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NEUROLOGY REVIEWS®

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New data bolster latitude's association with MS prevalence

DALLAS—Latitude continues to be associated with the prevalence of multiple sclerosis (MS), according to an updated meta-analysis presented at the 2019 ACTRIMS Forum.

After integrating data from 94 new studies, "the latitudinal gradient in MS prevalence ... significantly enhanced in magnitude," said presenting author Steve Simpson Jr., PhD, and his colleagues. Dr. Simpson is a researcher at the Melbourne School of Population & Global Health at the University of Melbourne and the Menzies Institute for Medical Research at the University of Tasmania.

For every degree of latitude increase, prevalence of MS per 100,000 people (i.e., the slope) increased by 3.64. The researchers' original study, published in 2011, found a slope of 2.68.

The researchers' original meta-analysis—based on 650 prevalence estimates from 321 studies—"confirmed the existence of a robust latitudinal gradient." To examine whether the gradient has changed, the researchers identified relevant studies published between 2010 and 2018.

They included complete, peer-reviewed articles in their analysis and extracted data about the study area, prevalence year, MS diagnostic criteria used, sample size, source population, crude prevalence, and age-specific prevalence. They combined the new prevalence estimates with those from their original

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Andexanet alfa effectively reverses factor Xa inhibition

HONOLULU—Andexanet alfa rapidly reverses factor Xa inhibition and effectively establishes hemostasis in patients with acute major bleeding, according to a study presented at the International Stroke Conference sponsored by the American Heart Association. The medication is associated with a low rate of mortality resulting from intracerebral hemorrhage (ICH), compared with the general population of patients with ICH receiving anticoagulation.

Factor Xa inhibitors such as apixaban and rivaroxaban effectively prevent thromboembolic events but may cause or exacerbate acute major bleeding. Andexanet alfa, a modified, recombinant, inactive form of human factor Xa, was developed and approved as a reversal agent for factor Xa inhibitors. In a 2015 study, andexanet rapidly and safely reversed anti–factor Xa activity in large cohorts of patients without bleeding.

A single-cohort study

Truman John Milling Jr., MD, an emergency medicine physician at Dell Seton Medical Center at the University of Texas in Austin, and his colleagues conducted the An-

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Survey of MS patients reveals numerous pregnancy-related concerns

Of those who became pregnant following diagnosis, 20% reported postpartum depression or anxiety.

DALLAS—When it comes to family planning and pregnancy-related decisions such as breastfeeding and medication management, patients with multiple sclerosis (MS) receive a wide variety of advice, guidance, and engagement from their health care providers, results from a single-center survey demonstrated.

"We want our patients to feel comfortable when they come to us in their 20s or 30s and they get diagnosed. They're scared, and it's all new to them," one of the study authors, Casey E. Engel, said in an interview at the 2019 ACRIMS Forum. "We want them to know that family planning is something to consider and that they can proceed with having a family with our help and guidance."

A survey of women with MS

In an effort to collect patient-experience data around family planning, pregnancy, and breastfeeding post-MS diagnosis, Ms. Engel and senior author Myla D. Goldman, MD, mailed a survey to 1,000 women with confirmed MS diagnosis who had received care at the University of Virginia Medical Center in Charlottesville. The researchers reported findings from 173 respondents, of whom 70% were receiving specialty care for MS. Most of the survey participants (137) did not become pregnant following their diagnosis, while 36 did.

Casey E. Engel

Of the 137 respondents who did not become pregnant following diagnosis, 22 (16%) indicated that their decision was driven by MS-related concerns, including MS worsening with pregnancy (64%), ability to care for a child secondary to MS (46%), lack of knowledge about options for pregnancy and MS (18%), passing MS on to child (18%), and stopping disease-modifying therapy (DMT) to attempt pregnancy (9%).

A high rate of postpartum depression

Of the 36 women who had a pregnancy following diagnosis, 20% reported postpartum depression or anxiety, a rate higher than the national average of 10%-15%. In addition, 79% reported not being on DMT at the time of conception, 9% were on either glatiramer acetate injection or interferon beta-1a at time of conception, and 3% were on fingolimod (Gilenya) at time of conception. The majority reported receiving inconsistent advice about when to discontinue DMT before attempting pregnancy (a range from 0 to 6 months).

"It's also noteworthy that 20% took a year to achieve pregnancy," said Dr. Goldman, a neurologist who directs the university's MS clinic. "If these women stop [their DMT] 6 months in advance and they take a year to achieve pregnancy, that's 18 months without therapeutic coverage. That's a concern to bring to light."

