of mRNA-1273 (Moderna) and 4 received a third dose of BNT162b2 (Pfizer-BioNTech), with a median interval between the second and third dose of 26.7 weeks (IQR, 22.3-29.0). Prior to receiving the booster dose, 12, 10, and 9 patients had cytotoxic T cells that were specific for the vaccine strain, the Delta variant, and the Omicron variant, respectively.

**REFERENCE**


Roche Announces New Trial in Alzheimer Disease

Roche has announced that it will be conducting SKYLINE (NCT05256134), a new phase 3 clinical trial to evaluate its subcutaneous investigational antiamyloid antibody, gantenerumab, as a preventive treatment for patients with early signs of Alzheimer disease. The trial will include an estimated 1200 participants aged 60 to 80 years who have amyloid positivity confirmed by...
IN THE HEADLINES

Deep Dive: Deep Dive into Activity in the Alzheimer Disease Pipeline

After a year of controversy and conversation in Alzheimer disease that saw the first approval for the field in 2 decades, Anton Porsteinsson, MD, the director of the Alzheimer’s Disease Care, Research, and Education Program at the University of Rochester, shared his perspective on the progress made and commented on the agents moving through the pipeline and the state of things heading into 2022.

WELLBEING CHECKUP: TAKING TIME TO PAUSE

Indu Subramanian, MD, the director of the Department of Veterans Affairs Southwest Parkinson’s Disease Research, Education, and Clinical Centers, spoke on the importance of taking time to pause in conversations with patients and colleagues, and how it can help improve communication and the digestion of information.

Transdermal System Wins FDA Approval in Alzheimer Disease Dementia

The FDA has approved Corium’s donepezil transdermal system (Adlarity) for the treatment of patients with mild, moderate, or severe Alzheimer disease (AD) dementia, making it the first and only once-weekly patch to continuously deliver consistent doses of donepezil through the skin.

Donepezil, a centrally acting reversible acetylcholinesterase inhibitor, was approved for medical use in the US in 1996 as a generic medication. This new formulation of the medication is delivered directly into a patient’s skin and bypasses the digestive system, resulting in a low possibility of gastrointestinal adverse effects and making it easier for patients with AD and their caregivers to administer the treatment.

The approved dosage is 5 mg/day or 10 mg/day formulations, and patients who were on oral donepezil may switch to the once-weekly transdermal system with the help of their prescriber. Expected to be available in early fall 2022, this new formulation was approved pursuant to the FDA’s 505(b)(2) regulatory pathway, with data from multiple clinical trials that demonstrated bioequivalence to donepezil hydrochloride (Aricept; Eisai/Pfizer), which was approved by the FDA for the treatment of severe AD in 2006.

REFERENCES

SECOND OPINION: CASE REPORT—A CHILD WITH STRANGE SPELLS

Eric Segal, MD, the codirector of epileptology at Hackensack Meridian Health, and director of pediatric epilepsy at Northeast Regional Epilepsy Group, and Jurriaan Peters, MD, PhD, a pediatric epileptologist and associate professor of neurology at Boston Children’s Hospital and Harvard Medical School, join Second Opinion to review a case study involving a child with strange spells.

WELLBEING CHECKUP: TAKING TIME TO PAUSE

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REFERENCES
Join us for the 1st Annual Giants of Multiple Sclerosis™ Awards Ceremony, taking place at the 2022 CMSC Annual Meeting, where we’ll recognize and celebrate pioneers, innovators, and difference-makers in Multiple Sclerosis. Enjoy heavy hors d’oeuvres and cocktails on June 2, 2022 from 7:15 pm – 10:00 pm at the Gaylord National Resort & Convention Center in National Harbor, Maryland.

RSVP at neurologylive.com/GiantsofMS

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TOP TWEETS

Gabrielle Macaron, MD | @GMacaronMD
Dr. Jennifer Graves, @sumadshah, and myself discussed oral therapy options for #MultipleSclerosis on @neurology_live - I enjoyed this dynamic conversation, hope you enjoy it too! https://t.co/6bI1Lv5P2u

Alzheimer’s Drug Discovery Foundation | @TheADDF
“Around 75% of #Alzheimers drugs now in development are nonamyloid & nontau,” @a_hfillit told @neurology_live. Fillit noted that research is moving toward a focus on addressing multiple pathways involved in Alzheimer disease, an approach long supported by ADDF.

National Headache Foundation (NHF) | @NHF
Thank you to @neurology_live for showcasing #NHF Board member, Dr Jan Brades for #NationalWomenPhysiciansDay!

Kathrin LaFaver, MD, FAAN, DipABLM | @LaFaverMD
@neurology_Live and @WNGtweets A1: the pandemic has amplified many preexisting challenges for women in medicine, especially for those with children. Many are making career changes or are considering leaving clinical practice. #WomenNeuroChat

American Academy of Sleep Medicine | @AASMorg
In observance of #RareDiseaseDay, @neurology_live shared an update on the current state of care and treatment for Kleine-Levin syndrome, a #SleepDisorder that affects an estimated 1-3 individuals per million. https://bit.ly/3swYh9P

THE NEED TO UNDERSTAND AND TACKLE STIGMA IN EPILEPSY: JOAN K. AUSTIN, PHD, RN, FAAN
The distinguished professor emerita at Indiana University School of Nursing speaks on the prevalence of stigma in the epilepsy field and how it affects patients’ daily life.
+ VIEW VIDEO neurologylive.com/epilepsy-stigma

DISCUSSING ECONOMIC BURDEN FOR PATIENTS WITH MULTIPLE SCLEROSIS: BRUCE BEBO, PHD
The executive vice president of research for the National Multiple Sclerosis Society discusses updated data from an analysis on economic burden that illustrate the disease’s “staggering” impact.
+ VIEW VIDEO neurologylive.com/ms-burden

EPSTEIN-BARR VIRUS’ RELATIONSHIP WITH MULTIPLE SCLEROSIS
Bridget A. Bagert, MD, MPH, director of Ochsner Multiple Sclerosis Center, offers her perspective on recent data on the relationship between Epstein-Barr virus and multiple sclerosis, which suggest the virus may be a root cause of the disease.
+ LISTEN neurologylive.com/mm-ep-56

ADDRESSING PARKINSON DISEASE VIRTUALLY WITH PRIME PD
Konstantin Karmazin, MD, clinical neurologist and chief medical officer at Prime PD, discusses the virtual wellness studio, its capabilities and goals for patients with Parkinson disease, and its benefits for physicians.
+ LISTEN neurologylive.com/mm-ep-58

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Indication and Important Safety Information

Indication
ZOLGENSMA is a gene therapy for pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) that is delivered as a single-dose, 1-hour intravenous infusion.

Limitations of Use
The safety and effectiveness of repeat administration or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

Important Safety Information

BOXED WARNING: Acute Serious Liver Injury and Acute Liver Failure
Acute serious liver injury, acute liver failure, and elevated aminotransferases can occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer a systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion. Please see Brief Summary of Prescribing Information on the adjacent page.
The efficacy of ZOLGENSMA was evaluated in STR1VE, a completed, open-label, single-arm, multicenter, Phase 3 clinical trial of patients with SMA Type 1 (genetically confirmed bi-allelic SMN1 deletion, 2 copies of SMN2, and <6 months of age at symptom onset and treatment; N=22).1,a,b

**WARNINGS AND PRECAUTIONS**

**Thrombocytopenia**
Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

**Thrombotic Microangiopathy**
Cases of thrombotic microangiopathy (TMA) were reported approximately 1 week after ZOLGENSMA infusion. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor for thrombocytopenia as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage if clinically indicated.

**Elevated Troponin-I**
Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

**ADVERSE REACTIONS**
The most commonly observed adverse reactions (incidence ≥5%) in clinical studies were elevated aminotransferases and vomiting.

Please see Brief Summary of Prescribing Information on the adjacent page.

The recommended dosage of ZOLGENSMA is $1.1 \times 10^{14}$ vector genomes per kilogram (vg/kg) in the presence of thrombocytopenia, further diagnostic evaluation for hemolytic anemia and renal insufficiency 12 days after ZOLGENSMA infusion and was found to have respiratory syncytial virus (RSV) and parainfluenza in respiratory secretions. The patient had episodes of serious hypotension, followed by seizures, and was found to have leukoencephalopathy (brain white matter defects) approximately 30 days after ZOLGENSMA infusion. The patient died after withdrawal of life support support 30 days after ZOLGENSMA infusion.

**INDICATIONS AND USAGE**

ZOLGENSMA is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

**Limitation of Use:** The safety and effectiveness of repeat administration of ZOLGENSMA or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

**DOSE AND ADMINISTRATION**

For single-dose intravenous infusion only.

The recommended dosage of ZOLGENSMA is $1.1 \times 10^{14}$ vector genomes per kilogram (vg/kg) of body weight.

- Administer ZOLGENSMA as an intravenous infusion over 60 minutes.
- Postpone ZOLGENSMA in patients with concurrent infections until the infection has resolved. Clinical signs or symptoms of infection should not be evident at the time of ZOLGENSMA administration.

Starting one day prior to ZOLGENSMA infusion, administer systemic corticosteroids equivalent to oral prednisone at 1 mg/kg of body weight per day for a total of 30 days. At the end of the 30-day period of systemic corticosteroid treatment, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose gradually over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed. Do not stop systemic corticosteroids abruptly. If liver function abnormalities continue to persist ≥ 2×ULN after the 30-day period of systemic corticosteroids, consult a pediatric gastroenterologist or hepatologist.

