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NEUROLOGY REVIEWS®

30TH ANNIVERSARY

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Any level of physical activity tied to better later-life memory

Any amount of exercise in middle age is associated with better cognition in later life, new research suggests. A prospective study of 1,400 participants showed that those who exercised to any extent in adulthood had significantly better cognitive scores later in life, compared with their peers who were physically inactive.

Maintaining an exercise routine throughout adulthood showed the strongest link to subsequent mental acuity, the researchers found.

Although these associations lessened when investigators controlled for such factors as childhood cognitive ability, socioeconomic background, and education, exercise and physical activity remained statistically significant.

"Our findings support recommendations for greater participation in physical activity across adulthood," said lead investigator Sarah-Naomi James, PhD, a research fellow at the Medical Research Council Unit for Lifelong Health and Ageing at the University College London.

"We provide evidence to encourage inactive adults to be active even to a small extent … at any point during adulthood," which can improve cognition and memory later in life, Dr. James said.

The findings were published online in the Journal of Neurology, Neurosurgery & Psychiatry.

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Even mild COVID is hard on the brain

Even mild cases of COVID-19 can affect the function and structure of the brain, early research suggests. "Our results suggest a severe pattern of changes in how the brain communicates as well as its structure, mainly in people with anxiety and depression with long-COVID syndrome, which affects so many people," study investigator Clarissa Yasuda, MD, PhD, from University of Campinas, São Paulo, said in a news release.

"The magnitude of these changes suggests that they could lead to problems with memory and thinking skills, so we need to be exploring holistic treatments even for people mildly affected by COVID-19," Dr. Yasuda added.

The findings were released ahead of the study's scheduled presentation at the 2023 annual meeting of the American Academy of Neurology.

Brain shrinkage

Some studies have shown a high prevalence of symptoms of anxiety and depression in COVID-19 survivors, but few have investigated the associated cerebral changes, Dr. Yasuda said.

The study included 254 adults

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KESIMPTA® IS
DIFFERENT FOR A REASON

The **Only** SC delivered B-cell RMS treatment[1,2]

Powerful efficacy.*
Early and continued relapse reduction over the study period[3,4]

Established safety profile in pivotal trials which included treatment-naïve patients[3,5]

1 Minute a Month,† when the patient is ready to administer[3,6]

EFFICACY

- Primary end point: relative reduction in adjusted ARR vs Aubagio® (teriflunomide) of 51% (0.11 vs 0.22) in ASCLEPIOS I and 58% (0.10 vs 0.25) in ASCLEPIOS II[3]
- Post hoc analysis of pooled data from ASCLEPIOS I and II: cumulative ARR by time interval (KESIMPTA N=946, Aubagio N=936). Reduction in ARR seen in the first 3 months and time intervals over 2 years[4,7]:
  - Month 0 to 3: 0.236 vs 0.373
  - Month 0 to 27: 0.123 vs 0.258
  - No conclusions can be drawn

SAFETY

- Adverse events with an incidence of ≥5% with KESIMPTA and a greater incidence than Aubagio were: upper respiratory tract infections (39% vs 38%), injection-related reactions (systemic) (21% vs 15%), headache (13% vs 12%), injection-site reactions (local) (11% vs 6%), urinary tract infection (10% vs 8%), back pain (8% vs 6%), and blood immunoglobulin M decrease (6% vs 2%)[3]
- The overall rate of infections and serious infections in patients treated with KESIMPTA was similar to patients who were treated with Aubagio (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively)[3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

Contraindication: KESIMPTA is contraindicated in patients with active hepatitis B virus infection.

WARNINGS AND PRECAUTIONS

Infections: An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections; some have been fatal in patients treated with other anti-CD20 antibodies. The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until resolved.

Consider the potential increased immunosuppressive effects when initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA.

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

Kesimpta®
(ofatumumab) 20 mg injection

Make KESIMPTA® your 1st choice

KesimptaHCP.com

ARR=annualized relapse rate; CDP=confirmed disability progression; CI=confidence interval; DMT=disease-modifying therapy; GdE=gadolinium-enhancing; MRI=magnetic resonance imaging; RMS=relapsing multiple sclerosis; SC=subcutaneous.

*__Study Design:__ ASCLEPIOS I and II were 2 identical randomized, active-controlled, double-blind Phase 3 studies in patients with RMS, approximately 40% of whom were DMT treatment-naïve. Patients were randomized to double-dummy subcutaneous KESIMPTA (20 mg every 4 weeks) or oral Aubagio (14 mg daily) for up to 30 months. Primary end point was ARR. Key MRI end points were number of GdE T1 lesions, and annualized rate of new or enlarging T2 lesions. A key clinical end point was reduction in risk of 3-month CDP. Treatment duration was variable based on end-of-study criteria. Maximum duration 120 weeks, median duration 85 weeks.[3]

__Post hoc Study Design:__ ARR by time intervals was analyzed from the pooled pivotal trials. The ARR (95% CI) was estimated separately for each time interval by fitting a negative binomial regression model adjusted for treatment as factor.[4,7]

†As per stability technical specification data, when the patient is ready to inject, it typically takes less than 1 minute a month to administer. Once-monthly dosing begins after the initial dosing period, which consists of 20 mg subcutaneous doses at weeks 0, 1, and 2. Please see Instructions for Use for more detailed instructions on preparation and administration of KESIMPTA.[3,6]

IMPORTANT SAFETY INFORMATION (cont)
WARNINGS AND PRECAUTIONS (cont)

Hepatitis B Virus: *Reactivation:* No reports of hepatitis B virus (HBV) reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with ofatumumab at higher intravenous doses for chronic lymphocytic leukemia (CLL) than the recommended dose in MS and in patients treated with other anti-CD20 antibodies.

Infection: KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. Perform HBV screening in all patients before initiation of KESIMPTA. Patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], should consult liver disease experts before starting and during KESIMPTA treatment.

Progressive Multifocal Leukoencephalopathy: No cases of progressive multifocal leukoencephalopathy (PML) have been reported for KESIMPTA in RMS clinical studies; however, PML resulting in death has occurred in patients being treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. In addition, JC virus infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. If PML is suspected, withhold KESIMPTA and perform an appropriate diagnostic evaluation. If PML is confirmed, KESIMPTA should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to starting KESIMPTA for inactivated vaccines. The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy. For infants whose mother was treated with KESIMPTA during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines. If the B-cell count has not recovered in the infant, do not administer the vaccine as having depleted B-cells may pose an increased risk in these infants.

Injection-Related Reactions: Injection-related reactions with systemic symptoms occurred most commonly within 24 hours of the first injection, but were also observed with later injections. There were no life-threatening injection reactions in RMS clinical studies.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If injection-related reactions occur, symptomatic treatment is recommended.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Fetal Risk: Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose.

Most common adverse reactions (>10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions.

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

References: 1. National Multiple Sclerosis Society. Medications. Accessed February 10, 2022. https://www.nationalmssociety.org/Treating-MS/Medications **2.** Torres JB, Roodselaar J, Sealey M, et al. Distribution and efficacy of ofatumumab and ocrelizumab in humanized-CD20 mice following subcutaneous or intravenous administration. P2.2-052. Poster presented at: 71st American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA. **3.** Kesimpta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **4.** Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab vs teriflunomide in relapsing multiple sclerosis: analysis of no evidence of disease activity (NEDA-3) from ASCLEPIOS I and II trials. LB62. Poster presented at: 6th Congress of the European Academy of Neurology; May 23-26, 2020; Virtual. **5.** Hauser SL, Bar-Or A, Cohen JA, et al; for the ASCLEPIOS I and ASCLEPIOS II trial groups. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med*. 2020;383(6):546-557. **6.** Data on file. Injection time. Novartis Pharmaceuticals Corp; East Hanover, NJ. June 2020. **7.** Data on file. OMB157G (ofatumumab). Summary of clinical efficacy in relapsing multiple sclerosis. Novartis Pharmaceuticals Corp; East Hanover, NJ. December 2019.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

10/22 246578

KESIMPTA® (ofatumumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

KESIMPTA is contraindicated in patients with:

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

5 WARNINGS AND PRECAUTIONS

5.1 Infections

An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies.

KESIMPTA has the potential for an increased risk of infections, including serious bacterial, fungal, and new or reactivated viral infections; some of these infections have been fatal in patients treated with other anti-CD20 antibodies. In Study 1 and Study 2 *[see Clinical Studies (14) in the full prescribing information]*, the overall rate of infections and serious infections in patients treated with KESIMPTA was similar to patients who were treated with teriflunomide (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in the randomized clinical relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until the infection is resolved.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1)* and *Clinical Pharmacology (12.2) in the full prescribing information]*. KESIMPTA has not been studied in combination with other MS therapies.

Hepatitis B Virus

Reactivation

There were no reports of HBV reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment) and in patients treated with other anti-CD20 antibodies.

Infection

KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients being treated with ofatumumab for CLL (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). HBV screening should be performed in all patients before initiation of treatment with KESIMPTA. At a minimum, screening should include Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with KESIMPTA. These patients should be monitored and managed following local medical standards to prevent HBV infection or reactivation.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

Although no cases of PML have been reported for KESIMPTA in the RMS clinical studies, PML resulting in death has occurred in patients being treated with ofatumumab for CLL (at substantially higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). In addition, JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. At the first sign or symptom suggestive of PML, withhold KESIMPTA and perform an appropriate diagnostic evaluation. Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

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

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of KESIMPTA for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines.

KESIMPTA may interfere with the effectiveness of inactivated vaccines.

The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy

In infants of mothers treated with KESIMPTA during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered, as indicated, prior to recovery from B-cell depletion, but an assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted.

5.2 Injection-Related Reactions

In Study 1 and Study 2, systemic and local injection reactions were reported in 21% and 11% of patients treated with KESIMPTA compared to 15% and 6% of patients treated with teriflunomide who received matching placebo injections, respectively *[see Adverse Reactions (6.1)* and *Clinical Studies (14) in the full prescribing information]*.

Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection, but were also observed with later injections. Symptoms observed included fever, headache, myalgia, chills, and fatigue, and were predominantly (99.8%) mild to moderate in severity. There were no life-threatening injection reactions in the RMS clinical studies.

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain.

Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical studies. The first injection of KESIMPTA should be performed under the guidance of an appropriately trained healthcare professional. If injection-related reactions occur, symptomatic treatment is recommended.

5.3 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 7.7% of patients treated with KESIMPTA compared to 3.1% of patients treated with teriflunomide in RMS clinical trials *[see Adverse Reactions (6.1)]*. Treatment was discontinued because of decreased immunoglobulins in 3.4% of patients treated with KESIMPTA and in 0.8% of patients treated with teriflunomide. No decline in immunoglobulin G (IgG) was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

5.4 Fetal Risk

Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA *in utero*. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Injection-Related Reactions *[see Warnings and Precautions (5.2)]*
- Reduction in Immunoglobulins *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

Approximately 1500 patients with RMS received KESIMPTA in clinical studies. In Study 1 and Study 2, 1882 patients with RMS were randomized, 946 of whom were treated with KESIMPTA for a median duration of 85 weeks; 33% of patients receiving KESIMPTA were treated for up to 120 weeks *[see Clinical Studies (14.1) in the full prescribing information]*. The most common adverse reactions occurring in greater than 10% of patients treated with KESIMPTA and more frequently than in patients treated with teriflunomide were upper respiratory tract infections, injection-related reactions (systemic), headache, and injection-site reactions (local). The most common cause of discontinuation in patients treated with KESIMPTA was low immunoglobulin M (3.3%), defined in trial protocols as IgM at 10% below the lower limit of normal (LLN).

Table 1 summarizes the adverse drug reactions that occurred in Study 1 and Study 2.

Table 1: Adverse Reactions in Patients With RMS With an Incidence of at Least 5% With KESIMPTA and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

Adverse Reactions	KESIMPTA 20 mg N = 946 %	Teriflunomide 14 mg N = 936 %
Upper respiratory tract infections[a]	39	38
Injection-related reactions (systemic)	21	15
Headache	13	12
Injection-site reactions (local)	11	6
Urinary tract infection	10	8
Back pain	8	6
Blood immunoglobulin M decreased	6	2

[a]Includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.

Injection-Related Reactions and Injection-Site Reactions

The incidence of injection-related reactions (systemic) was highest with the first injection (14.4%), decreasing with subsequent injections (4.4% with second, less than 3% with third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) patients treated with KESIMPTA reported serious injection-related reactions. There were no life-threatening injection-related reactions. Most frequently reported symptoms (2% or greater) included fever, headache, myalgia, chills, and fatigue.