Breastfeeding was reported in 71% of mothers in postdiagnosis pregnancy with a range between 1 week and 10 months, driven in part by variable guidelines regarding DMT reinitiation. In the meantime, respondents who did not breastfeed made this decision due to fear of relapse, glucocorticoids, or desire to reinitiate medication.

"Though our study was limited by low survey response, we hope that our work may highlight the difficulty our patients face and foster discussions within the MS community around these issues to improve the individual patient experience," the researchers wrote in their poster.

Ms. Engel worked on the study while an undergraduate at the University of Virginia. The study was supported by the ziMS Foundation. **NR**

—Doug Brunk

NEWSROUNDUP

AEDs may increase the risk of pneumonia in patients with Alzheimer's disease

In people with Alzheimer's disease, the use of antiepileptic drugs (AEDs) may increase the risk of incident pneumonia, according to an analysis published in the March 12 issue of the *Journal of Alzheimer's Disease*. Investigators identified 70,718 Finnish patients diagnosed with Alzheimer's disease between 2005 and 2011 using the MEDALZ dataset. They identified new AED users and matched them with a cohort of nonusers. AED use was associated with an increased risk of pneumonia (adjusted hazard ratio [aHR], 1.92). The incidence rate per 100 person years was 12.58 during AED use and 6.41 during nonuse. The investigators observed the highest risk during the first month of use (aHR, 3.59), and the risk remained elevated until two years of use. Among specific treatments, phenytoin, carbamazepine, valproic acid, and pregabalin were associated with an increased risk of pneumonia.

Taipale H, Lampela P, Koponen M, et al. Antiepileptic drug use is associated with an increased risk of pneumonia among community-dwelling persons with Alzheimer's disease-matched cohort study. *J Alzheimers Dis*. 2019;68(1):127-136.

FDA approves solriamfetol for excessive daytime sleepiness

The FDA has approved solriamfetol to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). The agency approved the drug in doses of 75 mg and 150 mg for patients with narcolepsy and in doses of 37.5 mg, 75 mg, and 150 mg for patients with OSA. Solriamfetol, to be marketed under the name Sunosi, is a dual-acting dopamine and norepinephrine reuptake inhibitor. In clinical trials, 150 mg of solriamfetol for patients with narcolepsy and all doses for patients with OSA improved wakefulness at Week 12, compared with placebo, as assessed in test sessions 1 (approximately one hour post dose) through 5 (approximately nine hours post dose) of the maintenance of wakefulness test. The drug is expected to be available during the coming months. Jazz Pharmaceuticals, headquartered in Dublin, will market solriamfetol.

Thrombolysis appears safe at more than 31 days after prior stroke

Findings question current guidelines that contraindicate stroke thrombolysis within 90 days of a prior stroke.

HONOLULU—Patients with an acute ischemic stroke who had a prior stroke more than 30 days previously may be candidates for thrombolytic treatment, based on a review of more than 40,000 U.S. stroke patients.

Current U.S. stroke management guidelines say that thrombolytic therapy with tissue plasminogen activator (tPA, alteplase, Activase) is contraindicated for index stroke patients who had a prior stroke within the previous 3 months. But an analysis of 293 U.S. patients who received thrombolytic treatment for an index acute ischemic stroke despite having had a recent prior stroke showed no increased risk for adverse outcomes when the prior stroke occurred more than 30 days previously, Shreyansh Shah, MD, said at the International Stroke Conference sponsored by the American Heart Association.

"The risk of symptomatic intracranial hemorrhage [ICH] after thrombolysis was highest among those with a history of prior ischemic stroke within the past 14 days," said Dr. Shah, a neurologist at Duke University in Durham, N.C. "Even after many adjustments, we still saw a high risk of symptomatic ICH within the first 2 weeks, suggesting that these patients are at especially high risk" from treatment with tissue plasminogen activator for the index stroke. These findings "are very important, because I don't see a randomized trial happening to test the hypothesis," Dr. Shah said in an interview.

He also suggested that prior treatment with tPA was not an important factor, just the occurrence of a recent, prior ischemic stoke that left blood vessels in the affected brain region "friable and at high risk for hemorrhage."

Thrombolysis and risk of ICH

His study examined data from 40,396 patients with an acute ischemic stroke who received treatment with tPA at any of 1,522 hospitals that participated in the Get With the Guidelines-Stroke program during 2009-2015. The analysis focused on 30,655 of these patients with no prior stroke history, who served as the controls, and 293 who had a prior ischemic stroke within the preceding 90 days. These 293 patients included 43 who received thrombolysis within 14 days of their prior stroke, 47 who had the treatment 15-30 days after their prior stroke, and 203 who underwent thrombolysis 31-90 days after their prior stroke. Patients ages' in both the no-stroke-history and recent-stroke subgroups averaged 80 years.