**WARNINGS AND PRECAUTIONS**

Acute Serious Liver Injury, Acute Liver Failure or Elevated Aminotransferases

Acute serious liver injury, acute liver failure and elevated aminotransferases can occur with ZOLGENSMA. Hepatotoxicity (which may be immune-mediated), generally manifested as elevated ALT and/or AST levels and at times as acute serious liver injury or acute liver failure, has been reported with ZOLGENSMA use. In order to mitigate potential aminotransferase elevations, administer systemic corticosteroids to all patients before and after ZOLGENSMA infusion. Immune-mediated hepatotoxicity may require adjustment of the corticosteroid treatment regimen, including longer duration, increased dose, or prolongation of the corticosteroid. Patients with preexisting liver impairment may be at higher risk for acute serious liver injury or acute liver failure. Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) ≥ 2×ULN have not been studied in clinical trials with ZOLGENSMA. The risks and benefits of infusion with ZOLGENSMA in patients with preexisting liver impairment should be weighed carefully against the risks of not treating the patient. Although in the clinical trials and in postmarketing experience, asymptomatic aminotransferase elevations were very commonly reported in the maintenance and in the postmarketing setting, cases of acute serious liver injury and acute liver failure have been reported. Some patients have experienced elevations in ALT and AST ≥ 2×ULN, prolonged prothrombin time and have been symptomatic (e.g., vomiting, jaundice), which resolved with the use of prednisolone, sometimes requiring prolonged duration and/or a higher dose. If acute serious liver injury or acute liver failure is suspected, consult a pediatric gastroenterologist or hepatologist. Prior to ZOLGENSMA infusion, assess liver function by clinical examination and laboratory testing (hepatic aminotransferases [AST and ALT], total bilirubin level, and prothrombin time). Continue to monitor liver function for at least 3 months after ZOLGENSMA infusion (weekly for the first month, and then every other week for the second and third months, until results are unremarkable).

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis afterwards (weekly for the first month; every other week for the second and third months until platelet counts return to baseline).

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported approximately one week after ZOLGENSMA infusion in the post-marketing setting. TMA is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. Concurrent immune system activation (e.g., infections, vaccinations) was identified in some cases. Monitor platelet counts, as well as signs and symptoms of TMA, such as hypertension, increased bruising, seizures, or decreased urine output. In case these signs and symptoms occur in the presence of thrombocytopenia, further diagnostic evaluation for hemolytic anemia and renal dysfunction should be undertaken. If clinical signs, symptoms and/or laboratory findings consistent with TMA occur, consult a pediatric hematologist and/or pediatric nephrologist immediately to manage TMA as clinically indicated.

Elevated Troponin-I

Increases in cardiac troponin-I levels (up to 0.176 mcg/L) were observed following ZOLGENSMA infusion in clinical trials. The clinical importance of these findings is not known. However, cardiac toxicity was observed in animal studies. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards (weekly for the first month, and then monthly for the second and third months until troponin-I level returns to baseline). Consider consultation with a cardiologist, if troponin elevations are accompanied by clinical signs or symptoms.

**ADVERSE REACTIONS**

The safety data described in this section reflect exposure to ZOLGENSMA in four open-label studies conducted in the United States, including one completed clinical trial, two ongoing clinical trials, and one ongoing observational long-term follow-up study of the completed trial. A total of 44 patients with SMA received intravenous infusion of ZOLGENSMA, 41 patients at or above the recommended dose, and 3 patients at a lower dose. The patient population ranged in age from 0.3 months to 7.9 months at the time of infusion (weight range 3.0 kg to 8.4 kg). The most frequent adverse reactions (incidence ≥ 5%) observed in the 4 studies were elevated aminotransferases* ≥ 27.3% (2/44) and vomiting 6.8% (3/44).

*Elevated aminotransferases include elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In the completed clinical trial, one patient (the patient infusion in that study) was enrolled prior to the protocol amendment instituting administration of prednisone before and after ZOLGENSMA infusion.

One patient in an ongoing non-United States clinical trial initially presented with respiratory insufficiency 12 days after ZOLGENSMA infusion and was found to have respiratory syncytial virus (RSV) and parainfluenza in respiratory secretions. The patient had episodes of serious hypotension, followed by seizures, and was found to have leukoencephalopathy (brain white matter defects) approximately 20 days after ZOLGENSMA infusion. The patient died after withdrawal of life support support 30 days after ZOLGENSMA infusion.

**Immunogenicity**

In ZOLGENSMA clinical trials, patients were required to have baseline anti-AAV antibody titers of ≤ 1:50, measured using an enzyme-linked immunosorbent assay (ELISA). Evidence of prior exposure to AAV9 was uncommon. The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Perform baseline testing for the presence of anti-AAV9 antibodies prior to ZOLGENSMA infusion. Retesting may be performed if anti-AAV9 antibody titers are reported as > 1:50.

Following ZOLGENSMA infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. In the completed clinical trial, anti-AAV9 antibody titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients. Re-administration of ZOLGENSMA in the presence of high anti-AAV9 antibody titer has not been evaluated.

**DRUG INTERACTIONS**

Where feasible, adjust a patient’s vaccination schedule to accommodate concomitant corticosteroid administration prior to and following ZOLGENSMA infusion. Certain vaccines, such as MMR and varicella, are contraindicated for patients on a substantially immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent).

**USE IN SPECIAL POPULATIONS**

Pediatric Use

Administration of ZOLGENSMA to premature neonates before reaching full-term gestational age is not recommended, because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until the corresponding full-term gestational age is reached. There is no information on whether breastfeeding should be restricted in mothers who may be seropositive for anti-AAV9 antibodies. The safety of ZOLGENSMA was studied in pediatric patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg). The efficacy of ZOLGENSMA was studied in pediatric patients who received ZOLGENSMA infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg).

Hepatic Impairment

ZOLGENSMA therapy should be carefully considered in patients with liver impairment. Cases of acute serious liver injury and acute liver failure have been reported with ZOLGENSMA in patients with preexisting liver abnormalities. In clinical trials, elevation of aminotransferases was observed in patients following ZOLGENSMA infusion.

**PATIENT COUNSELING INFORMATION**

See the ZOLGENSMA Full Prescribing Information for the Patient Counseling Information.

**Please visit ZOLGENSMA-HCP.com for Full Prescribing Information, including Boxed Warning.**

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Nusinersen Shows Long-term Safety, Benefits for Presymptomatic Infants With SMA

By Matt Hoffman

**INTRATHECALLY DELIVERED NUSINERSEN** (Spinraza; Biogen) is safe and beneficial over the long term for presymptomatic infants with spinal muscular atrophy (SMA) and 2 or 3 copies of SMN2, according to interim results from the ongoing phase 2 NURTURE study (NCT02386553).¹

The data were presented by Thomas O. Crawford, MD, codirector of the Muscular Dystrophy Association Clinic and professor of neurology at Johns Hopkins Medicine in Baltimore, Maryland, at the 2022 Muscular Dystrophy Association Clinical & Scientific Conference in March.

Data were assessed with a mean of 4.9 years (range, 3.9-5.7) of follow-up from the study, with a data cutoff of February 15, 2021. A total of 25 infants were enrolled in the study (2 SMN2 copies: n = 15; 3 SMN2 copies, n = 10).

At the data cutoff, all infants were alive and none required permanent ventilation. "These data demonstrate the continued long-term safety and benefit of infants who initiated nusinersen before onset of SMA symptoms, emphasizing the value of newborn screening/early treatment," Crawford et al wrote in the presentation poster.

Four infants from the 2 SMN2 copies cohort required respiratory intervention for 6 or more hours per day continuously for 7 or more days, though investigators noted that all cases were initiated during an acute reversible illness. The median time to death or respiratory intervention could not be estimated because there were no deaths and too few events requiring such interventions.

Every infant in the study achieved the World Health Organization motor milestone of sitting without support, 96% (n = 24) were able to walk with assistance, and 92% (n = 23) were able to walk unassisted. The majority achieved these milestones within the 99th percentile age window for healthy children (84% [n = 21] for sitting without support; 60% [n = 15] for walking assisted; 64% [n = 16] for independent walking). Notably, none of the motor skills gained during the study were lost during the observation period, nor were new safety concerns identified.

Almost all the participants (88%; n = 22) reached the maximum score on the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale, and the mean change improvement from baseline at the first evaluable assessment after day 700 in Hammersmith Functional Motor Scale Expanded (HFMSE) scores continued to show improvement over time. HFMSE scores were a mean of 16.1 (SE, 2.4) at month 36 (n = 11).

In September 2021, Biogen announced plans to initiate a phase 3b trial, ASCEND (NCT03067790), to study the safety and efficacy of higher doses of nusinersen in patients with SMA who had been treated previously with risdiplam (Evrysdi; PTC Therapeutics).²

**REFERENCES**


Ravulizumab Generates Positive Phase 3 Data in Myasthenia Gravis With FDA Review Pending

By Marco Meglio

FINDINGS FROM THE phase 3 CHAMPION MG trial (NCT03920293) showed that ravulizumab (Ultomiris; Alexion), a terminal complement C5 inhibitor, provided rapid and sustained improvement of symptoms in patients with generalized myasthenia gravis (gMG) for up to 26 weeks.¹ The FDA is reviewing a supplemental new drug application for the therapeutic in gMG; a decision is expected during the second quarter of 2022.²

These data, presented by Tuan Vu, MD, division director, Neuromuscular Medicine and EMG, University of South Florida, at the 2022 Muscular Dystrophy Association Clinical and Scientific Conference in March, build upon findings previously announced in July 2021. A total of 175 patients enrolled in 85 centers worldwide were randomly assigned 1:1 to receive either ravulizumab infusion or placebo for 26 weeks. Following that period, investigators observed that treatment with ravulizumab was associated with a statistically significant improvement in Myasthenia Gravis Activities of Daily Living (MG-ADL) total score compared with placebo (−3.1 vs −1.4 for placebo; P < .001).

In this phase 3, double-blind study, patients on the study drug received body weight–based induction doses of 2400 to 3000 mg on day 1, then 3000 to 3600 mg every 8 weeks on day 15. Patients had anti–acetylcholine receptor antibody-positive (AChR Ab+) gMG and were allowed to be on stable-dose AChR and immunosuppressant therapy throughout the study.