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

Laboratory Abnormalities

Immunoglobulins

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

6.2 Immunogenicity

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

Treatment-induced anti-drug antibodies (ADAs) were detected in 2 of 914 (0.2%) KESIMPTA-treated patients; no patients with treatment-enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient; however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of KESIMPTA.

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

Concomitant usage of KESIMPTA with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with KESIMPTA.

When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of potential additive immunosuppressive effects when initiating KESIMPTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies *(see Data)*.

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to ofatumumab *in utero*, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA *in utero* until B-cell recovery occurs *[see Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.2) in the full prescribing information]*.

Following administration of ofatumumab to pregnant monkeys, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans *(see Data)*.

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

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA *[see Warnings and Precautions (5.4)* and *Clinical Pharmacology (12.3) in the full prescribing information]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of KESIMPTA did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger subjects.

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T2022-52

FDA OKs first drug for Rett syndrome

The drug is designed to treat the core symptoms of Rett syndrome by potentially reducing neuroinflammation and supporting synaptic function.

The Food and Drug Administration (FDA) has approved trofinetide oral solution (Daybue, Acadia Pharmaceuticals) as the first treatment of Rett syndrome in adults and children aged 2 years and older.

> After 12 weeks, patients taking trofinetide showed a statistically significant improvement from baseline.

Rett syndrome is a rare, genetic neurodevelopmental disorder that affects about 6,000-9,000 people in the United States, mostly females. Symptoms typically present between 6 and 18 months of age, with patients experiencing a rapid decline with loss of fine motor and communication skills.

Trofinetide is a synthetic analogue of the amino-terminal tripeptide of insulinlike growth factor-1 (IGF-1), which occurs naturally in the brain. The drug is designed to treat the core symptoms of Rett syndrome by potentially reducing neuroinflammation and supporting synaptic function.

The approval of trofinetide was supported by results from the pivotal phase 3 LAVENDER study that tested the efficacy and safety of trofinetide versus placebo in 187 female patients with Rett syndrome, aged 5-20 years.

A total of 93 participants were randomly assigned to twice-daily oral trofinetide, and 94 received placebo for 12 weeks.

After 12 weeks, patients taking trofinetide showed a statistically significant improvement from baseline, compared with those taking placebo, on both the caregiver-assessed Rett Syndrome Behavior Questionnaire (RSBQ) and 7-point Clinical Global Impression-Improvement (CGI-I) scale.

The drug also outperformed placebo at 12 weeks in a key secondary endpoint: the composite score on the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist-Social (CSBS-DP-IT Social), a scale on which caregivers assess nonverbal communication.

> With the FDA decision, those impacted by Rett syndrome have a promising new treatment option.

The most common adverse events with trofinetide treatment were diarrhea and vomiting. Almost all these events were considered mild or moderate.

'Historic day'

"This is a historic day for the Rett syndrome community and a meaningful moment for the patients and caregivers who have eagerly awaited the arrival of an approved treatment for this condition," Melissa Kennedy, MHA, chief executive officer of the International Rett Syndrome Foundation, said in a news release issued by Acadia.

"Rett syndrome is a complicated, devastating disease that affects not only the individual patient, but whole families. With the FDA decision, those impacted by Rett syndrome have a promising new treatment option that has demonstrated benefit across a variety of Rett symptoms, including those that impact the daily lives of those living with Rett and their loved ones," Ms. Kennedy said.

Trofinetide is expected to be available in the United States by the end of April. **NR**

—Megan Brooks

NEUROLOGY REVIEWS

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Black people are less likely to receive dementia meds

Analysis of a large data set reveals racial inequities in the administering of medications for dementia symptoms.

Black people with dementia are less likely than their White peers to receive cognitive enhancers and other medications for dementia in the outpatient setting, preliminary data from a retrospective study show.

"There have been disparities regarding the use of cognition-enhancing medications in the treatment of dementia described in the literature, and disparities in the use of adjunctive treatments for other neuropsychiatric symptoms of dementia described in hospital and nursing home settings," said study investigator Alice Hawkins, MD, with the department of neurology, Icahn School of Medicine at Mount Sinai, New York. "However, less is known about use of dementia medications that people take at home. Our study found disparities in this area as well," Dr. Hawkins said.

The findings were released ahead of the study's scheduled presentation at the 2023 annual meeting of the American Academy of Neurology.

> "Black patients who were referred to a neurologist received cholinesterase inhibitors and NMDA antagonists at rates comparable with White patients."

More research needed

The researchers analyzed data on 3,655 Black and 12,885 White patients with a diagnosis of dementia who were seen at Mount Sinai. They evaluated utilization of five medication classes:

- cholinesterase inhibitors
- N-methyl D-aspartate (NMDA) receptor antagonists
- selective serotonin reuptake inhibitors (SSRIs)
- antipsychotics
- benzodiazepine

They found that Black patients with dementia received cognitive enhancers less often than White patients with dementia (20% vs. 30% for cholinesterase inhibitors; 10% vs. 17% for NMDA antagonists).

Black patients with dementia were also less likely to receive medications for behavioral and psychological symptom management, compared with White peers (24% vs. 40% for SSRIs; 18% vs. 22% for antipsychotics; and 18% vs. 37% for benzodiazepines).

These disparities remained even after controlling for factors such as demographics and insurance coverage.

"Larger systemic forces such as systemic racism, quality of care, and provider bias are harder to pin down, particularly in the medical record, though they all may be playing a role in perpetuating these inequities. More research will be needed to pinpoint all the factors that are contributing to these disparities," said Dr. Hawkins.

The researchers found Black patients who were referred to a neurologist received cholinesterase inhibitors and NMDA antagonists at rates comparable with White patients. "Therefore, referrals to specialists such as neurologists may decrease the disparities for these prescriptions," Dr. Hawkins said.

Crucial research

Commenting on the findings, Carl V. Hill, PhD, MPH, Alzheimer's Association chief diversity, equity, and inclusion officer, said the study "adds to previous research that points to inequities in the administering of medications for dementia symptoms, and highlights the inequities we know exist in dementia care."

"Cognitive enhancers and other behavioral/psychological management drugs, while they don't stop, slow, or cure dementia, can offer relief for some of the challenging symptoms associated with diseases caused by dementia. If people aren't being appropriately prescribed medications that may offer symptom relief from this challenging disease, it could lead to poorer health outcomes," said Dr. Hill.

"These data underscore the importance of health disparities research that is crucial in uncovering inequities in dementia treatment, care, and research for Black individuals, as well as all underrepresented populations.

"We must create a society in which the underserved, disproportionately affected, and underrepresented are safe, cared for, and valued. This can be done through enhancing cultural competence in health care settings, improving representation within the health care system, and engaging and building trust with diverse communities," Dr. Hill said.

> "We must create a society in which the underserved, disproportionately affected, and underrepresented are safe, cared for, and valued."

The Alzheimer's Association has partnered with more than 500 diverse community-based groups on disease education programs to ensure families have information and resources to navigate this devastating disease.

The study was supported by the American Academy of Neurology Resident Research Scholarship. Dr. Hawkins and Dr. Hill reported no relevant financial relationships. **NR**

—Megan Brooks

What's driving the 'world's fastest-growing' brain disease'?

The chemical trichloroethylene is associated with as much as a 500% increased risk for Parkinson's disease, suggests a new review of data.

A common chemical that is used in many commercial products may be the key culprit behind the dramatic increase in Parkinson's disease, researchers say. Researchers reviewed previous research and cited data that suggest the chemical trichloroethylene (TCE) is associated with as much as a 500% increased risk for Parkinson's disease.

Lead investigator Ray Dorsey, MD, professor of neurology, University of Rochester, N.Y., called Parkinson's disease "the world's fastest-growing brain disease," and said that it "may be largely preventable."

"Countless people have died over generations from cancer and other disease linked to TCE [and] Parkinson's may be the latest," he said. "Banning these chemicals, containing contaminated sites, and protecting homes, schools, and buildings at risk may all create a world where Parkinson's is increasingly rare, not common."

The paper was published online in the Journal of Parkinson's Disease.

Invisible, ubiquitous

TCE was first synthesized in 1864, with commercial production beginning in 1920, the researchers noted.

"Because of its unique properties, TCE has had countless industrial, commercial, military, and medical applications," including producing refrigerants, cleaning electronics, and degreasing engine parts. In addition, it's been used in dry cleaning, although a similar chemical (perchloroethylene [PCE]) is currently more widely used for that purpose. Nevertheless, the authors noted, in anaerobic conditions, PCE often transforms into TCE "and their toxicity may be similar."

Consumer products containing TCE include typewriter correction fluid, paint removers, gun cleaners, and aerosol cleaning products. Up until the 1970s, it was used to decaffeinate coffee.

TCE exposure isn't confined to those who work with it. It also pollutes outdoor air, taints groundwater, and contaminates indoor air. It's present in a substantial amount of groundwater in the United States and it "evaporates from underlying soil and groundwater and enters homes, workplaces, or schools, often undetected," the researchers noted.

"Exposure can come via occupation or the environment and is often largely unknown at the time it occurs," Dr. Dorsey said.

He noted that the rapid increase in Parkinson's disease incidence cannot be explained by genetic factors alone, nor can it be explained by aging alone. "Certain pesticides ... are likely causes but would not explain the high prevalence of Parkinson's disease in urban areas, as is the case in the U.S." Rather, "other factors" are involved, and "TCE is likely one such factor."

Yet, "despite widespread contamination and increasing industrial, commercial, and military use, clinical investigations of TCE and Parkinson's disease have been limited."

To fill this knowledge gap, Dr. Dorsey and his coauthors of the book, "Ending Parkinson's Disease: A Prescription for Action," took a deep dive into studies focusing on the potential association of TCE and Parkinson's disease.

"Like many genetic mutations (e.g., Parkin) and other environmental toxicants ... TCE damages the energy-producing parts of cells, i.e., the mitochondria," said Dr. Dorsey.

TCE and PCE "likely mediate their toxicity through a common metabolite." Because both are lipophilic, they "readily distribute in the brain and body tissues and appear to cause mitochondrial dysfunction at high doses," the researchers hypothesized.

Dopaminergic neurons are particularly sensitive to mitochondrial neurotoxicants, so this might "partially explain the link to Parkinson's disease."

Animal studies have shown that TCE "caused selective loss of dopaminergic neurons." Moreover, Parkinson's disease–related neuropathology was found in the substantia nigra of rodents exposed to TCE over time. In addition, studies as early as 1960 were showing an association between TCE and parkinsonism.

The authors describe TCE as "ubiquitous" in the 1970s, with 10 million Americans working with the chemical or other organic solvents daily. The review details an extensive list of industries and occupations in which TCE exposure continues to occur.

People working with TCE might inhale it or touch it; but "millions more encounter the chemical unknowingly through outdoor air, contaminated groundwater, and indoor air pollution."

They noted that TCE contaminates up to one-third of U.S. drinking water, has polluted the groundwater in more than 20 different countries on five continents, and is found in half of the 1,300 most toxic "Superfund" sites that are "part of a federal clean-up program, including 15 in California's Silicon Valley, where TCE was used to clean electronics."

Although the U.S. military stopped using TCE, numerous sites have been contaminated, including Marine Corps Base Camp Lejeune in North Carolina, where TCE and PCE were found in drinking water at 280 times the recommended safety standards.

The researchers highlighted seven cases of individuals who developed Parkinson's disease after likely exposure to TCE, including NBA basketball player Brian Grant, who developed symptoms of Parkinson's disease in 2006 at age 34.

Mr. Grant and his family had lived in Camp Lejeune when he was a child, during which time he drank, bathed, and swam in contaminated water, "unaware of its toxicity." His father also died of esophageal cancer, "which is linked to TCE," the authors of the study wrote. Mr. Grant has created a foundation to inspire and support patients with Parkinson's disease (briangrant.org).

All of the individuals either grew up in or spent time in an area where they were extensively exposed to TCE, PCE, or other chemicals, or experienced occupational exposure.

The authors acknowledged that the role of TCE in Parkinson's disease, as illustrated by the cases, is "far from definitive." For example, exposure to TCE is often combined with exposure to other toxins, or with unmeasured genetic risk factors. They highlighted the need for more research and called for cleaning and containing contaminated sites, monitoring TCE levels, and publicly communicating risk and a ban on TCE.