A comparison between all 293 patients who had a prior stroke within 90 days and the controls showed no statistically significant difference in the rate of symptomatic ICH (5% among those with no stroke history and 8% in those with a recent stroke). There was also no significant difference in the rate of in-hospital mortality, which occurred in 9% of those without a prior stroke, compared with 13% of those with a recent prior stroke. But the patients with no stroke history fared better by other measures, with a significantly lower rate of in-hospital death or discharge to a hospice, and also a significantly higher rate of 0-1 scores on the modified Rankin Scale, compared with patients with a history of prior stroke.

A more detailed analysis of the timing of the prior stroke showed that most of the risk from thrombolysis affected patients with a very recent prior stroke. The 43 patients with a prior stroke within the preceding 14 days had a rate of symptomatic ICH of 16% after thrombolysis, which was 3.7 times higher than the control patients in an adjusted analysis. Once the patients with a prior stroke within the past 14 days were removed, the remaining patients with prior strokes 15-30 days before, as well as those with a prior stroke 31-90 days previously, had rates of symptomatic ICH that were not significantly different from those of the controls, Dr. Shah reported.

The results also showed an increased rate of in-hospital mortality or discharge to a hospice clustered in patients treated either within 14 days or during 15-30 days after a prior stroke. In both subgroups, the rate of this outcome was about triple the control rate. In the subgroup treated with thrombolysis 31-90 days after a prior stroke, the rate of in-hospital mortality or discharge to a hospice was about the same as for the controls.

Potential ramifications for clinical practice

"It appears that some patients could benefit from tPA; there is a potential safety signal. It allows for some discretion when using thrombolytic treatment" in patients with a recent, prior stroke, Dr. Shah suggested. "This is by far the largest analysis ever reported" for thrombolytic treatment of patients following a recent, prior stroke, noted Ying Xian, MD, PhD, a Duke neurologist and study coauthor.

But Gregg C. Fonarow, MD, another coauthor, cautioned against immediately applying this finding to practice. "The findings of Dr. Shah's study suggest that selected patients with prior stroke within a 14- to 90-day window may be considered for tPA treatment. However, further study is warranted, given the relatively small number of patients," said Dr. Fonarow, professor of medicine and cochief of cardiology at the University of California, Los Angeles.

Dr. Shah and Dr. Xian had no disclosures. Dr. Fonarow had no relevant disclosures. **NR**

—Mitchel L. Zoler

Suggested Reading

Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e110.

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Total plasma tau correlates with dementia onset and Alzheimer's disease

It's not the Holy Grail of a simple Alzheimer's blood test for the clinic, but it could benefit research.

The total tau level in blood plasma appears to predict onset and progression of dementia and could be used to help refine research cohorts.

Blood samples from two large dementia research cohorts confirmed the finding. Each standard deviation in plasma tau above the median is associated with a 29% greater risk of incident all-cause dementia and a 35% increase in the risk of incident Alzheimer's disease, Matthew P. Pase, PhD, and colleagues wrote online ahead of print March 4 in *JAMA Neurology*. It also correlated positively with some neuropathologic aspects of dementia: smaller hippocampus and higher burden of neurofibrillary tangles in the medial temporal lobe, said Dr. Pase of the Florey Institute for Neuroscience and Mental Health in Victoria, Australia.

Plasma tau isn't the Holy Grail of a simple Alzheimer's blood test, but the finding could benefit research. As a study entry criterion, it could substantially decrease the number of subjects needed to validate an outcome of either all-cause dementia or Alzheimer's disease. Abnormal tau is also a required finding for a diagnosis of Alzheimer's disease in the revised NIA-AA Research Framework. And, the authors noted, although plasma tau wasn't quite as accurate a predictor as CSF tau, a needle in the arm would be much more acceptable to many patients than a lumbar puncture.

"Whereas we do not expect plasma t-tau cutoffs to enhance diagnostic certainty for any single patient, our results suggest that plasma t-tau could be associated with improved risk stratification at a population level, targeting persons for inclusion in prevention trials, thus improving the power and precision of clinical trials and potentially accelerating therapeutic pipelines and drug discovery," the team wrote.

The study drew on stored plasma samples from 1,453 subjects enrolled in the Framingham Heart Study and 367 participants in the Memento study, a multicenter cohort of persons with mild cognitive impairment or subjective cognitive complaints recruited from memory clinics across France.