Quantitative Myasthenia Gravis (QMG) total score, a secondary end point, showed statistically significant improvements following ravulizumab treatment compared with placebo (P < .001). Additionally, the proportion of patients who achieved an improvement of at least 5 points in QMG was also statistically significant relative to placebo (P = .005). Both improvements in MG-ADL and QMG scores were observed within 1 week, with maintenance of benefit through week 26.¹

Additionally secondary end points assessing quality of life measures, such as Revised 15-Component Myasthenia Gravis Quality of Life score (P = .064) and Neuro-QOL Fatigue score (P = .373), did not meet statistical significance at week 26. Furthermore, the proportion of patients who achieved an improvement of at least 3 points in MG-ADL score (ravulizumab: 56.7%; placebo: 34.1%; nominal P = .0005) was not considered statistically significant based on hierarchical testing.³

During the randomized controlled period, both groups showed minimal differences in adverse events (AEs), the most frequent being headache (ravulizumab: 18.6%; placebo: 25.8%), diarrhea (ravulizumab: 15.1%; placebo: 12.4%), and nausea (ravulizumab: 10.5%; placebo: 10.1%). Among serious AEs, the most frequent included MG crisis (ravulizumab: 1.2%) and MG worsening (placebo: 3.4%).

Ravulizumab is approved in the US for the treatment of adults and children 1 month and older with paroxysmal nocturnal hemoglobinuria. It is also approved in the US and Japan for atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy in adult and pediatric patients, as well as in the European Union for the treatment of adults and children with aHUS who have a body weight of at least 10 kg.

REFERENCES


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Tolebrutinib Shows Favorable Long-term Safety and Efficacy in Relapsing MS

By Marco Meglio

BRUTON TYROSINE KINASE inhibitor tolebrutinib (SAR442168; Sanofi) demonstrated a favorable safety profile with low annualized relapse rate at 60-mg doses among patients with relapsing multiple sclerosis (MS) in an 18-month long-term safety (LTS) extension of a phase 2b trial (NCT03996291). The results, presented at the Americas Committee for Treatment and Research in Multiple Sclerosis Forum 2022 in February, also showed that through 72 weeks of treatment with tolebrutinib 60 mg, new gadolinium (Gd)-enhancing lesion counts were low. By weeks 48 and 72, when all patients in the lower-dose groups switched to 60-mg doses, investigators again noticed a reduction in new Gd-enhancing lesions.

In the original phase 2b study, tolebrutinib demonstrated a dose-dependent reduction in the number of these lesions and was well tolerated among patients with relapsing-remitting MS or relapsing secondary progressive MS (SPMS). Following the conclusion of that trial, 125 of the 129 eligible participants continued to the LTS extension study, and 124 completed part A and transitioned to part B. In total, 118 (94%) remained in the study at the August 2021 cutoff.

In the study, which was led by Jiwoh Oh, MD, PhD, staff neurologist and medical director of the BARLO Multiple Sclerosis Program at St. Michael’s Hospital at the University of Toronto in Canada, participants first entered part A of the LTS extension study, where they received 5, 15, 30, or 60 mg per day of tolebrutinib. Once the dose of 60 mg was selected for the phase 3 trials, participants entered the open-label part B of the LTS extension study, where they all received tolebrutinib 60 mg/day.

At week 72, a low number of new Gd-enhancing lesions (mean, 0.62 [SD, 1.06]) were observed for those in the 60/60-mg arm, where dosing had not changed. For those in the 5/60-mg, 15/60-mg, and 30/60-mg arms, these lesions were reduced by mean counts of 0.68 (SD, 0.98), 0.86 (SD, 2.42), and 0.47 (SD, 1.33), respectively, at weeks 48 and 72. The investigators also wrote that new and/or enlarging T2 lesion counts remained low for the 60/60-mg arm through week 24 and increased slightly at weeks 48 and 72.

Slowly evolving lesion volume, another MRI outcome measure, was 441 (IQR, 69-630), 468 (IQR, 102-1317), 675 (IQR, 150-1230), and 284 (IQR, 168-504) mm³ in the 5/60-, 15/60-, 30/60-, and 60/60-mg arms, respectively, at week 72. Most patients did not demonstrate changes in paramagnetic rim lesion counts.

Most common adverse events (AE) were headache (12.8%), COVID-19 (12.8%), nasopharyngitis (10.4%), upper respiratory tract infection (8.0%), and arthralgia (5.6%). There was no dose-dependent relationship observed for treatment-emergent AEs or serious AEs in part A, and patients who switched to 60-mg tolebrutinib in part B showed no new safety signals as well.

Tolebrutinib has become a well-traveled investigational agent in the MS pipeline. In December 2020, the National Multiple Sclerosis Society announced the therapeutic is being evaluated in 4 phase 3 trials: GEMINI 1 and GEMINI 2 (NCT04410978; NCT04410991) in...
CONFERENCE HIGHLIGHTS

patients with relapsing forms of MS, HERCULES (NCT04411641) in nonrelapsing SPMS, and PERSEUS (NCT04458051) in primary progressive MS.\(^1\)

GEMINI 1, a randomized, double-blind study, is evaluating the safety and efficacy of 60-mg tolebrutinib in comparison with oral teriflunomide (Aubagio; Sanofi), an FDA-approved therapy. Patients in that study are randomly assigned to receive either treatment for up to 3 years. ■

REFERENCES


CNM-Au8 Shows Effects on Brain Bioenergetic Metabolism, Supports Candidacy in MS

By Matt Hoffman

**DATA FROM A PAIR** of poster presentations on CNM-Au8 (Clene Nanomedicine), an investigational disease-modifying treatment for multiple sclerosis (MS), suggest that the agent has effects on brain bioenergetic metabolism, offering support for the nanotherapeutic’s clinical development.\(^1\)

The first poster included data from the phase 2 REPAIR-MS clinical trial (NCT03993171) that suggested that CNM-Au8 treatment resulted in improvements in the NAD+/NADH ratio (primary end point), NAD+ and NADH levels (secondary end point), and homeostatic effects on brain bioenergetic phosphorous metabolites (exploratory end point).\(^1\)

The second poster offered an update on the phase 2 VISIONARY-MS clinical trial (NCT03536559), which showed that at each visit—weeks 12, 24, 36, and 48—the overall study population, who were randomly assigned 2:1 to active CNM-Au8 or placebo, reported mean improvements in the primary end point, low contrast letter acuity (\(P<.0001\)), as well as averaged Multiple Sclerosis Functional Composite (MSFC) scores (\(P<.0001\)). Additional improvements were observed in the MSFC domains, including Symbol Digit Modalities Test (\(P<.0001\)), 9-Hole Peg Test (9HPT) dominant hand (\(P<.001\)), and 9HPT nondominant hand (\(P<.002\)). All patients in the study were stable, had chronic optic neuropathy, and were being treated with disease-modifying therapy.\(^2\)

Both sets of results were presented by Robert Glanzman, MD, FAAN, chief medical officer of Clene Nanomedicine, at the Americas Committee for Treatment and Research in Multiple Sclerosis Forum 2022 in February.\(^3\)

The data from the prespecified integrated analysis on brain energy metabolism across REPAIR-MS and its twin trial, REPAIR-PD (NCT03815916), showed that there was a statistically significant increase of 10.4% (0.589 U) in brain NAD+/NADH ratio following 12 weeks of treatment with CNM-AU8 (\(P=.037\)). The REPAIR-MS trial alone demonstrated an improvement of 14.3% (0.8296 U; \(P=.14\)).\(^1\)

REPAIR-MS also incorporated a third high-resolution magnetic resonance spectroscopy (31P-MRS) scan following a 6-week washout period, which resulted in a return to baseline in mean NAD+/NADH ratio levels following the withdrawal of CNM-Au8 treatment. The exploratory end points showed that CNM-Au8 administration resulted in normalization of several critical biomarkers, including \(r\)-ATP levels (\(r^2=0.71; P=.14\)) and phosphorylation potential (\(r^2=0.68; P=.002\)).\(^1\)

The REPAIR-PD trial is one of the sequential group studies examining the brain metabolic effects, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8 in patients with Parkinson disease who received a diagnosis within 3 years of screening. Participants received CNM-Au8 orally each morning for 12 weeks. In August 2021, Clene announced that the therapy had achieved the primary end point in both trials.\(^4\)

REFERENCES


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Introducing a MEDIFLIX ORIGINAL film about one woman’s journey with Parkinson’s and her unexpected discoveries along the way.

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THE COVID-19 PANDEMIC has highlighted tremendous gaps in the care of individuals with Parkinson disease (PD). Perhaps a silver lining from this turbulent time will be the opportunity to work together to improve care in pressing areas of need for individuals with PD: mental health, women’s issues, and loneliness.

Individuals with PD and their caregivers often face great barriers in accessing mental health care. Several colleagues and I highlighted this in “Mind the Gap: Inequalities in Mental Health Care and Lack of Social Support in Parkinson Disease,” which was published in *Parkinsonism & Related Disorders* in 2021. Additionally, women’s issues in PD, especially from a psychosocial standpoint, have been overlooked, and we highlighted those in “Unmet Needs of Women Living With Parkinson’s Disease: Gaps and Controversies,” which was published in *Movement Disorders* in 2022. And finally, our research on the negative effects of loneliness in individuals with PD, “Synergy of Pandemics—Social Isolation Is Associated With Worsened Parkinson Severity and Quality of Life,” was published in *npj Parkinson’s Disease* in 2020.

**Mental Health**

Most providers still focus on motor issues such as tremor, stiffness, slowness, and gait disorders with little attention paid to nonmotor issues, including mental health issues, in individuals with PD. Results of a survey of patients with PD showed that 59% felt their doctors were not sensitive enough about PD-related issues in mental health treatment. Psychological symptoms can be as disabling as motor symptoms and are a key predictor of quality of life. Mental health issues often go undiagnosed because many patients and their caregivers do not know that apathy, depression, or anxiety can be associated with PD. Patients often feel embarrassed or hesitant to disclose issues in mental health unless specifically queried.