Recall bias?

Commenting on the research, Rebecca Gilbert, MD, PhD, chief scientific officer, American Parkinson Disease Association (APDA), noted that the authors "are very frank about the limitations of this approach [illustrative cases] as proof of causation between Parkinson's disease and TCE exposure."

Another limitation is that TCE exposure is very common, "as argued in the paper." But "most people with exposure do not develop Parkinson's disease," Dr. Gilbert pointed out. "By probing the TCE exposure of those who already have Parkinson's disease, there is a danger of recall bias."

Dr. Gilbert, associate professor of neurology at NYU Langone Health, who was not involved with the study, acknowledged that the authors "present their work as hypothesis and clearly state that more work is needed to understand the connection between TCE and Parkinson's disease."

In the meantime, however, there are "well-established health risks of TCE exposure, including development of various cancers," she said. Therefore, the authors' goals appear to be educating the public about known health risks, working to clean up known sites of contamination, and advocating to ban future use of TCE.

These goals "do not need to wait for [proof of] firm causation between TCE and Parkinson's disease," she stated.

Dr. Dorsey reported he has received honoraria for speaking at the American Academy of Neurology and at multiple other societies and foundations and has received compensation for consulting services from pharmaceutical companies, foundations, medical education companies, and medical publications; he owns stock in several companies. The other authors' disclosures can be found in the original paper. Dr. Gilbert is employed by the American Parkinson Disease Association and Bellevue Hospital Center in New York City. **NR**

—Batya Swift Yasgur

Suggested Reading

Ray DE et al. Trichloroethylene: An invisible cause of Parkinson's disease? J Parkinsons Dis. 2023;13(2):203-218.

Can a diabetes drug lower dementia risk?

Risk for dementia is doubled in adults with type 2 diabetes, say the authors of a new paper.

Treatment with the thiazolidinedione pioglitazone may offer the greatest protection against dementia for older adults with newly diagnosed type 2 diabetes mellitus who have a history of stroke or ischemic heart disease, new research suggests. Overall, in a large cohort study from South Korea, patients who took pioglitazone were 16% less likely to develop dementia over an average of 10 years than peers who did not take the drug.

> **Patients who took pioglitazone were 16% less likely to develop dementia over an average of 10 years than peers who did not take the drug.**

However, the dementia risk reduction was 54% among those with ischemic heart disease and 43% among those with a history of stroke.

"Our study was to see the association between pioglitazone use and incidence of dementia, not how (with what mechanisms) this drug can suppress dementia pathology," coinvestigator Eosu Kim, MD, PhD, Yonsei University, Seoul, South Korea, said in an interview. However, "as we found this drug is more effective in diabetic patients who have blood circulation problems in the heart or brain than in those without such problems, we speculate that pioglitazone's antidementia action may be related to improving blood vessels' health," Dr. Kim said.

This finding suggests that pioglitazone could be used as a personalized treatment approach for dementia prevention in this subgroup of patients with diabetes, the researchers noted.

The results were published online in Neurology.

Dose-response relationship

Risk for dementia is doubled in adults with type 2 diabetes, the investigators wrote. Prior studies have suggested that pioglitazone may protect against dementia, as well as a first or recurrent stroke, in patients with type 2 diabetes. This led Dr. Kim and colleagues to examine the effects of pioglitazone on dementia risk overall and in relation to stroke and ischemic heart disease.

Using the national Korean health database, the researchers identified 91,218 adults aged 50 and older with new-onset type 2 diabetes who did not have dementia. A total of 3,467 were treated with pioglitazone.

Pioglitazone exposure was defined as a total cumulative daily dose of 90 or more calculated from all dispensations during 4 years after type 2 diabetes diagnosis, with outcomes assessed after this period.

Over an average of 10 years, 8.3% of pioglitazone users developed dementia, compared with 10.0% of nonusers.

There was a statistically significant 16% lower risk for developing all-cause dementia among pioglitazone users than among nonusers (adjusted hazard ratio [aHR], 0.84; 95% confidence interval [CI], 0.75-0.95).

A dose-response relationship was evident; pioglitazone users who received the highest cumulative daily dose were at lower risk for dementia (aHR, 0.72; 95% CI, 0.55-0.94).

Several limitations

The reduced risk for dementia was more pronounced among patients who used pioglitazone for 4 years in comparison with patients who did not use the drug (aHR, 0.63; 95% CI, 0.44-0.90). The apparent protective effect of pioglitazone with regard to dementia was greater among those with a history of ischemic heart disease (aHR, 0.46; 95% CI, 0.24-0.90) or stroke (aHR, 0.57; 95% CI, 0.38-0.86) before diabetes diagnosis.

The incidence of stroke was also reduced with pioglitazone use (aHR, 0.81; 95% CI, 0.66-1.0).

"These results provide valuable information on who could potentially benefit from pioglitazone use for prevention of dementia," Dr. Kim said in a news release. However, "the risk and benefit balance of long-term use of this drug to prevent dementia should be prospectively assessed," he said in an interview.

The researchers cautioned that the study was observational; hence, the reported associations cannot address causal relationships. Also, because of the use of claims data, drug compliance could not be guaranteed, and exposure may have been overestimated. There is also the potential for selection bias, and no information on apolipoprotein E was available, they noted.

More data needed

In an accompanying editorial, Colleen J. Maxwell, PhD, University of Waterloo (Ont.), and colleagues wrote that the results "not only support previous studies showing the potential cognitive benefit of pioglitazone but also extend our understanding of this benefit through the mediating effect of reducing ischemic stroke."

However, because of their associated risks, which include fractures, weight gain, heart failure, and bladder cancer, thiazolidinediones are not currently favored in diabetes management guidelines – and their use has significantly declined since the mid to late 2000s, the editorialists noted.

They agreed that it will be important to reassess the risk-benefit profile of pioglitazone in type 2 diabetes as additional findings emerge.

They also noted that sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which have significant cardiovascular and renal benefits and minimal side effects, may also lower the risk for dementia.

"As both pioglitazone and SGLT-2 inhibitors are second-line options for physicians, the current decision would easily be in favor of SGLT-2 inhibitors given their safety profile," Dr. Maxwell and colleagues wrote.

For now, pioglitazone "should not be used to prevent dementia in patients with type 2 diabetes mellitus," they concluded.

The study was supported by grants from the National Research Foundation of Korea funded by the Korean government and the Ministry of Health and Welfare. The investigators and editorialists report no relevant financial relationships. **NR**

—Megan Brooks

Suggested Reading

Ha J et al. Pioglitazone use and reduced risk of dementia in patients with diabetes mellitus with a history of ischemic stroke. Neurology. 2023 Feb. 15 (Epub ahead of print).

Maxwell CJ et al. Pioglitazone and lower risk of dementia: Will this change practice? Neurology. 2023 Feb. 15 (Epub ahead of print).

‘Quick, affordable’ test helps predict CGRP response for migraine

Pretreatment nonictal cephalic allodynia identified galcanezumab responders with nearly 80% accuracy.

Testing for nonictal cephalic allodynia can help predict response to the anti–calcitonin gene-related peptide (CGRP) galcanezumab (Emgality, Eli Lilly) for patients with migraine, new research suggests.

The ictal phase refers to “sensitization occurring during a time when central trigeminovascular neurons receive massive nociceptive input from active meningeal nociceptors,” whereas the nonictal phase refers to “sensitization occurring during a time when central trigeminovascular neurons receive no or subliminal nociceptive input from meningeal nociceptors,” investigators noted.

> **Pretreatment nonictal cephalic allodynia was a statistically significant predictor of response to anti-CGRP therapy.**

In an observational, open-label cohort study, pretreatment nonictal cephalic allodynia identified galcanezumab responders with nearly 80% accuracy, and it identified nonresponders with nearly 85% accuracy.

“Detection of nonictal allodynia with a simplified paradigm of Quantitative Sensory Testing (QST) may provide a quick, affordable, noninvasive, and patient-friendly way to prospectively distinguish between responders and nonresponders to the prophylactic treatment of chronic and high-frequency episodic migraine with drugs that reduce CGRP signaling,” Sait Ashina, MD, of Beth Israel Deaconess Medical Center and Harvard Medical School, both in Boston, and colleagues wrote.

The findings were published online in Cephalalgia.

Immediate clinical relevance

Investigator Rami Burstein, PhD, also with Beth Israel Deaconess Medical Center and Harvard Medical School, developed the concept of predicting response to anti-CGRP treatment by testing for the presence or absence of nonictal cephalic allodynia in collaboration with the company CGRP Diagnostics.

In 43 anti-CGRP–naive patients with migraine, the researchers used a simplified QST algorithm to determine the presence/absence of cephalic or extracephalic allodynia during the nonictal phase of migraine – defined as the period from less than 12 hours after a migraine attack to less than 12 hours before the next attack.

Patients were considered to have allodynia if heat pain thresholds were between 32° C and 40° C, if cold pain thresholds were between 32° C and 20° C, or if the mechanical pain was threshold was less than 60 g.

Using these strict criteria, pretreatment nonictal cephalic allodynia was a statistically significant predictor of response to anti-CGRP therapy. It was present in 84% of the 19 nonresponders and was absent in 79% of the 24 responders, for an overall accuracy rate of 86% ($P < .0001$).

Nonictal cephalic allodynia was “consistently” predictive of response for patients with chronic migraine as well as for those with high-frequency episodic migraine, the researchers reported.

In contrast, they noted that assessing nonictal extracephalic allodynia with QST missed nearly 50% of the patients with allodynia among the nonresponders (accuracy rate of 42%) and added little to the assessment of allodynia among the responders.

Mark Hasleton, PhD, CEO of CGRP Diagnostics, said in an interview that the study shows it’s possible to determine response to anti-CGRP therapy and to prescribe these medications to patients who are most likely to respond.

Dr. Hasleton, who was not personally involved with the current study, noted that pretreatment testing for nonictal cephalic allodynia may also allow for earlier prescription of anti-CGRP therapy and potentially dispense without the need for the current trial-and-error approach to prescribing. He noted that if one anti-CGRP fails the patient, it is highly likely that others will also fail.

Given the “very high correlation of the presence of nonictal cephalic allodynia in responders to galcanezumab, our recommendation would be to routinely pretest all potential anti-CGRP candidates prior to prescription,” he said.

End of trial-and-error prescribing

Commenting on the study findings, Shaheen Lakhan, MD, a neurologist and researcher in Boston, said this research is “very noteworthy, moving us one step closer to predictive, precision medicine and away from the practice of trial-and-error prescribing.”

“The trial-and-error approach to migraine management is daunting. These are very costly therapies, and when they don’t work, there is continued tremendous suffering and loss of quality of life for patients,” said Dr. Lakhan, who was not involved in the study.

He added that the failure of drugs to benefit individual patients “may lead to distrust of the health care provider” and to the system as a whole, which in turn could lead to less access to care for other conditions or for preventive measures.

“I envision a time when these predictive measures collectively (interictal allodynia, as in this study, plus biobehavioral data) will assist us neurologists in appropriately selecting migraine therapies,” Dr. Lakhan said.

“Beyond that, we will eventually test new therapies not in cells, animals, and even humans but in silico. In the very near future, we will have solutions tailored to not people suffering a disease but to you – an individual with a unique genetic, protein, physical, developmental, psychological, and behavioral makeup,” he added.

The study was funded in part by Eli Lilly, the National Institutes of Health, and the anesthesia department at Beth Israel Deaconess Medical Center. Galcanezumab was provided by Eli Lilly. Dr. Lakhan reported no relevant financial relationships. **NR**

—Megan Brooks

Suggested Reading

Ashina S et al. Pre-treatment non-ictal cephalic allodynia identifies responders to prophylactic treatment of chronic and episodic migraine patients with galcanezumab: A prospective quantitative sensory testing study (NCT04271202). Cephalalgia. 2023;43(3).

Blood pressure lowering after thrombectomy may be harmful

Using an antihypertensive drug to target systolic blood pressure to below 160 mm Hg or 140 mm Hg after thrombectomy may not be beneficial.

Artificially lowering blood pressure in stroke patients following endovascular therapy is not necessarily a good strategy, new research suggests. Preliminary results of a new study showed that using an antihypertensive drug to target systolic blood pressure to below 160 mm Hg or 140 mm Hg in these patients may not be beneficial, and may even be harmful.

"This line of inquiry is probably not worth pursuing," said stroke neurologist Eva A. Mistry, MBBS, MSCI, assistant professor of clinical neurology and rehabilitation medicine, University of Cincinnati.