The Framingham Heart Study

The Framingham cohort was followed for up to 10 years between baseline examination to incident event (median 6 years). Over that time, 134 (9.2%) cases of dementia developed; most of these (105) were due to possible, probable, or definite Alzheimer's disease.

Plasma tau levels rose in a linear fashion as the cohort aged. Higher plasma t-tau levels were associated with proven Alzheimer's disease risk factors, including female sex, lower education, and higher vascular risk factors. They did not differ by *APOE* e4 status.

After adjusting for age and sex, each standard deviation unit increase in the log of tau was associated with a 29% greater risk of incident all-cause dementia and a 35% increase in the risk of incident Alzheimer's dementia. Subjects with tau levels above the median had a 62% increased risk of all-cause dementia and a 76% greater risk of Alzheimer's disease. Adding *APOE* e4 status and vascular risk factors to the analysis did not alter the associations.

"Plasma t-tau level improved risk discrimination for all dementia and Alzheimer's dementia beyond age and sex," the investigators wrote. "[It] was associated with improved risk discrimination … in both *APOE* e4 carriers and noncarriers."

In a hypothetical 5-year clinical trial, enrolling subjects with total plasma tau greater than the median could reduce the estimated necessary sample size by 38% for an outcome of all-cause dementia and by 50% for one of Alzheimer's. Selecting participants with elevated plasma tau and *APOE* e4 could reduce the required sample by 69% for all-cause dementia outcomes and by 80% for Alzheimer's disease outcomes.

In the neuropathologic study, each standard deviation unit increase was associated with more neurofibrillary tangles in the medial temporal lobe, more microinfarcts, and smaller hippocampal volume. The researchers found no association with amyloid plaque in any brain region.

The Memento Study

Subjects in the Memento study had a mean of 4 years of follow-up. Over that time, 76 cases of incident dementia developed, 55 of which were probable Alzheimer's disease.

Each standard deviation unit increase was associated with a nonsignificant 14% greater risk of all-cause dementia and a significant 54% increase in the risk of incident Alzheimer's disease.

CSF was drawn on the same day as plasma in 140 of these subjects. The addition of CSF increased the predictive value; each standard deviation increase more than doubled the risk of Alzheimer's disease (HR, 2.33). Each standard deviation unit increase in CSF t-tau increased the risk by 2.14.

"Plasma t-tau was weakly correlated with CSF t-tau in our study. This finding is consistent with previous studies showing that the associations of plasma t-tau with CSF t-tau have been weak or nonexistent," the authors wrote. "Despite a weak correlation between plasma and CSF t-tau, plasma t-tau was at least as strongly associated with the development of incident Alzheimer's disease dementia.

"Use of plasma t-tau in this manner could be likened to the measurement of the *APOE* e4 allele, which is not a biomarker of Alzheimer's disease pathology providing diagnostic certainty for Alzheimer's disease dementia, but is still routinely used to power clinical trials by selecting at-risk individuals," they concluded. Dr. Pase had no financial disclosures. **NR**

—Michele G. Sullivan

Suggested Reading

Pase MP, Beiser AS, Himali JJ, et al. Assessment of plasma total tau level as a predictive biomarker for dementia and related endophenotypes. *JAMA Neurol.* 2019 Mar 4 [Epub ahead of print].

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Mild aerobic exercise speeds sports concussion recovery

Subsymptom levels of aerobic exercise shortened recovery time, compared with stretching, in adolescent athletes.

Mild aerobic exercise significantly shortened recovery time from sports-related concussion in adolescent athletes, compared with a stretching program, in a randomized trial of 103 participants.

Sports-related concussion (SRC) remains a major public health problem with no effective treatment, wrote John J. Leddy, MD, of the State University of New York at Buffalo, and his colleagues.

> "Moderate levels of physical activity, including prescribed subsymptom threshold aerobic exercise, after the first 48 hours following SRC can safely and significantly speed recovery."

Exercise tolerance after SRC has not been well studied. However, given the demonstrated benefits of aerobic exercise training on autonomic nervous system regulation, cerebral blood flow regulation, cardiovascular physiology, and brain neuroplasticity, the researchers hypothesized that exercise at a level that does not exacerbate symptoms might facilitate recovery in concussion patients.

Days to symptom resolution

In a study published in *JAMA Pediatrics*, researchers randomized 103 adolescent athletes aged 13–18 years to a program of subsymptom aerobic exercise or a placebo stretching program. The participants were enrolled in the study within 10 days of an SRC and were followed for 30 days or until recovery.