There have been disparities in the care of patients with Parkinson disease based on race, gender/sex, age, geography, disability, and sexual orientation. Multidisciplinary specialty centers and advanced therapies are disproportionately accessible to affluent, urban-dwelling White individuals. Inclusion and diversity are lacking in research, and the majority of PD clinical trials do not report race or ethnicity statistics, with one study noting that among 32 clinical trials conducted in the United States over a 23-year period, only 9 reported detailed racial/ethnic composition of trial participants—of those, only 1.7% were Black, and 1.3% were Latino/Hispanic. Often, among those trials that do, Black and Hispanic participants each constitute less than 1% of study populations.

Patients with young-onset PD (occurring in those younger than 50 years) face additional mental health stressors such as the impact of the disease on romantic relationships, family dynamics, and employment. Anxiety and impulse control disorder are highly prevalent in patients with young-onset PD.

A recent review highlighted the higher burden of social isolation, discrimination, and stigma in sexual and gender minority groups that could lead to higher mental health issues and barriers to care. Intersectional aspects of identity may compound the impact of a PD diagnosis. A young Black woman facing economic...
There is a scarcity of resources to address the mental health needs of individuals with PD, and telehealth has been proposed as one solution. However, many at-risk individuals with PD cannot afford a computer, smartphone, or internet access. This barrier excludes the most vulnerable populations from remote-care models and inhibits social prescription strategies that have been relied upon during the pandemic.

COVID-19 has unmasked the mental health crisis and is compounding the effects of earlier traumas, including adverse childhood experiences and their consequences such as posttraumatic stress disorder. Little attention has been paid to the effects of trauma on patients with PD, and the ongoing societal burden of lingering mental and physical health consequences of COVID-19. Many individuals with PD have had family and friends die from the virus and have not had the chance to grieve because of social distancing. Other individuals with PD have had COVID-19 and are dealing with the physical and psychological effects of long COVID-19 syndrome. Caregivers also face mental health issues, depression, and burnout due to social isolation, which has reduced their opportunities for respite.

The current health care delivery model has led to a lack of focus and time to address mental health issues in patients with PD. A fee-for-service insurance model often leads to little or no incentive to pursue patient-centered care. Most physicians see patients every 6 months for 15 to 30 minutes, which generally is insufficient to address all of the issues in the motor and nonmotor domains. Even when identified, mental health complaints are often inadequately addressed, with 38.5% of patients with PD failing to receive a referral for mental health care.

During the pandemic, mask use (which obscures expressions) and reduced in-person contact further complicated the identification of disordered mental states. Neurologists may spend most of the visit adjusting medications for motor impairment, and mental health issues are often unrecognized until they become a crisis. Erratic time points for accessing mental health resources may lead to a relationship with mental health providers that lacks continuity. Hence, without long-term treatment relationships, individuals with PD may not develop coping strategies to reinforce their emotional well-being.

**Women With PD**

There are significant gaps in research, advocacy, and treatment of women with PD, and the existing data are very conflicting in almost every aspect. "Unmet Needs of Women Living With Parkinson's Disease: Gaps and Controversies" provides an overview of the current knowledge, gaps, and possible strategies to deal with issues facing women with PD and focuses on the clinical and psychosocial aspects. This paper is unique in that 3 women with PD who are in health care lend their voices to this publication as authors.

The gaps we identified included the following:

- Women-inclusive drug and device studies, genetic, and hormones need to be considered. Women with PD need to learn how to communicate their symptoms and needs, become engaged in research, organize as a community, and support one another.
- Women with PD need tools to help track and convey their unique motor and nonmotor symptoms, and psychological and social support needs. The management of PD needs to be customized for the unique stages of women's lives, including menstrual cycles, pregnancy, perimenopause, menopause, and post menopause.
- Specific guidelines for use of hormonal treatments and customized dopamine replacement dosing need to be developed.
- Basic core competencies for clinicians treating women with PD should be established, such as accurately diagnosing, proactively identifying, and managing the symptoms of PD in women, including timely referral for specialty care, advanced therapies, and research studies.
- Caregivers and families need guidance on holistically supporting women with PD.

PD is often thought of as a disease affecting older White men. Results from a survey of public knowledge showed that elderly males were most frequently mentioned as likely to have PD. Although there have been efforts to modify this perception, more needs to be done. For women, there often is a delay in receiving an accurate diagnosis of PD and a referral to a movement disorder specialist. Clinical differences in presentation are not solely responsible for delays in the diagnosis of PD. Some factors lie with women themselves, such as a decreased tendency to disclose or emphasize bothersome symptoms during medical assessments. Perceptions by physicians that PD is more common in men may also contribute to delays. These inequities are further magnified in marginalized communities within countries where traditionally underserved minorities are more likely to have a missed diagnosis or to have received a delayed diagnosis.

Delays in diagnosis may lead to more dissatisfaction with care in women with PD versus men with PD. Women with PD may feel they are not being heard or that what matters to them most is not taken into consideration. Negative care experiences can affect symptom reporting. Women may not consistently share their concerns or symptoms with their providers, particularly around mental health and other sensitive topics (eg, pelvic floor problems) and thus are not treated for these issues. Women with PD may downplay their symptoms or not associate these symptoms with PD and thus do not receive treatment. A study of older patients with PD found that women prioritize symptoms that affect their ability to organize and strengthen social relationships and they were more likely to become distressed when unable to fulfill their domestic responsibilities.
Loneliness in Patients With PD

The goal of our study “Synergy of Pandemics—Social Isolation Is Associated With Worsened Parkinson Severity and Quality of Life” was to evaluate the effect of social isolation on PD symptom severity and quality of life. The primary outcome measures were the Patient-Reported Outcomes in PD (PRO-PD) and questions from PROMIS Global related to social health. PRO-PD scores increased as social performance and social satisfaction scores diminished. Individuals who reported being lonely reported a 55% greater symptom severity ($P < .01$). Individuals who documented having many friends had 21% fewer symptoms ($P < .01$). Social isolation was associated with greater patient-reported PD severity and lower quality of life. In essence, the social isolation of individuals with PD has been further compounded by the COVID-19 pandemic. The results emphasize the need to keep individuals with PD socially connected and prevent loneliness in this time of social distancing. Proactive use of virtual modalities for support groups and social prescribing should be explored.

There have been comparisons in the literature of social isolation being as detrimental to aging populations’ health as smoking or obesity. After accounting for multiple covariates, a key study reported the increased likelihood of death was 26% for reported loneliness, 29% for social isolation, and 32% for living alone. Investigators have identified 3 dimensions of loneliness reflecting the particular relationships that are missing. Intimate, or emotional, loneliness is the yearning for a close confidante or emotional partner. Relational, or social, loneliness is the longing for close friendships and social companionship. Collective loneliness is the need for a network or community of those who share one’s sense of purpose and interests. Loneliness can be felt if any 1 of these dimensions is not satisfied; for instance, it is possible to be happily married and still feel lonely.

Social prescribing is a novel concept in which clinicians recommend or prescribe resources or activities in the community to help patient develop healthy social connections. The Department of Veterans Affairs recently created the “Compassionate Contact Corps Program,” which uses volunteers to call veterans who are lonely and check in on them. Volunteering can also help loneliness, and it has been proposed that veterans be paired up with each other to make such calls.

The National Health Service in the United Kingdom designed a link worker social prescribing program that lists referrals to group exercise classes, art-based therapies, volunteer opportunities, self-help groups for specific conditions, and community activities such as gardening and cooking. Proactive screening of individuals with PD using questions from the UCLA loneliness scale and referring lonely individuals with PD to social support resources could help keep them socially connected during the pandemic and beyond.

Taking time to reflect on whom we are not serving well and how we can do better has been an important consequence of the COVID-19 pandemic. Addressing disparities in the care of women with PD, improving barriers to mental health care, and keeping individuals with PD socially connected have been important areas of unmet needs. Educating ourselves and advocating for our patients are critical steps to improving the disparities in the care of individuals with PD.

For a full list of references, see the article on NeurologyLive.com.
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Increased levodopa exposure by up to 74%, helping more levodopa be available to reach the brain¹,²

Started to reduce off time as early as 1 week*, with significant reductions of 2 hours vs. 1 hour with placebo seen at 14/15 weeks†—studied through 1 year¹,²

No titration required— one capsule, taken at bedtime¹
• Patients should not eat food for 1 hour before and at least 1 hour after taking ONGENTYS¹

ONGENTYS was generally well tolerated in clinical studies.¹

*At Week 1: -1.24 hours vs -0.42 hours for placebo in Study 1; -1.22 hours vs -0.47 hours for placebo in Study 2.²
†For Study 1: -1.95 hours vs -0.93 hours with placebo (P=0.002) at Week 14/15; adjusted P value was calculated using Dunnett’s alpha level adjustment to control for multiplicity.

INDICATION & USAGE
ONGENTYS® (opicapone) capsules is indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease (PD) experiencing “off” episodes.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
ONGENTYS is contraindicated in patients with:
• Concomitant use of non-selective monoamine oxidase (MAO) inhibitors.
• Pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.

WARNINGS & PRECAUTIONS
Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT)
Possible arrhythmias, increased heart rate, and excessive changes in blood pressure may occur with concomitant use of ONGENTYS and drugs metabolized by COMT, regardless of the route of administration (including inhalation). Monitor patients treated concomitantly with ONGENTYS and drugs metabolized by COMT.

Falling Asleep During Activities of Daily Living and Somnolence
Patients treated with dopaminergic medications and medications that increase levodopa exposure, including ONGENTYS, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes has resulted in accidents. If a patient develops daytime sleepiness or somnolence, consider discontinuing ONGENTYS or adjusting other dopaminergic or sedating medications and advise patients to avoid driving and other potentially dangerous activities.