> **Decisions to target lower blood pressure levels in stroke patients following endovascular therapy should be done on an individual basis.**

Following current blood pressure guidelines in these patients (targeting blood pressure under 180/105 mm Hg) "is probably reasonable," unless the patient's systolic blood pressure goes above 180, Dr. Mistry said. "Artificially trying to lower it may result in harm, at least in terms of the disability outcome."

The findings were presented at the 2023 International Stroke Conference.

Endovascular therapy has become standard of care for patients with large vessel occlusion after studies showed "massive benefit," yet about 50% of patients remain disabled or die at 90 days, Dr. Mistry said. "We have been on the quest to understand if there's something we can do to improve these outcomes."

One approach could be optimizing medical management. Previous observational studies showed that higher blood pressure values after thrombectomy are associated with worse outcomes.

Taking it forward

"We wanted to take that forward in a randomized inquiry to see first with this trial if [artificially] lowering blood pressure using medications is safe, and preliminarily understand if it could be efficacious in a larger trial," she said.

This blood pressure–lowering strategy is already practiced in some centers. A nationwide survey conducted by Dr. Mistry and her colleagues showed a wide range of targets, with some institutions aiming it as low as under 120 mm Hg after thrombectomy, which she found "surprising."

The Blood pressure after Endovascular Stroke Treatment-II (BEST-II) study included 120 ischemic stroke patients at three stroke centers, mean age 70 years and 57% female, who had undergone endovascular treatment. They were randomized to one of three target blood pressure groups: 180 mm Hg or under, less than 160 mm Hg, or under 140 mm Hg.

To lower blood pressure, researchers used intravenous nicardipine, a calcium channel blocker, as a first line. This was started within 1 hour of the endovascular treatment and given for 24 hours if the patient's systolic blood pressure was above the target of their group.

In the highest target group (≤180 mm Hg), the average systolic blood pressure reached 129 mm Hg. In the middle target group (<160 mm Hg), the average systolic blood pressure was 131 mm Hg, and in the lowest target group (<140 mm Hg), systolic blood pressure was lowered to an average of 123 mm Hg.

Mean infarct volumes

At 36 hours, the mean adjusted infarct volume was slightly lower in the lowest blood pressure target group (32.4), compared with the other groups (46.4 for the 180 mm Hg group and 50.7 for the under-160 mm Hg group).

"Based on a model or a slope that would be associated with serial lowering of blood pressure targets, we found the point estimate of the effect size was slightly in the direction of benefit of lower blood pressure targets in terms of lower infarct volume," Dr. Mistry said.

But this was not conclusive. While the point estimate was in the direction of benefit, Dr. Mistry stressed that the trial design doesn't "definitely rule out" the possibility of harm.

Researchers also measured functional status at 90 days with the modified Rankin Scale (mRS). They found that the utility-weighted mRS was slightly lower in the lowest blood pressure target group (0.507), compared with the higher target groups (0.584 and 0.475, respectively, for the 180 mm Hg and under-160 mm Hg groups).

"The effect size was slightly in the direction of harm," Dr. Mistry said. "To me, that means there might be safety issues associated with the lower blood pressure target."

Probably futile

The results suggest that studying this issue further is probably futile. "If lowering blood pressure improves outcomes, that improvement is fairly marginal, and there are trends that suggest that, in fact, it might be harmful," Dr. Mistry said. Her researcher team "believes it would not be the wisest decision" to pursue this strategy any further in a phase 3 study, she said.

"We wanted to understand whether or not we should spend millions of dollars to do a thousand-patient or two thousand-patient trial, and the answer to that is probably not." And there are other therapeutics "we can test that might be more promising than this approach," she added.

In the meantime, Dr. Mistry stressed that clinicians should be cautious about automatically lowering blood pressure in this patient population and that decisions to target lower levels should be done on an individual basis.

Timely and important

In a comment, Karen Furie, MD, MPH, chair of neurology, Brown University, Providence, R.I., said that the study is "timely and important," given the uncertainty about management of blood pressure after opening the vessel again using endovascular treatment.

"We already knew that letting the blood pressure go very high after reperfusion was bad, and this study shows that lowering it may also pose a risk, and I think that's an important message for the community."

The results send a cautionary message to clinicians but do not provide definitive evidence, she added. "Perhaps in the future we will have a better understanding of what the optimal range is."

Dr. Furie stressed that this was a small pilot study and conclusions are "guarded."

"I think the authors didn't want to overinterpret the results so they ended up concluding that because the final disability might have been worse in the patients who had their blood pressure significantly lowered, recommending that as an approach across the board is sort of discouraged."

Instead, the authors indicated that there may be factors such as degree of recanalization, size of the infarct, or other patient-specific factors "that would dictate where you target blood pressures," Dr. Furie said.

The study was funded by the National Institutes of Health/National Institute of Neurological Disorders and Stroke. Dr. Mistry receives funding from the Patient-Centered Outcomes Research Institute and compensation from the American Heart Association for editorial activities, and is a consultant for RapidAI. Dr. Furie has declared no relevant financial relationships. **NR**

—Pauline Anderson

Focused ultrasound ablation reduces dyskinesia in Parkinson's disease

The procedure can be used to "treat patients when other surgical procedures can't be applied."

An incisionless surgical procedure that uses focused ultrasound ablation (FUSA) to target the globus pallidus internus of patients with Parkinson's disease significantly reduced tremors and improved mobility for those with advanced disease, new research shows.

> "In some patients with Parkinson's disease, you get dyskinesias, and ablation of the globus pallidus significantly reduces those dyskinesias and motor impairment."

The technique requires no sedation or brain implants. Surgeons use MRI to identify the globus pallidus internus, a part of the basal ganglia involved in movement disorders, and a focused ultrasound beam to heat and destroy the tissue.

Investigators performed the procedure with a device called Exablate Neuro, which was first approved by the Food and Drug Administration in 2016 to treat essential tremor.

On the basis of the results of a multicenter, randomized, sham-controlled trial, the agency expanded the indication in 2021 to include unilateral pallidotomy to treat advanced Parkinson's disease for patients with mobility, rigidity, or dyskinesia symptoms.

"In some patients with Parkinson's disease, you get dyskinesias, and ablation of the globus pallidus significantly reduces those dyskinesias and motor impairment," said lead investigator Vibhor Krishna, MD, associate professor of neurosurgery at the University of North Carolina at Chapel Hill. "It could be used to treat patients when other surgical procedures can't be applied."

The study was published online in the New England Journal of Medicine.

Strong response

For the study, 94 patients with advanced Parkinson's disease who had dyskinesias or motor fluctuations and motor impairment in the off-medication state wore transducer helmets while lying in an MRI scanner. Patients were awake during the entire procedure.

The treatment group received unilateral FUSA on the side of the brain with the greatest motor impairment. The device initially delivered target temperatures of 40°-45° C. Ablative temperatures were gradually increased following evaluations to test for improvement of motor symptoms. The maximum temperature used was 54.3° C.

Patients in the control group underwent an identical procedure with the sonication energy disabled.

The primary outcome was a response to therapy at 3 months, defined as a decrease of at least three points from baseline either in the score on the Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part III, while off medication or in the score on the Unified Dyskinesia Rating Scale (UDRS) while on medication.

At 3 months, 69% of the treatment group reported a response, compared with 32% of the control group (P = .003).

When researchers analyzed MDS-UPDRS scores, they found that 29% of the treatment group and 27% of the control group showed improvement. For UDRS scores, 12% of the treatment group demonstrated improvement. In the control group, there was no improvement on this score. Improvements in both scores were reported in 28% of the treatment group and 5% of the control group.

Among those who reported a response at 3 months, 77% continued to show a response at 12 months.

'Unforgiving' area of the brain

While the response rate was a promising sign of this finding, it was not what interested Dr. Krishna the most. "The most surprising finding of this trial is how safe focused ultrasound pallidotomy is in treating patients with Parkinson's disease," he said.

The globus pallidus internus is an area of the brain that Dr. Krishna calls "unforgiving."

"One side is motor fibers, and any problem with that can paralyze the patient, and just below that is the optic tract, and any problem there, you would lose vision," Dr. Krishna said. "It is a very tough neighborhood to be in."

By using MRI-guided ultrasound, surgeons can change the target and temperature of the ultrasound beam during the procedure to allow more precise treatment.

Pallidotomy-related adverse events in the treatment group included dysarthria, gait disturbance, loss of taste, visual disturbance, and facial weakness. All were mild to moderate, Dr. Krishna said.

> "The most surprising finding of this trial is how safe focused ultrasound pallidotomy is in treating patients with Parkinson's disease."

More study is needed

Dyskinesia is a challenge in the management of Parkinson's disease. Patients need antiparkinsonian medications to slow deterioration of motor function, but those medications can cause the involuntary movements that are a hallmark of dyskinesia.

The most common treatment for this complication, deep-brain stimulation (DBS), has its own drawbacks. It's an open procedure, and there is a low-level risk for intracranial bleeding and infection. In addition, the electrode implants require ongoing maintenance and adjustment.

But the findings of this study show that, for patients who aren't candidates for other therapies, such as DBS and ablative radiofrequency, FUSA may be an alternative, wrote Anette Schrag, PhD, professor of clinical neurosciences at University College London, in an accompanying commentary.

"The results confirm that it is effective in reducing motor complications of Parkinson's disease, at least in the short term," Dr. Schrag wrote. However, more long-term studies are needed, she added.

One-third of patients in the treatment group had no response to the treatment, and investigators aren't sure why. Dr. Krishna noted that the benefits of the procedure waned in about a quarter of patients within a year of treatment.

Investigators plan to probe these questions in future trials.

"The results of this trial are promising," Dr. Schrag wrote, "but given the nonreversible nature of the intervention and the progressive nature of the disease, it will be important to establish whether improvements in motor complications are maintained over longer periods and whether treatment results in improved overall functioning and quality of life for patients."

The study was funded by Insightec. Disclosure forms for Dr. Krishna and Dr. Schrag are provided on the journal's website. **NR**

—Kelli Whitlock Burton

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MS looks homogeneous

An analysis of clinical factors and treatment responses calls for personal rather than precision medicine.

SAN DIEGO – Clinical characteristics and treatment responses in multiple sclerosis (MS) show unimodal distributions, which suggests that it is a homogeneous condition with lots of variation, rather than a mixture of conditions with different genetic or other causes, according to a new analysis. The work suggests that personalized therapy based on clinical characteristics is likely to be the best approach, rather than precision medicine based on molecular or other subtypes.

Think MS is heterogeneous? Think again

The work drew upon data from 22,000 individuals, 32,000 attacks, 156,000 EDSS scores, 250,000 observation years, and 110,000 treatment years recorded in the Swedish MS registry. The researchers examined distributions in age of onset, severity, and distribution of relapses. Among patients treated with one of 12 disease-modifying therapies, they examined patterns of EDSS progression, appearance of new lesions, and relapses.

"Regardless of which clinical characteristic of the MS syndrome that I study, I find a uniform distribution with very few if any outliers. That argues that MS is likely to be a homogeneous condition with some variation, but it's highly unlikely that MS is a mixture of different conditions masquerading as the same thing," said Jan Hillert, MD, PhD, who presented the study during a poster session at the annual meeting held by the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

"There are big efforts out there trying to decipher the molecular basis of the MS syndrome, thinking that it's a mixture of different things. And I would argue that our data very strongly argue against that," said Dr. Hillert, who is a professor of neurology at Karolinska Institutet in Solna, Sweden.

Specific subtypes should produce individual groupings rather than a broad distribution. "If you have a multitude of factors, then this (finding of a broad distribution) is what you have. If you have a small number of strongly acting factors, like if there were genetic subgroups, then you would have a different distribution. So this is in line with the polygenic, complex nature of MS that we have been thinking about for many, many years, and which the genetics also support," said Dr. Hillert.

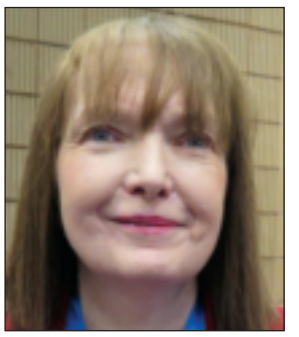
The findings suggest that physicians should be emphasizing personalized treatment of MS based on factors like age, weight, disease activity and severity, disability, side effects, and other factors. "Personalized medicine I embrace, but the concept of precision medicine is naive. It's not founded on any sound scientific evidence," said Dr. Hillert.

An evolving definition

The conclusion is compelling, according to Patricia Coyle, MD, who was asked to comment on the study. "I have not seen this sort of analysis before. I think it doesn't absolutely prove the case in talking about very small numbers, but it does make a very logical argument. This is not showing any meaningful large subgroups that you can call out," said Dr. Coyle, who is a professor of neurology and director of the MS Comprehensive Care Center at Stonybrook Neurosciences Institute in New York.

"I think that it's interesting, because we have routinely said we think this is heterogeneous, because no two patients are alike. But this is speaking against meaningful heterogeneity in MS. When you look at these sorts of statistical results, this is what you'd expect in a normal population, not in a disease where you might say, genetically, or molecularly, you could define significant subsets of individuals," said Dr. Coyle.

Jan Hillert, MD, PhD



Patricia Coyle, MD

The study isn't the last word. "You would probably like to see some follow-up data, perhaps in other very large databases to make it more convincing, but I think you're not hearing as many people talk about MS heterogeneity anymore. We know there's a focal inflammatory component, we know there's a neurodegenerative component. Both are present in all MS. People are even arguing that maybe it's not meaningful to call out progressive and relapsing MS. I don't agree with that, but I think the concept that there are meaningful subsets of patients is probably incorrect. [The idea that] one set is due to perhaps an infection, another might be molecular mimicry. ... Maybe that's not the case at all," said Dr. Coyle.

For example, some companies are looking into whether B cell depletion treatments might be more effective for one set of patients versus another. "The issue is, can you dissect out subsets where hitting B cells is really good and others where it doesn't seem to matter? That really hasn't [been successful]," said Dr. Coyle.

Dr. Hillert has served on scientific advisor boards for or received speaker's fees from Biogen, Bristol Myers Squibb/Celgene, Janssen, Novartis, Teva, Merck KGaA, Sandoz, and Sanofi Genzyme. He has received research support from Biogen, Bristol Myers Squibb/Celgene, Merck, Janssen, Novartis, Roche, and Sanofi-Genzyme. Dr. Coyle has consulted for or received speaker fees from Accordant, Biogen, Bristol Myers Squibb, GlaxoSmithKline, Horizon Therapeutics, LabCorp, Eli Lilly and Company, Mylan, Novartis, Sanofi Genzyme, TG Therapeutics. She has received research support from Actelion, Alkermes, Celgene, CorEvitas, Genentech/Roche, Janssen, MedDay, NINDS, Novartis, and Sanofi Genzyme. **NR**

—Jim Kling

Even mild COVID is hard on the brain

continued from page 1

(177 women, 77 men, median age 41 years) who had mild COVID-19 a median of 82 days earlier. A total of 102 had symptoms of both anxiety and depression, and 152 had no such symptoms.

On brain imaging, those with COVID-19 and anxiety and depression had atrophy in the limbic area of the brain, which plays a role in memory and emotional processing. No shrinkage in this area was evident in people who had COVID-19 without anxiety and depression or in a healthy control group of individuals without COVID-19.

The researchers also observed a "severe" pattern of abnormal cerebral functional connectivity in those with COVID-19 and anxiety and depression. In this functional connectivity analysis, individuals with COVID-19 and anxiety and depression had widespread functional changes in each of the 12 networks assessed, while those with COVID-19 but without symptoms of anxiety and depression showed changes in only 5 networks.

Mechanisms unclear

"Unfortunately, the underpinning mechanisms associated with brain changes and neuropsychiatric dysfunction after COVID-19 infection are unclear," said Dr. Yasuda. "Some studies have demonstrated an association between symptoms of anxiety and depression with inflammation. However, we hypothesize that these cerebral alterations may result from a more complex interaction of social, psychological, and systemic stressors, including inflammation. It is indeed intriguing that such alterations are present in individuals who presented mild acute infection," Dr. Yasuda added.

"Symptoms of anxiety and depression are frequently observed after COVID-19 and are part of long-COVID syndrome for some individuals. These symptoms require adequate treatment to improve the quality of life, cognition, and work capacity," she said. Treating these symptoms may induce "brain plasticity, which may result in some degree of gray matter increase and eventually prevent further structural and functional damage," Dr. Yasuda said.

A limitation of the study was that symptoms of anxiety and depression were self-reported, meaning people may have misjudged or misreported symptoms.

Commenting on the findings, Cyrus Raji, MD, PhD, with the Mallinckrodt Institute of Radiology, Washington University, St. Louis, said the idea that COVID-19 is bad for the brain isn't new. Dr. Raji was not involved with the study.

Early in the pandemic, Dr. Raji and colleagues published a paper in the Journal of Alzheimer's Disease detailing COVID-19's effects on the brain, and Dr. Raji followed it up with a TED talk on the subject.

"Within the growing framework of what we already know about COVID-19 infection and its adverse effects on the brain, this work incrementally adds to this knowledge by identifying functional and structural neuroimaging abnormalities related to anxiety and depression in persons suffering from COVID-19 infection," Dr. Raji said.

The study was supported by the São Paulo Research Foundation. The authors have no relevant disclosures. Dr. Raji is a consultant for Brainreader, Apollo Health, Pacific Neuroscience Foundation, and Neurevolution LLC.

NR

—Megan Brooks

Any level of physical activity tied to better later-life memory

continued from page 1

Exercise timing

Previous studies have established a link between fitness training and cognitive benefit later in life, but the researchers wanted to explore whether the timing or type of exercise influenced cognitive outcomes in later life.

> **Those who exercised to any extent in adulthood had significantly better cognitive scores later in life, compared with their peers who were physically inactive.**

The investigators asked more than 1,400 participants in the 1946 British birth cohort how much they had exercised at ages 36, 43, 60, and 69 years.

The questions changed slightly for each assessment period, but in general, participants were asked whether in the past month they had exercised or participated in such activities as badminton, swimming, fitness exercises, yoga, dancing, football, mountain climbing, jogging, or brisk walks for 30 minutes or more; and if so, how many times they participated per month.

Prior research showed that when the participants were aged 60 years, the most commonly reported activities were walking (71%), swimming (33%), floor exercises (24%), and cycling (15%).

When they turned 69, researchers tested participants' cognitive performance using the Addenbrooke's Cognitive Examination–III, which measures attention and orientation, verbal fluency, memory, language, and visuospatial function. In this study sample, 53% were women, and all were White.

Physical activity levels were classified as inactive, moderately active (one to four times per month), and most active (five or more times per month). In addition, they were summed across all five assessments to create a total score ranging from 0 (inactive at all ages) to 5 (active at all ages).

Overall, 11% of participants were physically inactive at all five time points; 17% were active at one time point; 20% were active at two and three time points; 17% were active at four time points; and 15% were active at all five time points.

'Cradle to grave' study?

Results showed that being physically active at all study time points was significantly associated with higher cognitive performance, verbal memory, and processing speed when participants were aged 69 ($P < .01$).

Those who exercised to any extent in adulthood – even just once a month during one of the time periods, fared better cognitively in later life, compared with physically inactive participants. ($P < .01$).

Study limitations cited include a lack of diversity among participants and a disproportionately high attrition rate among those who were socially disadvantaged.

"Our findings show that being active during every decade from their 30s on was associated with better cognition at around 70. Indeed, those who were active for longer had the highest cognitive function," Dr. James said.

> **"Our findings show that being active during every decade from their 30s on was associated with better cognition at around 70."**

"However, it is also never too late to start. People in our study who only started being active in their 50s or 60s still had higher cognitive scores at age 70, compared with people of the same age who had never been active," she added.

Dr. James intends to continue following the study sample to determine whether physical activity is linked to preserved cognitive aging "and buffers the effects of cognitive deterioration in the presence of disease markers that cause dementia, ultimately delaying dementia onset."

"We hope the cohort we study will be the first 'cradle to grave' study in the world, where we have followed people for their entire lives," she said.

Encouraging finding

In a comment, Joel Hughes, PhD, professor of psychology and director of clinical training at Kent (Ohio) State University, said the study contributes to the idea that "accumulation of physical activity over one's lifetime fits the data better than a 'sensitive period' – which suggests that it's never too late to start exercising."

Dr. Hughes, who was not involved in the research, noted that "exercise can improve cerebral blood flow and hemodynamic function, as well as greater activation of relevant brain regions such as the frontal lobes."

While observing that the effects of exercise on cognition are likely complex from a mechanistic point of view, the finding that "exercise preserves or improves cognition later in life is encouraging," he said.

The study received funding from the UK Medical Research Council and Alzheimer's Research UK. The investigators and Dr. Hughes report no relevant financial relationships. **NR**

—Eve Bender

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Martin KR et al. Patterns of leisure-time physical activity participation in a British birth cohort at early old age. PLoS One. 2014 Jun 9;9(6):e98901.

Is slowing, not stopping, Alzheimer's disease a better goal for clinical trials?

The authors of a new report call for a "reframing" of how researchers define "clinically meaningful" in randomized controlled trials.

Slowing progression of, rather than stopping, Alzheimer's disease has measurable benefits for patients and families and may be a more realistic goal for clinical Alzheimer's disease drug trials, a new report suggests. The report is a yearlong undertaking by an expert work group convened by the Alzheimer's Association and was prompted, in part, by the fallout from the U.S. Food and Drug Administration's (FDA) controversial decision to grant aducanumab (Aduhelm) accelerated approval, which came over the objection of an advisory panel that found the drug was ineffective.

> Settling on a definition of "clinically meaningful" that everyone agrees upon will be a challenge.

The report's authors call for a "reframing" of how researchers define "clinically meaningful" in randomized controlled trials, noting that it's time to adjust expectations of outcomes from relatively short clinical trials. "Without lowering the bar, are we expecting too much from a clinical trial by expecting that unless the disease is halted in its tracks and there's no progression, we failed at treatment?" said Ronald C. Petersen, MD, PhD, lead author, chair of the work group, and professor of neurology at the Mayo Clinic, Rochester, Minn.

Interpretations of clinical meaningfulness are used in the drug approval process and in decisions about whether an insurer will cover the cost of treatment, the authors noted.

While the report doesn't provide a consensus definition of clinically meaningful benefit, it does offer a starting point for a conversation about how the phrase should be defined in the context of randomized controlled trials for disease-modifying therapies in Alzheimer's disease, Dr. Petersen said.

"What we tried to do was to put it into some kind of perspective and at least have people reflect on this: If you're going to design the perfect drug trial in Alzheimer's disease, what would it be? We wanted to get people to think about it without digging in their heels for or against," he added.

The report was published online in Alzheimer's and Dementia: The Journal of the Alzheimer's Association.

A proactive measure

The expert group began its work in January 2022, less than a year after the FDA approved aducanumab. Since the panel began its work, the FDA has approved a second Alzheimer's disease drug, lecanemab (Leqembi), and denied accelerated approval of a third medication, donanemab.

"At the time we started this group, we had one approved treatment, and we just knew that there were others on the way, and we needed to be prepared to have this conversation and be more proactive than reactive," Christopher Weber, PhD, director of global science initiatives for the Alzheimer's Association and coauthor of the report, said in an interview.

The work group suggests that simply slowing disease progression might be a desired goal for drug trials, especially early on, before cognition and memory are affected. They also note that a benefit identified during an 18-month clinical trial may ultimately lead to even more meaningful changes over coming years, well beyond the trial's end.

In addition, the report authors call for the development of better research tools to more accurately assess meaningful change. The Clinical Dementia Rating (CDR) scale is currently the key instrument used as a primary outcome measure in randomized controlled trials. However, the report's authors note that it may not be adequate to measure meaningful change in early-stage disease.

"Developing better tools certainly should be on the radar screen for all of us, because I think we can do better," Dr. Petersen said. "The CDR, as good as it is and as long as it's been used in the field, is a pretty blunt instrument, and it's the result of subjective ratings."

'Quality of mind'

Jason Karlawish, MD, professor of medicine, medical ethics, health policy, and neurology at the University of Pennsylvania, Philadelphia, said measuring the actual impact of a drug on a patient's disease and quality of life has been a hot topic in the Alzheimer's disease field for some time, but settling on a definition of "clinically meaningful" that everyone agrees upon will be a challenge. "I think the idea of 'clinically meaningful' is truly a socially constructed idea," said Dr. Karlawish, codirector of Penn's Memory Center, who did not work on the report.

"You can come up with objective measures of cognition, but a measure to call something 'clinically meaningful' ultimately requires some sort of negotiated social order among clinicians and patients and others who have immediate interest in the health and well-being of the patient."