Please see additional Important Safety Information on back of page.

SEE THE FULL STORY AT ONGENTYSHCP.COM
**Pharmacokinetic Study Design:** A randomized, open-label, Phase 1 study to assess the pharmacokinetics and pharmacodynamics of repeated doses of ONGENTYS 50 mg administered orally as adjunctive therapy to stable regimen of levodopa/carbidopa in patients with PD (N=16). Patients were randomized to receive immediate-release levodopa/carbidopa, either every 3 hours (n=7) or every 4 hours (n=9). The data for this every-4-hour, or Q4H, population are shown above. All patients received once-daily ONGENTYS 50 mg in the evening from Days 1 to 14.²

**Pivotal Studies Design:** ONGENTYS was studied in two 14- to 15-week, double-blind, randomized, parallel-group studies of patients with PD experiencing off episodes being treated with levodopa/DDCI (alone or in combination with other PD medications). The double-blind period for each study began with an up to 3-week levodopa/DDCI adjustment period, followed by a stable maintenance period of 12 weeks. The primary endpoint of both studies was mean change in off time, based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. After the double-blind period, patients were able to enroll in a 1-year open-label extension of ONGENTYS. Patients who had been on placebo or active comparator in the double-blind period received ONGENTYS in the open-label period. For the majority of the extension period, investigators were able to adjust patients’ levodopa/DDCI according to clinical response.¹²

**IMPORTANT SAFETY INFORMATION (CONT’D)**

**WARNINGS & PRECAUTIONS**

**Hypotension/Syncope**
Monitor patients for hypotension and advise patients about the risk for syncope. If these adverse reactions occur, consider discontinuing ONGENTYS or adjusting the dosage of other medications that can lower blood pressure.

**Dyskinesia**
ONGENTYS potentiates the effects of levodopa which may result in dyskinesia or exacerbate pre-existing dyskinesia. Reducing the patient’s levodopa dosage or the dosage of another dopaminergic drug may reduce dyskinesia that occurs during treatment with ONGENTYS.

**Hallucinations and Psychosis**
Consider stopping ONGENTYS if hallucinations or psychotic-like behaviors occur. Patients with a major psychotic disorder should ordinarily not be treated with ONGENTYS.

**Impulse Control/Compulsive Disorders**
Patients may experience intense urges (eg, gambling, sexual, spending money, binge eating) and the inability to control them. It is important for prescribers to specifically ask patients or their caregivers about the development of new or increased urges. Re-evaluate the patient’s current therapies for Parkinson’s disease and consider stopping ONGENTYS if a patient develops such urges while taking ONGENTYS.

**Withdrawal-Emergent Hyperpyrexia and Confusion**
A symptom complex resembling neuroleptic malignant syndrome (elevated temperature, muscular rigidity, altered consciousness, and autonomic instability) has been reported in association with rapid dose reduction or withdrawal of drugs that increase central dopaminergic tone. There were no reports of neuroleptic malignant syndrome in ONGENTYS controlled clinical studies. When discontinuing ONGENTYS, monitor patients and consider adjustment of other dopaminergic therapies as needed.

**ADVERSE REACTIONS**
The most common adverse reactions (incidence at least 4% and greater than placebo) were dyskinesia, constipation, blood creatine kinase increased, hypotension/syncope, and weight decreased. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

**Please see adjacent page for brief summary of PI and visit ONGENTYShcp.com/pi for full PI.**

**References:**
ONGENTYS® (opicapone) capsules, for oral use
The following is a brief summary; for full Prescribing Information and Patient Information, refer to package insert.

INDICATIONS AND USAGE
ONGENTYS is indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease (PD) experiencing “off” episodes.

CONTRAINDICATIONS
ONGENTYS is contraindicated in patients with:
- Concomitant use of non-selective monoamine oxidase (MAO) inhibitors.
- Pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.

WARNINGS AND PRECAUTIONS
Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT)
Possible arrhythmias, increased heart rate, and excessive changes in blood pressure may occur with concomitant use of ONGENTYS and drugs metabolized by COMT (e.g., isoproterenol, epinephrine, norepinephrine, dopamine, and dobutamine), regardless of the route of administration (including inhalation). Monitor patients treated concomitantly with ONGENTYS and drugs metabolized by COMT.

Falling Asleep During Activities of Daily Living and Somnolence
Patients treated with dopaminergic medications and medications that increase levodopa exposure, including ONGENTYS, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes has resulted in accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event.

Before initiating treatment with ONGENTYS, advise patients of the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence with dopaminergic therapy, such as concomitant sedating medications or the presence of a sleep disorder. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require full attention (e.g., driving a motor vehicle, conversations, eating), consider discontinuing ONGENTYS or adjusting other dopaminergic or sedating medications. If a decision is made to continue ONGENTYS, patients should be advised not to drive and to avoid other potentially dangerous activities.

Hypotension/Syncope
In Study 1 and Study 2, hypotension (orthostatic and non-orthostatic), syncope, and presyncope occurred in 5% of patients treated with ONGENTYS 50 mg compared to 1% of patients who received placebo. Monitor patients for hypotension (orthostatic and non-orthostatic) and advise patients about the risk for syncope and presyncope. If these adverse reactions occur, consider discontinuing ONGENTYS or adjusting the dosage of other medications that can lower blood pressure.

Dyskinesia
ONGENTYS potentiates the effects of levodopa and may cause dyskinesia or exacerbate pre-existing dyskinesia.

In controlled clinical trials (Study 1 and Study 2), dyskinesia occurred in 20% of patients treated with ONGENTYS 50 mg compared to 6% of patients who received placebo. Dyskinesia was also the most common adverse reaction leading to discontinuation of ONGENTYS.

Reducing the patient’s daily levodopa dosage or the dosage of another dopaminergic drug may mitigate dyskinesia that occurs during treatment with ONGENTYS.

Hallucinations and Psychosis
In Study 1 and Study 2, hallucinations (hallucinations, auditory hallucinations, visual hallucinations, mixed hallucinations) occurred in 3% of patients treated with ONGENTYS 50 mg compared to 1% of patients who received placebo. Delusions, agitation, or aggressive behavior occurred in 1% of patients treated with ONGENTYS 50 mg, and in no patient who received placebo. Consider stopping ONGENTYS if hallucinations or psychotic-like behaviors occur.

Patients with a major psychotic disorder should ordinarily not be treated with ONGENTYS because of the risk of exacerbating the psychosis with an increase in central dopaminergic tone. In addition, treatments for psychosis that antagonize the effects of dopaminergic medications may exacerbate the symptoms of PD.

Impulse Control/Compulsive Disorders
Patients treated with ONGENTYS can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more dopaminergic therapies that increase central dopaminergic tone. In some cases, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with ONGENTYS.

In Study 1 and Study 2, impulse control disorders occurred in 1% of patients treated with ONGENTYS 50 mg, and in no patient who received placebo. Re-evaluate the patient’s current therapy(ies) for Parkinson’s disease and consider stopping ONGENTYS if a patient develops such urges while taking ONGENTYS.

Use with caution in Parkinson’s patients with suspected or diagnosed dopamine dysregulation syndrome.

Withdrawal-Emergent Hyperpyrexia and Confusion
A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone. In the controlled clinical studies of ONGENTYS, patients discontinued ONGENTYS treatment without dose tapering or gradual withdrawal. There were no reports of neuroleptic malignant syndrome in ONGENTYS controlled clinical studies. When discontinuing ONGENTYS, monitor patients and consider adjustment of other dopaminergic therapies as needed.
ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT)
- Falling Asleep During Activities of Daily Living and Somnolence
- Hypotension/Syncope
- Dyskinesia
- Hallucinations and Psychosis
- Impulse Control/Compulsive Disorders
- Withdrawal-Emergent Hyperpyrexia and Confusion

Clinical Trials Experience

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

The safety of ONGENTYS was evaluated in 265 patients with Parkinson’s disease (PD) in two 14-15 week placebo- and active-controlled (Study 1) or placebo-controlled (Study 2) studies. All patients were taking a stable dose of levodopa and a DOPA decarboxylase inhibitor, alone or in combination with other PD medications. In Study 1 and Study 2, the mean age of patients was 63.6 years, 59% of patients were male, and 89% of patients were Caucasian. At baseline, the mean duration of PD was 7.6 years.

Adverse Reactions Leading to Discontinuation of Treatment

In Study 1 and Study 2, a total of 8% of ONGENTYS 50 mg-treated patients and 6% of patients who received placebo discontinued due to adverse events. The most common adverse reaction leading to discontinuation was dyskinesia, reported in 3% of ONGENTYS 50 mg-treated patients and 0.4% of patients who received placebo.

Common Adverse Reactions

Adverse reactions that occurred in the pooled studies at an incidence of at least 2% and greater than placebo are presented in Table 1. The most common adverse reactions (incidence at least 4% and greater than placebo) were dyskinesia, constipation, blood creatine kinase increased, hypotension/syncope, and weight decreased.

Table 1: Adverse Reactions with an Incidence of at Least 2% in Patients Treated with ONGENTYS and Greater than on Placebo, in Pooled Study 1 and Study 2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ONGENTYS 50 mg N=265 %</th>
<th>Placebo N=257 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination¹</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood creatine kinase increased</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension/syncope²</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Includes hallucinations, hallucinations visual, hallucinations auditory, and hallucinations mixed
² Includes hypotension, orthostatic hypotension, syncope, and presyncope

DRUG INTERACTIONS

Non-Selective Monoamine Oxidase (MAO) Inhibitors

Both ONGENTYS and non-selective MAO inhibitors (e.g., phenelzine, isocarboxazid, and tranylcypromine) inhibit catecholamine metabolism, leading to increased levels of catecholamines. Concomitant use may increase the risk of possible arrhythmias, increased heart rate, and excessive changes in blood pressure.