Dr. Karlawish added that he's interested in the conversations the report might prompt and the challenges it could highlight, especially when it comes to how meaningful clinical benefit can be measured, regardless of how it's defined.

"Hidden in this conversation about clinically meaningful treatments in Alzheimer's disease is, frankly, not quality of life, but quality of mind," said Dr. Karlawish. "No measure captures acceptably the very thing that everyone actually cares a lot about and why we view this disease as so dreadful, which is damage to our mind."

More evidence needed

The development of such tools will take time. What does that mean for drugs already in the pipeline? Members of the work group argue that those trials must move forward at the same time new tools are being created.

"We need to continue to refine, develop better instruments, [and] develop tools that are going to assess the disease in its more subtle features early on, even in the so-called 'presymptomatic' stage of the disease," said lead author Dr. Petersen. "We shouldn't wait for the development of that before intervening if we have a drug that seems to work."

However, not everyone who agrees with the premise of the report agrees with this position, including Joel S. Perlmutter, MD, professor of neurology, Washington University, St. Louis, who also commented on the report.

Dr. Perlmutter was one of three physicians who resigned from the FDA advisory panel that voted against approving aducanumab after the agency moved forward anyway.

"We have to be careful not to recommend disease-modifying therapies that we hope will help without strong evidence, especially when potential side effects are not trivial," Dr. Perlmutter said. "We have to have evidence before making these recommendations so we don't end up harming people more than helping them."

The report received no specific funding. Dr. Petersen received consulting fees from Roche, Nestle, Merck, Biogen, Eisai, and Genentech. Full disclosures are included in the original article. Dr. Perlmutter and Dr. Karlawish report no relevant financial relationships. **NR**

—Kelli Whitlock Burton

Suggested Reading

Petersen RC et al. Expectations and clinical meaningfulness of randomized controlled trials. Alzheimers Dement. 2023 Feb. 7 (Epub ahead of print).

Aerobic and breathing exercises tied to faster concussion recovery

Heart rate variability biofeedback and progressive aerobic exercise were each helpful, but combining them led to even greater improvement in cognition, depression, and mood.

A combination of gradual aerobic exercise and breathing practice can help ease persistent postconcussive symptoms, preliminary findings from a new study suggest. Heart rate variability biofeedback (HRVB) and progressive aerobic exercise (PAE) were each helpful on their own, but combining them led to even greater improvement in cognition, depression, and mood.

"Managing persistent concussion symptoms is particularly challenging as there are no standard therapies," study investigator R. Davis Moore, PhD, from the University of South Carolina, Columbia, said in a news release.

"These therapies are inexpensive, easy to implement, and can be self-administered, making them feasible and accessible for everyone with persistent symptoms," Dr. Moore noted.

The study was released early, ahead of its scheduled presentation at the 2023 annual meeting of the American Academy of Neurology.

Targeting autonomic dysfunction

Concussion can affect the autonomic nervous system, and it is "increasingly clear that this underlies the inability to tolerate exercise, problems with thinking skills, and mood issues in those with persisting symptoms," Dr. Moore explained.

Preliminary research suggests that HRVB and PAE can improve cardio-autonomic dysfunction and clinical symptoms. However, until now, no study has evaluated whether there is additional benefit from combining the two.

The investigators randomly assigned 30 teens with postconcussive symptoms that had lasted more than 1 month to a 6-week intervention consisting of either HRVB, PAE, or HRVB plus PAE.

The HRVB group practiced resonant-frequency breathing using a handheld biofeedback device for 20 minutes 4 nights a week. The PAE group completed a 3-day-a-week aerobic exercise protocol that gradually increased in intensity and duration. The HRVB plus PAE group did both. Concussion symptoms, HRV, cognition, and mood were assessed at baseline and again 6 weeks later.

All participants experienced improvement in sleep, mood, cognition, and autonomic function, but those who received the combined biofeedback and exercise intervention experienced greater improvements than peers who engaged in exercise or received biofeedback alone.

The study's top-line results, which were released ahead of the presentation, show that HRVB plus PAE is associated with a twofold greater reduction in symptom severity, compared with PAE only, and a 1.3 times greater reduction in symptom severity, compared with HRVB only.

Similarly, HRVB plus PAE led to a 1.2 times greater reduction in symptoms of depression, compared with PAE only, and a 1.3 times greater reduction, compared with HRVB only.

The combined group also experienced more than 1.4 times the reduction in total mood disturbance than was provided by exercise or biofeedback alone.

The combined group also experienced significantly greater improvements in attention and working memory, as well as greater changes in metrics of HRV, than the groups that participated in exercise or biofeedback alone.

Dr. Moore and colleagues caution that the current results are preliminary and that future studies are needed with larger groups of people.

A limitation of the study was that it did not include a control group of people with persistent postconcussive symptoms who received no intervention.

Complex problem

Commenting on the study, José Posas, MD, director of the Ochsner Neurology Residency Program, New Orleans, who wasn't involved in the study, said these preliminary results are "promising" but cited the small number of participants as a limitation.

Dr. Posas said the results "fit with what's known about the role of postconcussion autonomic dysfunction in persisting postconcussive symptoms.

"Managing persistent concussion symptoms can be challenging," he added, and this study supports "exercise as medicine" as well as taking a "mind-body, holistic approach" to postconcussion recovery, said Dr. Posas.

Also weighing in, Michael F. Bergeron, PhD, clinical and scientific advisor, Department of Performance Health, Women's Tennis Association, noted that "each of these therapeutic interventions has been around for some time now. Neither is new.

"Heart rate variability biofeedback based on variation in heart rate corresponding to breathing has been shown to be effective in treating numerous conditions, including reducing (nonclinical) stress, anxiety, depression, anger, and posttraumatic stress disorder in veterans and in some instances enhancing athletic performance. Of course, the validity and reliability of the commercially available apps and devices are potential significant limitations, as well as the stability of the user's technique," Dr. Bergeron said.

"It's also been recognized that low-level aerobic exercise treatment normalizes the cerebrovascular physiological dysfunction in patients with concussion by increasing CO_2 sensitivity, which normalizes exercise ventilation and cerebral blood flow and thus reduces some symptoms," Dr. Bergeron added.

"The combination of treatments is likely the novel aspect, which makes sense because brain injury is complex, and effective interventions need to utilize a complex, integrated biological systems approach across the multiple interdependent domains of influence," Dr. Bergeron said.

The study was supported by the nonprofit Woodcock Institute at Texas Woman's University. Dr. Moore, Dr. Bergeron, and Dr. Posas have disclosed no relevant financial relationships. **NR**

—Megan Brooks

To prevent MS, should we target Epstein-Barr virus?

Can a vaccine against EBV reduce MS incidence on a population level? Two experts debate.

SAN DIEGO – Epstein-Barr virus (EBV) infection is widely recognized as a contributor to risk of multiple sclerosis (MS). Although most adults have been exposed, it is very rare to find MS in an individual with no prior EBV exposure. That apparent relationship has driven interest in a vaccine against EBV in an effort to reduce MS incidence on a population level.

At a session at the annual meeting held by the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), two researchers debated the potential benefits and pitfalls of such a program. The issues included the possible benefit in MS and other EBV-related conditions such as mononucleosis and various cancers, and whether EBV infection is a sufficient cause for MS, as well as concerns about vaccinating a healthy at-risk population.

> "We think perhaps a role for preventing infection or modifying the initial infection could be important."

Reducing the risk of MS by targeting EBV

Jeffrey I. Cohen, MD, spoke first, and cited several lines of evidence supporting the importance of EBV in MS. One study showed a 32-fold increased risk of MS following primary infection with EBV, and another showed that higher EBV nuclear antigen (EBNA) antibody titers were associated with a 36-fold higher risk of MS. "So we have two completely independent studies suggesting that EBV is really very important as a cofactor for development of MS," said Dr. Cohen, chief of the laboratory of infectious diseases and chief of the medical virology section at the National Institutes of Health, Bethesda, Md.

EBV is also latent in B cells, and anti-B cell therapy is an effective therapeutic strategy for MS. However, the mechanism remains unknown.

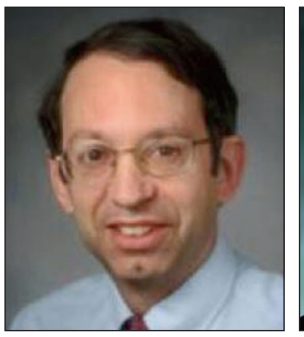
Targeting EBV could involve attacking infected cells, or a therapeutic vaccine could be employed to treat EVB-infected individuals, similar to the shingles vaccine. "In all of these methods, one would end up with fewer EBV infected B cells and as a result, presumably you'd have reduced antigenic stimulation of EBV-infected B cells to stimulate either antibodies or T cells that could damage the nervous system. By reducing this, one might be able to [treat] MS," said Dr. Cohen.

He did acknowledge concerns. It isn't yet understood whether destroying EBV-infected cells would actually improve outcomes. It also may be more difficult to reduce a latent infection than to prevent infection, since almost all B cells become latently infected. "Thus we think perhaps a role for preventing infection or modifying the initial infection could be important," said Dr. Cohen.

The most advanced vaccine candidate is a soluble form of EBV glycoprotein gp 350, which is the dominant glycoprotein on the surface of the virus and infected cells. It reduced the risk of mononucleosis by 78%, but it did not prevent EBV infection. There were no safety concerns. Two more vaccines are currently in clinical trials – an mRNA vaccine against a gp 350 sponsored by Moderna, and a gp 350 nanoparticle vaccine by the NIH.

Dr. Cohen acknowledged that safety is the most important factor, since it would be given to healthy individuals, and probably children. There are worries that a vaccine using EBV proteins could worsen MS. In particular, higher titers of antibodies against EBNA have been linked to developing MS and the anti-EBNA antibody has been implicated in molecular mimicry related to MS. However, the current vaccines avoid EBNA. Another worry is that a vaccine could delay onset of disease to an older age, when infection might be more dangerous. However, no delay in onset has been noted with the varicella vaccine or polio vaccines, which prompted similar concerns.

Vaccinating against EBV could also reduce other conditions such as mononucleosis and several cancers.



Jeffrey I. Cohen, MD

Peter Calabresi, MD

Does EBV infection even matter?

In his talk, Peter Calabresi, MD, made the case that EBV is not the sole cause of MS, and thus targeting it may prove ineffective. Dr. Calabresi is director of the division of neuroimmunology at Johns Hopkins Medicine, Baltimore.

Why was he asked to provide a rebuttal? "About this time last year, I commented at a meeting that we should be thoughtful as we think about what to do about EBV and MS. I do believe that constructive dialogue is the foundation of science," he said. He also stated that he is not opposed to vaccines. "I congratulate Dr. Cohen on all of his vaccine successes," he said.

Still, he is unconvinced that EBV is solely responsible for MS. "I think it's hard to draw a straight line between EBV and MS as one might with HPV [human papillomavirus] and cervical cancer. For example, we know that EBV accounts for more than 1% of all cancers, and EBV can also cause other autoimmune diseases such as lupus and Sjogren's, so it's complicated. And MS of course has genetic susceptibility that's not limited to the major histocompatibility complex (MHC) genes that are associated with presenting viral peptides," said Dr. Calabresi.

> "I think it's hard to draw a straight line between EBV and MS as one might with HPV and cervical cancer."

Evidence relating MS vulnerability to other genetic and environmental factors, including diet, sunlight, smoking, and even pollution, calls into question a direct causal relationship between EBV and MS, he said.

The age prevalence of EBV would complicate efforts to eradicate it. Seroprevalence is 55% by age 5-11 and 75% among university students. "This is important because the duration of the vaccine response–induced protection in young seronegative children is not lengthy. Vaccinated individuals may become susceptible to natural infection at an age where the consequences of infection are more severe, especially leading to infectious mononucleosis, and hopefully not MS. This then raises the issue of the need for boosters, which we're all well aware of during the COVID pandemic. This may be a problem, especially in young adults due to noncompliance," said Dr. Calabresi.

He pointed out that not all vaccine attempts went well. In the 1960s, early respiratory syncytial virus (RSV) vaccines caused enhanced respiratory disease and 2 deaths. "We need to be careful when we think about targeting healthy at-risk young people," said Dr. Calabresi.

Rather than pursue vaccination, Dr. Calabresi favors research into EBV latency in B cells as well as how EBV-infected B cells may cause or exacerbate MS, with the hopes of developing interventions. "It's tempting to speculate that the success of the anti-CD20 monoclonal antibody therapies is related to depletion of EBV infected B cells. In fact, I think that may be the case," he said.

Dr. Cohen has no relevant financial disclosures. Dr. Calabresi has served on a scientific advisory board or data monitoring board for Biogen and Disarm Therapeutics. **NR**

—Jim Kling

Two diets tied to lower Alzheimer's disease pathology at autopsy

Those who most closely followed these diets had almost 40% lower odds of having an Alzheimer's disease diagnosis at death.

A novel study provides strong evidence supporting the adoption of a healthy diet to protect the aging brain. In a cohort of deceased older adults, those who had adhered to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) and Mediterranean diets for nearly a decade before death had less global Alzheimer's disease–related pathology, primarily less beta-amyloid, at autopsy.

> "Following the MIND and Mediterranean diets may improve brain health and protect cognition."

Those who most closely followed these diets had almost 40% lower odds of having an Alzheimer's disease diagnosis at death. The findings offer one mechanism by which healthy diets protect cognition.

"While our research doesn't prove that a healthy diet resulted in fewer brain deposits of amyloid plaques ... we know there is a relationship, and following the MIND and Mediterranean diets may be one way that people can improve their brain health and protect cognition as they age," study investigator Puja Agarwal, PhD, of RUSH University Medical Center in Chicago, said in a statement.

The study was published online in Neurology.

Green leafy veggies key

The MIND diet was pioneered by the late Martha Clare Morris, ScD, a Rush nutritional epidemiologist, who died of cancer in 2020 at age 64. Although similar, the Mediterranean diet recommends vegetables, fruit, and three or more servings of fish per week, whereas the MIND diet prioritizes green leafy vegetables, such as spinach, kale, and collard greens, along with other vegetables. The MIND diet also prioritizes berries over other fruit and recommends one or more servings of fish per week. Both diets recommend small amounts of wine.

The current study focused on 581 older adults who died while participating in the Rush Memory and Aging Project (MAP). All participants agreed to undergo annual clinical evaluations and brain autopsy after death. Participants completed annual food frequency questionnaires beginning at a mean age of 84. The mean age at death was 91. Mean follow-up was 6.8 years.

Around the time of death, 224 participants (39%) had a diagnosis of clinical dementia, and 383 participants (66%) had a pathologic Alzheimer's disease diagnosis at time of death.

The researchers used a series of regression analyses to investigate the MIND and Mediterranean diets and dietary components associated with Alzheimer's disease pathology. They controlled for age at death, sex, education, APO-epsilon 4 status, and total calories.

Overall, both diets were significantly associated with lower global Alzheimer's disease pathology (MIND: beta = –0.022, P = .034; and Mediterranean: beta = –0.007, P = .039) – specifically, with less beta-amyloid (MIND: beta = –0.068, P = .050; and Mediterranean: beta = –0.040, P = .004).

The findings persisted when the analysis was further adjusted for physical activity, smoking, and vascular disease burden and when participants with mild cognitive impairment or dementia at the baseline dietary assessment were excluded.

Individuals who most closely followed the Mediterranean diet had average beta-amyloid load similar to being 18 years younger than peers with the lowest adherence. And those who most closely followed the MIND diet had average beta-amyloid amounts similar to being 12 years younger than those with the lowest adherence.

A MIND diet score 1 point higher corresponded to typical plaque deposition of participants who are 4.25 years younger in age.

Regarding individual dietary components, those who ate seven or more servings of green leafy vegetables weekly had less global Alzheimer's disease pathology than peers who ate one or fewer (beta = –0.115, P = .0038). Those who ate seven or more servings per week had plaque amounts in their brains corresponding to being almost 19 years younger in comparison with those who ate the fewest servings per week.

"Our finding that eating more green leafy vegetables is in itself associated with fewer signs of Alzheimer's disease in the brain is intriguing enough for people to consider adding more of these vegetables to their diet," Dr. Agarwal said in the news release.

Previous data from the MAP cohort showed that adherence to the MIND diet can improve memory and thinking skills of older adults, even in the presence of Alzheimer's disease pathology.

Novel study, intriguing results

Heather Snyder, PhD, vice president of medical and scientific relations with the Alzheimer's Association, noted that a number of studies have linked overall nutrition – especially a balanced diet low in saturated fats and sugar and high in vegetables – with brain health, including cognition, as one ages.

This new study "takes what we know about the link between nutrition and risk for cognitive decline a step further by looking at the specific brain changes that occur in Alzheimer's disease. The study found an association of certain nutrition behaviors with less of these Alzheimer's brain changes," said Dr. Snyder, who was not involved in the study.

"This is intriguing, and more research is needed to test via an intervention if healthy dietary behaviors can modify the presence of Alzheimer's brain changes and reduce risk of cognitive decline."

The Alzheimer's Association is leading a 2-year clinical trial known as US POINTER to study how targeting known dementia risk factors in combination may reduce risk of cognitive decline in older adults. The MIND diet is being used in US POINTER.

"But while we work to find an exact 'recipe' for risk reduction, it's important to eat a heart-healthy diet that incorporates nutrients that our bodies and brains need to be at their best," Dr. Snyder said.

The study was funded by the National Institutes of Health. Dr. Agarwal and Dr. Snyder have disclosed no relevant financial relationships. **NR**

—Megan Brooks

Suggested Reading

Agarwal P et al. Association of Mediterranean-DASH intervention for neurodegenerative delay and Mediterranean diets with Alzheimer disease pathology. Neurology. 2023 March 8 (Epub ahead of print).

Physical activity is a growing priority for patients with MS

Recent research suggests that exercise may benefit patients with MS.

SAN DIEGO – As mounting evidence points to the benefits of physical activity for patients with multiple sclerosis (MS), researchers have developed a mobile app to encourage young patients with the disease to become more active. The smartphone-based app provides tailored physical activity information, coaching advice, and tools to increase social connectedness.

A pilot study examining whether the intervention changes activity, depression, and fatigue levels should be wrapped up later this year, but it looks as though the app is succeeding.

"The feedback we've gotten so far from our coaches is that the kids seem highly motivated," said one of the creators, E. Ann Yeh, MD, professor in the faculty of medicine at the University of Toronto and director of the pediatric MS and neuroinflammatory disorders program at the Hospital for Sick Children.

Preliminary work showed that use of the app was associated with a 31% increase in physical activity.

They discussed this and other studies of the role of exercise in MS at the 2023 annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

Higher levels of depression and fatigue

Studies show that youths with MS who are less physically active are more likely to experience higher levels of fatigue and depression. Evidence suggests just 15-30 more minutes of moderate to vigorous physical activity (MVPA) makes a clinical difference in terms of improved depression and fatigue scores, said Dr. Yeh.

With moderate physical activity (for example, a brisk walk or raking the yard), the maximal heart rate (HRmax) reaches 64%-76%, while with vigorous physical activity (which includes jogging/running or participating in a strenuous fitness class), the HRmax reaches 77%-93%.

Dr. Yeh described vigorous physical activity as "the stuff that makes you sweat, makes your heart rate go up, and makes you not be able to talk when you're moving."

As it stands, kids get very little MVPA – 9.5 min/day, which is well below the recommended 60 min/day. Adults do a bit better – 18.7 min/day of MVPA – but this is still below the recommended 30 min/day.

Being physically active improves fatigue for adults with MS as well as kids, said Dr. Yeh. She referred to a network meta-analysis of 27 studies involving 1,470 participants that evaluated 10 types of exercise interventions, including yoga, resistance training, dance, and aquatic activities. It found that exercise "does move the needle," she said. "Regardless of the kind of activity that was studied, fatigue seemed to improve."

> **Just 15-30 more minutes of moderate to vigorous physical activity makes a clinical difference.**

The authors of that study ranked aquatic exercise as the most effective intervention. "It's possible that aquatics worked better because people who can't move well feel more comfortable in the water," Dr. Yeh said.

But she cautioned that the one study in the meta-analysis that found a "quite strong" effect of aquatic exercise was "very small."

With regard to depression, which affects about 30% of people with MS, Dr. Yeh told meeting attendees, "unfortunately, the data are less clear" when it comes to physical activity for adults. One meta-analysis of 15 randomized controlled trials involving 331 exercising participants and 260 control persons found that only a few studies showed positive effects of exercise on depressive symptoms.

However, Dr. Yeh noted that in this review, the baseline depressive symptoms of participants were "above the cutoff level," which makes it more difficult to demonstrate change in depression levels.

Clear structural effects

Researchers have also described clear brain structural and functional effects from being physically active. For example, MVPA has been shown to affect brain volume, and it has been associated with better optical coherence tomography (OCT) metrics, which measures retinal thinning.

As for the impact of exercise on memory deficits, which is of interest, given the current focus on Alzheimer's disease, "the jury is still out," said Dr. Yeh. One 24-week randomized controlled trial found no difference in results on the Brief Repeatable Battery of Neuropsychological tests between participants who engaged in progressive aerobic exercise and control persons.

However, said Dr. Yeh, "the problem may not be with the intervention but with the outcome measures" and potentially with the populations studied.

It might be a different story for high-intensity exercise, though. A study by Danish researchers assessed the effects of a 24-week high-intensity intervention among 84 adult patients with mild-severe impairment.

The primary outcome of that study, which was the percentage of brain volume change, was not met, possibly because the study was too short. There were significant results for some secondary endpoints, including improved cardiorespiratory fitness and lower relapse rate.

"Even though on the face of it, it sounds like a negative study, there were important outcomes," said Dr. Yeh.

Research into the possible mechanisms behind positive effects of physical activity is limited with regard to patients with MS, said Dr. Yeh. Some studies have implicated certain circulating factors, such as the cytokine irisin and brain-derived neurotrophic factor, but more work is needed, she said.

"There is need for further mechanistic knowledge related to exercise in MS, and this must be accomplished through prospective, randomized studies."

While exercise likely makes some difference for MS patients, the problem is in getting them to be more active. "You can't just write a prescription," said Dr. Yeh. "Patients should be doing whatever they can, but gradually, and should not go crazy at the beginning because they'll just burn out," she said.

She stressed that patients need to find what works for them personally. It's also important for them to find ways to be active with a friend who can be "a motivator" to help sustain physical activity goals, said Dr. Yeh.

Patients can also look online for remote physical activity programs geared to people with MS, which popped up during the pandemic.

Improved mood, cognition, pain, sleep

In a comment, Marwa Kaisey, MD, assistant professor of neurology at Cedars-Sinai Medical Center, in Los Angeles, who cochaired the session highlighting the presentation, praised Dr. Yeh's "excellent talk," which highlighted the "strong benefit" of exercise for patients with MS.

"As a clinician, I often talk to my patients about the importance of physical exercise and have heard countless anecdotes of how their workout programs helped improve mood, cognition, pain, or sleep."

However, she agreed there are several areas "where we need more data-driven solutions and a mechanistic understanding of the benefits of physical exercise."

The pilot study was funded by the Consortium of Multiple Sclerosis Centers. The MS Society of Canada funded early work on the app, and the National MS Society is funding the trial of the app. Dr. Yeh receives support from the MS Society of Canada. Dr. Kaisey reports no relevant financial relationships. **NR**

—Pauline Anderson

Immunotherapy predicts fewer relapses: MOGAD study results

IVIG therapy appears to be the most effective for reducing relapses.

SAN DIEGO – A new retrospective analysis of patients with myelin oligodendrocyte glycoprotein antibody disease (MOGAD) indicates that treatment with immunotherapy is associated with a lower risk of relapse. The authors note that many patients with MOGAD never experience a relapse and it is difficult to predict which ones will.

MOGAD can cause optic neuritis, transverse myelitis, and acute disseminated encephalomyelitis (ADEM). It was first described in 2007, and the best approaches to therapy are not yet understood. This study is at least a starting point for understanding treatment outcomes, according to Philippe Bilodeau, MD, who presented the study during a poster session at the annual meeting held by the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

Predicting which patients will relapse

"I think one of the biggest unanswered clinical questions in MOGAD is trying to determine who's going to go on to have relapsing MOGAD. About 30% to 40% of patients with MOGAD will never have a second attack. So one of the big questions is: How can we identify patients who would benefit from immunotherapy, and how can we identify patients who will have a more benign disease course and may not need to be started on a treatment," said Dr. Bilodeau, a neurology resident at Massachusetts General Hospital/Brigham and Women's Hospital, Boston.