Concomitant use of ONGENTYS with non-selective MAO inhibitors is contraindicated. Selective MAO-B inhibitors can be used concomitantly with ONGENTYS.

Effect of ONGENTYS on Other Drugs

Drugs Metabolized by Catechol-O-Methyltransferase (COMT)

Concomitant use of ONGENTYS with drugs metabolized by COMT may affect the pharmacokinetics of those drugs, which may increase the risk of possible arrhythmias, increased heart rate, and excessive changes in blood pressure. Drugs known to be metabolized by COMT should be administered with caution. Monitor for changes in heart rate, rhythm, and blood pressure in patients concomitantly treated with ONGENTYS and drugs metabolized by COMT.

OVERDOSAGE

No specific antidotes for ONGENTYS are known. As a general measure, removal of ONGENTYS by gastric lavage and/or inactivation by administering activated charcoal should be considered. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an over-exposure occurs, call your poison control center at 1-800-222-1222 or www.poison.org.

For further information on ONGENTYS, call 1-833-ONGENTYS (833-664-3689) or visit www.ongentys.com

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CP-OPC-US-0111 09/2020
PDE10A Inhibition in Tourette Syndrome

By Jennifer S. Sun, PhD

TOURETTE SYNDROME (TS) IS A common neuropsychiatric disorder that affects approximately 0.3% to 1% of the global population and is characterized by multiple chronic tics (eg, involuntary movements and uncontrollable vocalizations).1,2 TS begins in childhood or adolescence and exhibits a pronounced bias toward males.1,3 Dysfunction of frontostriatal circuits is the common neurobiological basis for several neuropsychiatric disorders, including TS.4 Neuroimaging and neuropathology studies implicate the major connections of the ganglia in TS.4 Particularly, overactivation of habitual actions or failure of automatic inhibition appear to contribute to TS.2 TS propensity has also been associated with interactions between environmental factors (eg, mother smoked during pregnancy, pregnancy complications, low birth weight, and infections during childhood) and genetic perturbations.5 Probable risk genes have been identified (eg, CELSR3, WWC1, OPA1, NIPBL, FN1, and FBN2).2,6 CELSR3 and WWC1 encode proteins involved in cell polarity, suggesting a role for cell polarity defects in the pathogenesis of TS.2,3 TS is often accompanied by other psychiatric conditions such as depression,4 obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder;2 in fact, there is significant overlap of de novo damaging sequence variants between patient populations with TS and OCD consistent with a subset of genetic risk loci being shared between these conditions.2 Yet no clear cause of TS has been identified, nor are there treatment options that completely eliminate symptoms.2,3

Strategies to treat neuropsychiatric disorders (eg, pharmacotherapy, gene therapy, immunotherapy) are urgently needed because the symptoms and discomforts accompanying TS have a large impact on patients’ quality of life.4 TS is traditionally treated with antipsychotics or behavioral interventions, although both have limited efficacy and the former is associated with significant motor and metabolic adverse effects (AEs).1,2,4,7 Deep-brain stimulation (DBS) of the globus pallidus (GPi) is another intervention option that has shown efficacy in controlling TS tics and comorbidities.2 A double-blind, randomized crossover trial included 14 patients (11 male; mean age, 35.57 years; SD, 15.68 years) with severe TS who were actively using psychiatric medications.3 The study also included 8 healthy volunteers (5 female; mean age, 33.13 years; SD, 6.79 years) who did not exhibit any neurological conditions, psychiatric or physical illnesses, or did not have a history of head injury or alcohol or drug abuse.3 Patients with TS were tested on the stop signal task prior to surgery and again upon completion of the trial (with the GPi-DBS activated), whereas healthy controls did not undergo surgery and were tested only once.3 Unfortunately, reaction time measures of inhibition were not significantly altered by GPi-DBS surgery, although these results may not be representative because of sample characteristics (ie, small sample size, age, comorbidities, and type of inhibitory task).3

TS can be triggered by abnormal metabolism of dopamine in the brain4; this neurotransmitter plays a central role in regulation of motor and cognitive functions.5,8,9 The enzyme phosphodiesterase 10A (PDE10A) partially regulates dopamine neurotransmission; thus, PDE10A has received attention as an attractive target for antipsychotic drugs.5,8,10 PDE10A has very limited distribution and is mainly expressed in medium spiny neurons (MSNs) of the striatum and substantia nigra (FIGURE).7,9-11 Synergistic dopamine type D1 and D2 receptors are also expressed on striatal MSNs.4 PDE10A acts postsynaptically on dopamine signaling by controlling the availability of the second messengers cyclic adenosine monophosphate and cyclic guanosine monophosphate,4,8-11 which in turn dictates neuronal cell functions that, when dysregulated, can lead to cognitive, motor, or psychiatric disturbances.4

Inactivation of PDE10A enhances the effect of dopamine D1 receptor activation in the striatoniargal (direct) pathway and counteracts the inhibitory effect of D2 receptor signaling in the striatopallidal (indirect) pathway.4,10 PDE10A inhibitors have been tested for safety and tolerability in patients with Huntington disease (NCT02197130) and schizophrenia (NCT01568203, NCT02019329, NCT02477020).4 In 2021, Noema Pharma in-licensed the PDE10A inhibitor NOE-105 from Roche12,13 for a clinical study of this drug candidate in reducing the involuntary tics of TS.14 NOE-105 was previously found to be safe in adults at repeated doses of up to 30 mg per day.1,7 Importantly, NOE-105 is not associated with the motor and metabolic AEs typical of second-generation antipsychotics (eg, insulin resistance and type 2 diabetes).7,15 The NOE-105 12-week, multicenter, interventional, dose-ranging, open-label...
Inflammatory and apoptotic cascades and can increase blood flow.

PDE10A is a potential therapeutic target for the treatment of several neurodegenerative disorders; thus, medicinal chemists have been focused on developing potent PDE10A inhibitors with minimal AEs. In preclinical computational biology approaches to drug design, a receptor-based pharmacophore model can refine the protein structure and active site of PDE10A and use molecular docking and molecular dynamics simulations to predict ligand binding affinity. Pharmacophore-based screening of existing databases was performed to identify potential PDE10A inhibitors with matching pharmacophoric features, then filtered to retain only compounds with drug-likeness properties and central nervous system (CNS) activity (relatively small, moderately lipophilic, small polar surface area, and blood/brain partition coefficient of 0.1-2.5). The value of CNS in the range of 0-2). Zinc42657360 from the zinc database was 1 of 2 compounds with the highest affinity to PDE10A from the docking simulations. In the PDE-Glo phosphodiesterase assay, Zinc42657360 indeed exhibited significant inhibitory activity of 1.60 mM against PDE10A. Zinc42657360 could thus be further developed into potent analogues with improved affinity, for use as a PDE10A inhibitor.

Currently, no PDE10A inhibitors have been approved as treatments for neurodegenerative disorders, possibly because of the lack of comprehensive research in this area, as well as the observed extrapyramidal AEs. Animals housed under standard laboratory conditions are not representative test models for the evaluation of cognition-enhancing drugs because of the resulting impoverished brains, which results in false-positive results and lack of translatable to humans. There is thus a need for deeper understanding of the complex interactions and cross talk between the direct and indirect pathways, and their involvement in TS pathology.

Moreover, better understanding of the subcellular localization of PDEs will aid in maximizing the specificity of therapeutic.

Notably, current PDE inhibitors exhibit off-target effects on inflammatory and apoptotic cascades and can increase blood flow and glucose metabolism. Structure-based drug design promises to improve PDE10A selectivity of drug candidates, which will benefit patients by minimizing adverse effects.

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REFERENCES

Boundary Between Chronic and Episodic Migraine Is “in Flux”

David Kudrow, MD, provides expert insight on the newest options for migraine management and prevention.

By Matt Hoffman

THE TREATMENT OF PATIENTS with migraine has undergone massive change since the turn of the century. And with the introduction of calcitonin gene-related peptide (CGRP)–targeted medicines in 2018, the field was transformed once again. Clinicians now have a variety of migraine-specific treatment options available after many years without such therapeutic approaches.

Even with the availability of treatment options, challenges remain. One of the major roadblocks is the limited number of headache specialists available to treat the more than 40 million individuals with the disease. The need has never been greater for a wider range of physicians to understand migraine and available therapies.

In a recent NeurologyLive Insights™ series, DAVID B. KUDROW, MD, medical director of California Medical Clinic for Headache in Santa Monica, offered his perspective on treating patients with migraine and discussed the impact of these new medicines.

Differences Between Episodic and Chronic Migraine

Chronic migraine is defined as at least 8 migraine days per month in a total of 15 or more migraine and headache days per month. Episodic migraine, on the other hand, includes headache occurring at a frequency of up to 14 headache days per month.

Because of how the disease functions, “I find that 15-day limit between the 2 diagnostic categories to be rather arbitrary,” Kudrow said. “Three percent of patients who have episodic migraine will become chronic over the course of 1 year, and [approximately] 25% of patients who have chronic migraine may revert to episodic migraine over the course of a year.”

Kudrow pointed out the American Headache Society’s Harold G. Wolff Lecture Award given in 2021 to Ryotaro Ishii, MD, PhD, for his examination of a large database of patients with migraine. Study results showed that with respect to the degree of disability that patients experience, those with 8 to 14 migraine days per month were not significantly different from patients with 15 to 23 migraine days per month. Those who had 24 or more headache days per month had the greatest degree of disability.

“That traditional arbitrary boundary between chronic and episodic is in flux at this point,” Kudrow said. “Why is that important? Because there are some medications that we use for patients who have chronic migraine that may be beneficial for patients who have less than chronic migraine. It’s important to understand and recognize that those diagnostic categories are relatively fluid.”