The researchers analyzed data from 143 patients seen at Massachusetts General or Brigham and Women's Hospital who had presented with their first attack. Over a follow-up period of 5 years, the relapse rate was 61.8%. The researchers examined various factors, including age of onset, high MOG titer, attack type, and male sex, and found that only the latter came close to predicting relapse, though it fell short of clinical significance (hazard ratio [HR], 0.61; $P = .07$).

However, treatment with mycophenolate, azathioprine, intravenous immunoglobulins (IVIG), rituximab, or tocilizumab strongly predicted a lower probability of relapse (HR, 0.25; $P < .0001$).

The most effective treatment for relapsing MOGAD

In a separate poster, his team examined a subset of the cohort of 88 patients who were treated with mycophenolate mofetil, B-cell depletion, rituximab, or IV immunoglobulins (IVIG) during a first or second relapse, as well as an analysis of every relapse experienced by any patient during the course of their disease. "Using a negative binomial regression, we looked at the annualized relapse rates and incidence rate ratios between the different treatments. No matter how you looked at the data – even if you looked at total time on IVIG, if you looked at time on monotherapy, excluding if they were on prednisone at the same time if they were on both IVIG and rituximab, if you only consider patients that were on high dose IVIG – IVIG was by far the best treatment and rituximab was always the least effective, and mycophenolate was always between IVIG and rituximab. So I think in that cohort, we can say with some confidence that IVIG is the most effective treatment for relapsing MOGAD," said Dr. Bilodeau.

Other studies had suggested efficacy of individual treatments, but "I think what hadn't been done is taking one cohort and comparing those treatments head to head, so that's what we were trying to do," said Dr. Bilodeau.

> **The best approaches to therapy are not yet understood. This study is at least a starting point for understanding treatment outcomes.**

Both studies have the usual caveats of a retrospective study and so cannot prove causality. "We need to find more covariates to make sure that there's no confounding (factor) explaining this and to make sure that there aren't other demographic or clinical factors that explain the association. But as it stands, I think at this time starting treatment with immunotherapy is the only thing that we know will reduce the risk of having a future relapse. There's a lot of further analysis that we need to do," said Dr. Bilodeau.

He said that the study also provided some preliminary insight into treatment of pediatric disease. "We have interesting data from that analysis that pediatric-onset MOGAD actually had a particularly good response to [mycophenolate], more so than in adults," he said.

"At this point, I think a rational approach if you have someone coming in with a first relapse is, you have to assess their risk tolerance. If they're a very risk-averse patient, I think it's reasonable to start them on treatment. I think it's reasonable to monitor their titer. There's some data that if they seroconvert to negative, you might be able to stop immunotherapy. If someone has established relapsing disease, and they have adult onset [disease], IVIG should be the first-line treatment. If they're pediatric onset, either [mycophenolate] or IVIG are probably good first line treatments," he said.

'A good beginning'

The studies are a good beginning to getting a better understanding of MOGAD treatment, according to Michael Cossoy, MD, who attended the poster session and was asked to comment on the study.

"It's interesting because MOG antibody-associated disease is so relatively new that we don't have a great idea yet about who needs to be treated. Should we put them on some immunosuppressive therapy or should we wait? At the moment this is a bit of a tautology. You know that if you put people on therapy from the very first event, some of those people are not going to have a second event. And some of the people are, but you've decreased the risk of them having that second (event) if your treatment is effective. So that's what they've shown, which is great. But the question is, can you predict who's going to have a second event and know who to put on treatment and not put on treatment? It's too early to know, but this is a good start," said Dr. Cossoy, assistant professor of ophthalmology at the University of Manitoba.

Dr. Bilodeau and Dr. Cossoy have no relevant financial disclosures. **NR**

—Jim Kling

Suggested Reading

O'Connor KC et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. Nat Med. 2007 Feb;13(2):211-7.

Can particles in dairy and beef cause cancer and MS?

Researchers found single-stranded DNA rings that originated in viruses, which they named bovine meat and milk factors, in the intestines of patients with colon cancer.

In Western diets, dairy and beef are ubiquitous. But what if dairy products and beef contained a new kind of pathogen that could infect you as a child and trigger cancer or multiple sclerosis (MS) 40-70 years later?

Researchers from the German Cancer Research Center (DKFZ) suspect that such zoonoses are possibly widespread and are therefore recommending that infants not be given dairy products until they are at least age 1 year. However, in two joint statements, the German Federal Institute for Risk Assessment (BfR) and the Max Rubner Institute (MRI) have rejected such theories.

In 2008, Harald zur Hausen, MD, DSc, received the Nobel Prize in Medicine for his discovery that human papillomaviruses cause cervical cancer. His starting point was the observation that sexually abstinent women, such as nuns, rarely develop this cancer. So it was possible to draw the conclusion that pathogens are transmitted during sexual intercourse, explained Dr. zur Hausen and his wife Ethel-Michele de Villiers, PhD, both of DKFZ Heidelberg.

Papillomaviruses, as well as human herpes and Epstein-Barr viruses (EBV), polyomaviruses, and retroviruses, cause cancer in a direct way: by inserting their genes into the DNA of human cells. With a latency of a few years to a few decades, the proteins formed through expression stimulate malignant growth by altering the regulating host gene.

Acid radicals

However, viruses – just like bacteria and parasites – can also indirectly trigger cancer. One mechanism for this triggering is the disruption of immune defenses, as shown by the sometimes drastically increased tumor incidence with AIDS or with immunosuppressants after transplants. Chronic inflammation is a second mechanism that generates acid radicals and thereby causes random mutations in replicating cells. Examples include stomach cancer caused by *Helicobacter pylori* and liver cancer caused by *Schistosoma*, liver fluke, and hepatitis B and C viruses.

According to Dr. de Villiers and Dr. zur Hausen, there are good reasons to believe that other pathogens could cause chronic inflammation and thereby lead to cancer. Epidemiologic data suggest that dairy and meat products from European cows (*Bos taurus*) are a potential source. This is because colon cancer and breast cancer commonly occur in places where these foods are heavily consumed (that is, in North America, Argentina, Europe, and Australia). In contrast, the rate is low in India, where cows are revered as holy animals. Also noteworthy is that women with a lactose intolerance rarely develop breast cancer.

Viral progeny

The researchers found single-stranded DNA rings that originated in viruses, which they named bovine meat and milk factors (BMMF), in the intestines of patients with colon cancer. They reported, "This new class of pathogen deserves, in our opinion at least, to become the focus of cancer development and further chronic diseases." They also detected elevated levels of acid radicals in these areas (that is, oxidative stress), which is typical for chronic inflammation.

The researchers assume that infants, whose immune system is not yet fully matured, ingest the BMMF as soon as they have dairy. Therefore, there is no need for adults to avoid dairy or beef because everyone is infected anyway, said Dr. zur Hausen.

'Breast milk is healthy'

Dr. de Villiers and Dr. zur Hausen outlined more evidence of cancer-triggering pathogens. Mothers who have breastfed are less likely, especially after multiple pregnancies, to develop tumors in various organs or to have MS and type 2 diabetes. The authors attribute the protective effect to oligosaccharides in breast milk, which begin to be formed midway through the pregnancy. They bind to lectin receptors and, in so doing, mask the terminal molecule onto which the viruses need to dock. As a result, their port of entry into the cells is blocked.

The oligosaccharides also protect the baby against life-threatening infections by blocking access by rotaviruses and noroviruses. In this way, especially if breastfeeding lasts a long time – around 1 year – the period of incomplete immunocompetence is bridged.

Colon cancer

To date, it has been assumed that around 20% of all cancerous diseases globally are caused by infections, said the researchers. But if the suspected BMMF cases are included, this figure rises to 50%, even to around 80%, for colon cancer. If the suspicion is confirmed, the consequences for prevention and therapy would be significant.

The voice of a Nobel prize winner undoubtedly carries weight, but at the time, Dr. zur Hausen still had to convince a host of skeptics with his discovery that a viral infection is a major cause of cervical cancer. Nonetheless, some indicators suggest that he and his wife have found a dead end this time.

Institutional skepticism

When his working group made the results public in February 2019, the DKFZ felt the need to give an all-clear signal in response to alarmed press reports. There is no reason to see dairy and meat consumption as something negative. Similarly, in their first joint statement, the BfR and the MRI judged the data to be insufficient and called for further studies. Multiple research teams began to focus on BMMF as a result.

The findings presented in a second statement by the BfR and MRI at the end of November 2022 contradicted the claims made by the DKFZ scientists across the board. In no way do BMMF represent new pathogens. They are variants of already known DNA sequences. In addition, they are present in numerous animal-based and plant-based foods, including pork, fish, fruit, vegetables, and nuts.

BMMF do not possess the ability to infect human cells, the institutes said. The proof that they are damaging to one's health was also absent. It is true that the incidence of intestinal tumors correlates positively with the consumption of red and processed meat – which in no way signifies causality – but dairy products are linked to a reduced risk. On the other hand, breast cancer cannot be associated with the consumption of beef or dairy.

Therefore, both institutes recommend continuing to use these products as supplementary diet for infants because of their micronutrients. They further stated that the products are safe for people of all ages.

Association with MS?

Unperturbed, Dr. de Villiers and Dr. zur Hausen went one step further. They posited that MS is also associated with the consumption of dairy products and beef. Here too geographic distribution prompted the idea to look for BMMF in the brain lesions of patients with MS. The researchers isolated ring-shaped DNA molecules that proved to be closely related to BMMF from dairy and cattle blood. "The result was electrifying for us."

However, there are several other factors to consider, such as vitamin D3 deficiency. This is because the incidence of MS decreases the further you travel from the poles toward the equator (that is, as solar radiation increases). Also, EBV clearly plays a role because patients with MS display increased titers of EBV antibodies. One study also showed that people in Antarctica excreted reactivated EBV in their saliva during winter and that vitamin D3 stopped the viral secretion.

Under these conditions, the researchers hypothesized that MS is caused by a double infection of brain cells by EBV and BMMF. EBV is reactivated by a lack of vitamin D3, and the BMMF multiply and are eventually converted into proteins. A focal immunoreaction causes the Schwann cells and oligodendrocytes to malfunction, which leads to the destruction of the myelin sheaths around the nerve fibers. **NR**

—Angela Speth, MD

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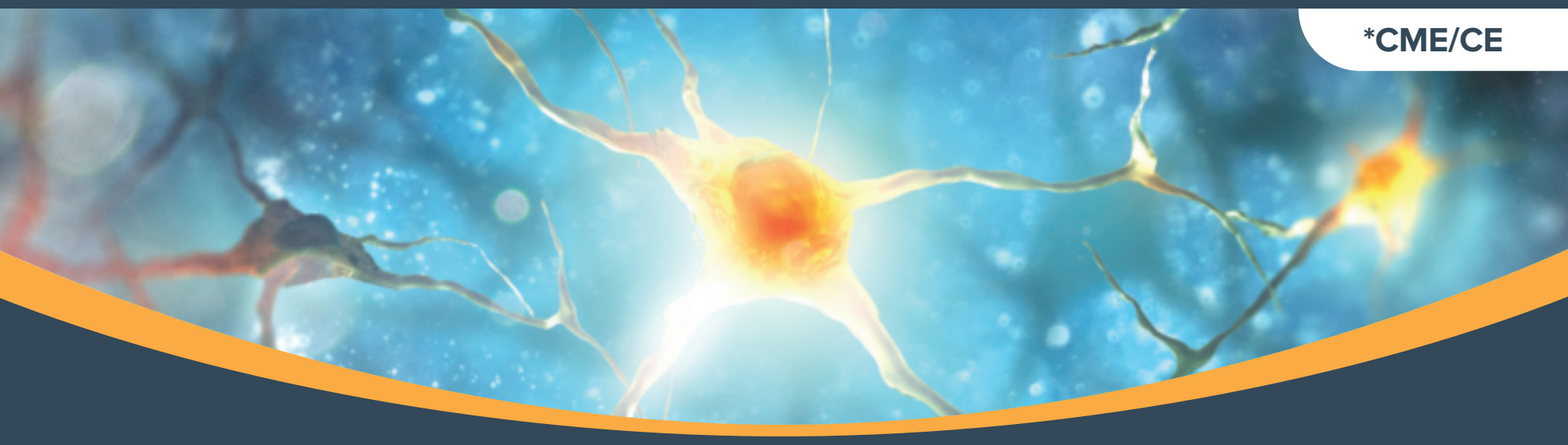

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