Kudrow explained that the difference in the acute migraine attacks themselves is essentially null for these patients, whether they have episodic or chronic disease. As for symptoms, they have similar characteristics with only the frequency differing. Kudrow explained that migraine attack is defined as moderate to severe headache that tends to be unilateral and can be associated with nausea, light sensitivity, and sound sensitivity. Patients don't want to move, the headache worsens with exertion, and the headache can occur with a visual aura.

“Migraine is a long-lasting phenomenon. We recognize the acute attack as the most obvious clinical observation in a patient who has migraine, but there’s a prodrome to the attack that can be several hours to days in duration,” Kudrow said. “There’s also a postdrome
Great scientific thinkers have introduced these therapies that are... migraine-specific, effective, and better tolerated. Why would we need to jump through hoops and try things that are less effective...?

—DAVID B. KUDROW, MD

to the attack that can be several hours to days in duration, which prolongs the time of the acute migraine attack. The more frequent migraine becomes, the fewer headache-free days a patient has. That’s important to point out in recognizing how increasing frequency of migraine contributes to disability of the patient’s experience and the need for effective acute and preventive therapeutics.

Deciding on Treatment Options
Kudrow explained that the process of treatment, whether prescribing an acute pharmacotherapy or a preventive therapy for migraine, always begins with a discussion with the patient. An informed patient is more likely to be adherent to the medication regimen that’s prescribed, and more information and dialogue improve the process for all involved.

But the variability in how each patient’s disease responds to treatment options complicates the process. “With respect to acute treatment for migraine, there are patients who have varying intensities or severities of migraine. Some patients can get away with using an OTC medication for some of their migraines, or the same patient may have more severe migraines that require a more migraine-specific abortive agent. Everybody who has migraine should be armed with an acute migraine medication,” Kudrow said.

When it comes to preventive treatment, Kudrow said that the bar for success is changing because of the recent introduction of migraine-specific, mechanism-specific medications that have better adverse effect profiles and better efficacy compared with older options. The American Headache Society recommends that patients with as few as 2 migraine days per month be considered for preventive treatment if those migraine days are accompanied by significant disability and that any patient with at least 4 migraine days per month should be considered for migraine preventive therapy, irrespective of the degree of disability.

“In my own practice, it’s a sliding scale,” Kudrow said. “I have patients who may have 4 to 6 migraine days per month, and they’ve been using a triptan that works very effectively for them without much in the way of adverse events. They don’t want to take preventive medication and want to just keep using their acute medication. That’s a reasonable choice.

“On the other hand, there are patients who have 1 or 2 severe migraine days per month and are debilitated by them. Even if they use their acute medication, that medication may help the headache but then has adverse effects that incapacitate the patient or prevent them from working. Not many patients can tolerate losing 1 or 2 days of work per month without getting fired. If we can’t get those headaches under control with a good acute treatment, then even those patients should be considered for preventive therapy,” he said.

Ultimately, it begins with a physician-patient discussion. Ensuring that patients are educated about adverse effects and are part of the treatment decision process is important. Kudrow said that the discussion of when and whether to start a preventive treatment and which treatment to select is critical for the therapeutic regimen’s success.

Advice for Neurologists
“It has become easier to treat patients who have migraine. We have a new class of medications that has a very favorable safety profile, a favorable tolerability profile, and a favorable efficacy profile,” Kudrow said, adding that he would advise not fearing the use of the CGRP class of medications, either monoclonal antibodies or small molecule antagonists, because of the adverse effect profile and tolerability profiles.

Kudrow noted that expense was the greatest barrier to new therapeutics coverage. For those without insurance, the new medications can be “phenomenally expensive,” he said. For those with insurance, many of the pharmaceutical manufacturers are offering the medicines at discounts for at least 1 year, though not all patients are eligible for those discounts. But even for those with insurance, many payers are inquiring with physicians about attempting traditional oral preventive medications prior to using the new anti-CGRP monoclonal antibodies or small molecule antagonists. “In many cases, physicians are going to have to step through those options before being able to use these medications,” Kudrow said.

“My attitude is a little different,” he said. “We’ve come a long way. Great scientific thinkers have introduced these therapies that are disease-specific, migraine-specific, effective, and better tolerated. Why would we need to jump through hoops and try things that are less effective, during which time patients continue to [experience] migraine attacks, disability, and affected quality of life?”

To view the entire NeurologyLive® Insights™ series
“Expert Perspectives on the Management of Acute and Preventive Migraine,”
go to neurologylive.com/kudrow-migraine.
CAP-1002 Builds Momentum in DMD With Phase 3 HOPE-3 Study

By Marco Meglio

The study evaluating 68 boys and young men with Duchenne muscular dystrophy will consist of therapy with off-the-shelf cardiosphere-derived cells.

CAP-1002, AN ALLOGENEIC off-the-shelf cell therapy developed by Capricor Therapeutics, will be evaluated as a treatment for patients with Duchenne muscular dystrophy (DMD) in an upcoming pivotal phase 3 trial, HOPE-3 (NCT05126758), a multicenter, randomized, double-blind, placebo-controlled study that will include both nonambulatory and ambulatory boys and young men who meet eligibility criteria (TABLE).

The therapy consists of allogeneic, off-the-shelf cardiosphere-derived cells (CDCs), which have been the subject of more than 100 peer-reviewed scientific publications since they were discovered in 2007. In CAP-1002, the cells release exosomes that are taken up largely by macrophages and T cells and begin a cycle of repair. CAP-1002 has been granted orphan drug designation by the FDA.

HOPE-3 is expected to be complete in late June 2024. An estimated 68 participants will be randomly assigned to receive CAP-1002 at a dose of 150 million CDCs or placebo every 3 months for a total of 4 doses over a 12-month period. Led by Craig M. McDonald, MD, professor and chair of the Department of Physical Medicine and Rehabilitation at University of California, Davis, the study will use mean change in full upper limb function at month 12 as measured by Performance of the Upper Limb (PUL) version 2.0 scores as the primary end point. The secondary outcome will be cardiac muscle function and structure as measured by change from baseline in ejection fraction.

The study will include only males at least 10 years or older at time of consent who have genetically confirmed DMD. Participants are expected to have reduced ability to walk/run, have up-to-date immunizations, and have received treatment with systemic glucocorticoids for at least 12 months and at a stable dose for at least 6 months prior to study participation. The trial will include visits at screening, baseline/day 1, and months 3, 6, and 9. Safety evaluations will include adverse events, concomitant medications, physical exam, vital signs, 12-lead electrocardiogram, and clinical laboratory testing.

In September 2021, the company announced positive data from its phase 2 HOPE-2 study (NCT03406780), which showed that CAP-1002 met its primary end point on decline in mid-PUL version 1.2. Patients showed a slowing of this outcome by 71% (P = .01) compared with placebo. Additionally, the trial also met additional end points, with significant differences seen on the full PUL version 2.0 (P = .04) and cardiac end point of ejection fraction (P = .02) compared with placebo.

HOPE-2, conducted across 9 sites in the US, enrolled 20 participants (12 placebo and 8 treated) with DMD. In total, 80% of the patients were nonambulatory, with other demographic and baseline characteristics similar between the 2 groups. Besides 2 hypersensitivity reactions seen early in the trial—which were mitigated with a common premedication regimen—CAP-1002 was well tolerated with no serious safety signals.

“This groundbreaking study is extremely exciting as we saw statistically significant changes of CAP-1002 in both skeletal and cardiac function. For these older [patients] who have limited therapeutic options, these data support the belief that CAP-1002 may become an important therapeutic option and possibly slow the progression of DMD,” McDonald said in a statement following announcement of the results.

CAP-1002 also was previously evaluated in the HOPE-Duchenne phase 1/2 trial (NCT02485938) for DMD-associated cardiomyopathy, which enrolled 25 participants across 3 sites in the US. All participants had significant cardiac scarring and approximately two-thirds were dependent on wheelchairs at the time they began the trial. During the 12-month course of the trial, CAP-1002 demonstrated a safe and well-tolerated profile, along with significant and sustained signals of improvement in cardiac and skeletal muscle function in patients with DMD.

In January 2022, Capricor Therapeutics announced that it had entered a partnership with Nippon Shinyaku Co (NS Pharma) for the exclusive commercialization and distribution of the therapy in the US. Linda Marthin, PhD, CEO of Capricor, said in a news release that the partnership “aligns us with a larger, seasoned pharmaceutical company experienced in rare disease with specific expertise in DMD.” She cited NS Pharma’s 2020 approval and launch of vilinoral (Viltupe) for patients with DMD amenable to exon 53 skipping, which was at the time was only the second FDA-approved therapy for this specific DMD gene mutation.

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

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TABLE. HOPE-3 (NCT05126758)

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>Randomization</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males 10 years or older</td>
<td>11 to each CAP-1002 (150 million cardiosphere-derived cells every 3 months for a total of 4 doses) or placebo</td>
<td>Evaluate upper limb function at month 12 using PUL version 2.0 scores</td>
</tr>
<tr>
<td>Diagnosis of genetically confirmed DMD</td>
<td></td>
<td>DMD, Duchenne muscular dystrophy; PUL, Performance of the Upper Limb.</td>
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<tr>
<td>Reduced ability to walk/run (if ambulatory)</td>
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<tr>
<td>Up-to-date immunizations</td>
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<tr>
<td>Treatment with systemic glucocorticoids for at least 12 months and at a stable dose at least 6 months prior to study participation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DMD, Duchenne muscular dystrophy; PUL, Performance of the Upper Limb.

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COVID-19 Shutdowns and the Disruption to Deep Brain Stimulation Treatment

Mustafa Saad Siddiqui, MD
Professor of Neurology at Wake Forest School of Medicine

COVID-19 PANDEMIC SHUTDOWNS disrupted care for all patients, including those with Parkinson disease (PD) treated with deep brain stimulation (DBS). Hospitals, overwhelmed by COVID-19 cases, postponed elective procedures such as the initial DBS device implantation and implantable pulse generator (IPG) replacements for depleted batteries. DBS is the most widely used surgical treatment for patients with PD, with thousands of implantations done each year in the US.

At Wake Forest School of Medicine in Winston-Salem, North Carolina, investigators carried out the largest survey of DBS practices in North America to better understand the impact of COVID-19 pandemic–related shutdowns on DBS care.1 To understand the results of the survey, it is important to understand the processes involved in a DBS surgery. A new DBS implantation typically involves a multidisciplinary evaluation by a movement disorders neurologist, a neuropsychologist, a functional neurosurgeon, and occasionally a psychiatrist. Besides confirming the medical refractoriness of the PD symptoms, a neurologist also examines a patient both with and without PD medications, also known as an OFF/ON evaluation, to confirm which symptoms respond to levodopa. A neuropsychologist administers standardized tests and conducts an interview to evaluate the patient’s cognitive status and identify any psychiatric red flags for undergoing DBS surgery.

DBS surgery has 2 stages. First, the electrode is implanted in the brain, which usually requires the patient to stay overnight after surgery. The second stage, done a few weeks later as an outpatient procedure under general anesthesia, involves implanting and connecting the IPG in the chest to the implanted electrode. Typically, a postoperative CT scan of the brain is done to confirm the location of the DBS leads before the first programming session. After the surgery, a DBS patient undergoes 3 to 4 visits in the first 6 months to optimize settings and adjust medications. Moving forward, most patients need visits only every 6 months. There are 2 types of IPGs: a primary cell that has to be changed in 3 to 5 years because of battery depletion and a rechargeable cell that has a battery life of more than 15 years.

The Wake Forest survey was conducted during the first pandemic-associated shutdown in May 2020. It was carried out on behalf of the Functional Neurosurgical Working Group, part of the Parkinson Study Group (PSG), the largest organization of PD investigators in North America, with representation from most high-volume DBS centers in the US and Canada. The
objective was to understand the impact of the pandemic-associated shutdown on care of DBS patients so that contingency plans could be developed in case of a future shutdown. Twenty-three DBS centers, 19 from the US and 4 from Canada, participated in the survey, and all except 2 were academic tertiary care centers. Participating sites reported that COVID-19 shutdown restrictions were in place from 4 to 16 weeks.

DBS care delivery was affected at all sites and levels, including preoperative assessments, surgeries, and postoperative DBS programming. Although all institutions reported that DBS assessments and surgeries were postponed because of institutional policy mandates, 87% of the sites reported that patients also elected to postpone DBS electrode implantation because of concerns for COVID-19 exposure. One-third of the sites discontinued preoperative evaluations, whereas the remaining experienced reduction in the number of preoperative evaluations. Telehealth was widely used for preoperative assessments as well as postoperative care because of restrictions for in-person visits. Although telehealth was used for preoperative assessments by neurology and neurosurgery at two-thirds of the sites, only one-third of the sites reported its use for neuropsychology assessments.

A follow-up study to evaluate the discrepancy of neuropsychology evaluations compared with neurology and neurosurgery identified a lack of support by insurance providers for telehealth neuropsychological assessments, concerns regarding the validity of testing methods via telehealth, and lack of availability of appropriate devices—such as tablets and laptops—for patients to undergo remote testing. No site made a surgical decision for patients with PD without an OFF/ON medication evaluation of the PD symptoms, indicating the importance of this test and the limitation of administering this test via telehealth. A telehealth version of this assessment has been standardized in-person examinations. This is particularly important in the number of preoperative evaluations. Telehealth was widely used for preoperative assessments as well as postoperative care because of restrictions for in-person visits. Although telehealth was used for preoperative assessments by neurology and neurosurgery at two-thirds of the sites, only one-third of the sites reported its use for neuropsychology assessments.

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In the Wake Forest study, all sites reported postponement of initial electrode implantations, given that it was an elective procedure. In addition, 70% of the sites also postponed IPG battery replacements. Loss of DBS therapy can have serious consequences for patients with PD, and it is recommended that IPG replacement, whether for battery depletion or hardware malfunction, should not be considered an elective procedure. Similarly, IPG removal due to infection should not be considered an elective procedure. In all, 38% of the sites reported a complete halt in postoperative DBS programming, whereas only 25% of the sites reported continuation. All sites reported that remote DBS programming should be available. Moreover, any technical, regulatory, and reimbursement barriers should be addressed to make remote programming more likely to be accepted.

Despite disrupting DBS care, the pandemic-related shutdown offered opportunities to develop contingency plans in case a shutdown occurs again. Suggestions for DBS and other device management during a pandemic have been published. Many outpatient DBS assessments can be done via telehealth, provided that telehealth examinations are validated against standardized in-person examinations. This is particularly important for neuropsychological testing and OFF/ON medication evaluations. Remote DBS programming can address travel limitations for patients, but its use would depend on wider adoption by DBS device manufacturers and changes in regulatory and reimbursement policies.

REFERENCES

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CHALLENGES OF IDENTIFYING OFF EPISODES IN PARKINSON DISEASE

Laxman Bahroo, DO, and Sanjay Iyer, MD, discuss common challenges in identifying OFF episodes in patients with Parkinson disease, the importance of educating patients, and utilizing symptom tracking diaries in this episode of a NeurologyLive Peers & Perspectives series.

View video: neurologylive.com/identifying-off-episodes
Hear experts share compelling stories about populations most vulnerable to infectious disease as we break down the social factors that create and widen healthcare disparities in hospitals, labs, academics, and communities.

Scan the QR Code or visit contagionlive.com/podcasts to listen now
BioXcel Therapeutics announced in January that Matt Wiley had been appointed senior vice president and chief commercial officer. “With [more than] 25 years of commercial and industry expertise across multiple product launches, including neuroscience products, Matt will be invaluable in spearheading critical launch initiatives,” Vimal Mehta, PhD, CEO of BioXcel Therapeutics, said in a news release. Wiley joined BioXcel from VYNE Therapeutics, where he was the chief compliance officer. He also previously was vice president of marketing and business unit lead for the sleep medicine unit at Jazz Pharmaceuticals. “[BioXcel’s] AI-driven approach to drug development represents a novel way of identifying, developing, and commercializing transformative neuroscience therapeutics, and I’m excited to join the leadership team in driving this innovative vision,” Wiley said in the news release.

Michael Gutch, PhD, Is Appointed CFO of Noema Pharma
Noema Pharma, a Switzerland-based clinical-stage company developing therapies for orphan central nervous system (CNS) diseases, announced that Michael Gutch, PhD, has joined the company as chief financial officer. He most recently served as chief business officer and chief financial officer at Entasis Therapeutics, an AstraZeneca spinoff. “[BioXcel’s] Al-driven approach to drug development represents a novel way of identifying, developing, and commercializing transformative neuroscience therapeutics, and I’m excited to join the leadership team in driving this innovative vision,” Wiley said in the news release.

INSTITUTION INITIATIVES
MJFF Launches Bachmann-Strauss Fellowship in Dystonia Research
The Michael J. Fox Foundation for Parkinson’s Research (MJFF) has announced the launch of the Bachmann-Strauss Fellowship in Dystonia Research. The initiative supports investigators studying dystonia, which is estimated to affect more than 30% of individuals with Parkinson disease. Fellowship awards were granted to the University of Lübeck in Germany and Yale University in New Haven, Connecticut, to support training. The lead gift for the funding was given by MJFF board member Bonnie Strauss and her husband, Tom. “This fellowship program has the ability to benefit not only [patients] and families living with dystonia but also the millions living with Parkinson and other movement disorders. We need the brightest minds in research to help move scientific breakthroughs forward from the lab to the clinic,” Deborah W. Brooks, cofounder and CEO of MJFF, said in a statement.

RESEARCH AWARDS
AANEM Honors Janice Massey, MD, With Lifetime Achievement Award
Janice Massey, MD, a professor of neurology and senior vice chair of the Neurology Department at Duke University School of Medicine in Durham, North Carolina, has received the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Lifetime Achievement Award. The AANEM award honors Massey for 3 decades of patient care as an international leader in the field of neurology and mentor to women neurologists. “In addition to being a superb educator, Dr Massey has served as a formal and informal career mentor to numerous neurologists from training programs at Duke and through her national and international teaching and leadership activities,” Vern Juel, MD, a professor and division chief of neuromuscular disorders at Duke University of Medicine, said. “At national meetings she is often surrounded by the many [individuals] she has trained and mentored who reach out to her in gratitude.”

Greer Receives 2022 A.B. Baker Award for Lifetime Achievement in Neurologic Education
David M. Greer, MD, MA, a professor and chair of the Department of Neurology at Boston University School of Medicine and Richard B. Silfka Chief of Neurology at Boston Medical Center in Massachusetts, has received the 2022 A.B. Baker Award for Lifetime Achievement in Neurological Education. The American Academy of Neurology (AAN) honors recipients who have shown leadership and devotion to neurological education and who have published widely and influenced generations of trainees. Greer has had leadership roles in the Neurocritical Care Society, Society of Critical Care Medicine, American Stroke Association, American Neurological Association, and AAN. Greer has authored more than 300 peer-reviewed manuscripts, reviews, chapters, guidelines, and books.

Rare As One Awards Third-Year Funding to LGS Foundation
The Lennox-Gastaut Syndrome (LGS) Foundation was recently awarded third-year funding as part of the Chan Zuckerberg Initiative (CZI) Rare As One (RAO), which will help to create a diverse and inclusive network for this patient population, their families, and investigators. The foundation is 1 of 30 patient-driven rare-disease organizations to receive this funding since 2019 when the RAO Network was launched by CZI. Funding was extended another year following the observed success of organizations that benefited from the collaborative nature of the network. Thanks to funding, the organization has been able to host its LGS Research Meeting of the Minds, initiate a request for applications to fund new projects, increase communication with the LGS community, hire additional team members, participate in CZI-organized trainings, and more.
Explore MS Website

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

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

Truths vs Myths

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

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

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

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

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