Athletes in the aerobic exercise group recovered in a median of 13 days, compared with 17 days for those in the stretching group ($P = 0.009$). Recovery was defined as "symptom resolution to normal," based on normal physical and neurological examinations, "further confirmed by demonstration of the ability to exercise to exhaustion without exacerbation of symptoms" according to the Buffalo Concussion Treadmill Test (BCTT), the researchers wrote.

No demographic differences or difference in previous concussions, time from injury until treatment, initial symptom severity score, initial exercise treadmill test, or physical exam were noted between the groups.

The average age of the participants was 15 years, and 47% were female. The athletes performed the aerobic exercise or stretching programs for approximately 20 minutes per day, and reported their daily symptoms and compliance via a website. The aerobic exercise consisted of walking or jogging on a treadmill or outdoors, or riding a stationary bike while wearing a heart rate monitor to maintain a target heart rate. The target heart rate was calculated as 80% of the heart rate at symptom exacerbation during the BCTT at each participant's initial visit.

Prescribed exercise was safe

No adverse events related to the exercise intervention were reported, which supports the safety of subsymptom threshold exercise, Dr. Leddy and his associates noted.

The researchers also found lower rates of persistent symptoms at 1 month in the exercise group, compared with the stretching group (2 participants vs. 7 participants), but this difference was not statistically significant.

The study findings were limited by several factors, including the unblinded design and failure to address the mechanism of action for the effects of exercise. In addition, the results are not generalizable to younger children or other demographic groups, including those with concussions from causes other than sports and adults with heart conditions, the researchers noted.

However, "the results of this study should give clinicians confidence that moderate levels of physical activity, including prescribed subsymptom threshold aerobic exercise, after the first 48 hours following SRC can safely and significantly speed recovery," Dr. Leddy and his associates concluded.

The study was supported by grants from the National Institutes of Health. The researchers had no financial conflicts to disclose.

Concussion management evolves to include exercise

In 2009 and 2010, the culture of sports concussion care began to shift with the publication of an initial study by Leddy et al. on the use of exercise at subsymptom levels as part of concussion rehabilitation, Sara P. D. Chrisman, MD, MPH, wrote in an accompanying editorial. Previous guidelines had emphasized total avoidance of physical activity, as well as avoidance of screen time and social activity, until patients were asymptomatic; however, "no definition was provided for the term asymptomatic, and no time limits were placed on rest, and as a result, rest often continued for weeks or months," Dr. Chrisman said.

Additional research over the past decade supported the potential value of moderate exercise, and the 2016 meeting of the Concussion in Sport Group resulted in recommendations limiting rest to 24–48 hours, which prompted further studies of exercise intervention.

The current study by Leddy et al. is a clinical trial using exercise "to treat acute concussion with a goal of reducing symptom duration," said Dr. Chrisman, of the Center for Child Health, Behavior, and Development, Seattle Children's Research Institute. Despite the study's limitations, including the inability to estimate how much exercise was needed to achieve the treatment outcome, "this is a landmark study that may shift the standard of care toward the use of rehabilitative exercise to decrease the duration of concussion symptoms.

"Future studies will need to explore the limits of exercise treatment for concussion," and should address questions including the timing, intensity, and duration of exercise and whether the strategy is appropriate for other populations, such as those with mental health comorbidities, Dr. Chrisman concluded.

Dr. Chrisman had no financial conflicts to disclose. **NR**

—Heidi Splete

Suggested Reading

Chrisman SPD. Exercise and recovery time for youth with concussions. *JAMA Pediatr.* 2019 Feb 4 [Epub ahead of print].

Leddy JJ, Haider MN, Ellis MJ, et al. Early subthreshold aerobic exercise for sport-related concussion: a randomized clinical trial. *JAMA Pediatr.* 2019 Feb 4 [Epub ahead of print].

Incidence of treated depression nearly 100% higher in patients with MS

Patients with MS have a higher incidence of new treated depression, compared with matched patients without MS.

DALLAS—Patients with multiple sclerosis (MS) have a nearly 100% higher incidence of new treated depression, compared with matched patients without MS, according to an analysis of data from patients in the United Kingdom.

After a diagnosis of MS, the incidence of new treated depression is 229 per 10,000 person-years. In comparison, the incidence of new treated depression among matched patients without MS is 121 per 10,000 person-years, Neil Minton, MD, drug safety head at Celgene, reported at the 2019 ACTRIMS Forum.

MS causes changes in the CNS that are associated with depression, but "data on rates of incident depression after MS diagnosis ... are limited," Dr. Minton and his research colleagues said. To examine rates of treated incident depression in patients with MS after an MS diagnosis, compared with rates in a matched population of patients without MS, the researchers analyzed data from the U.K. Clinical Practice Research Datalink.

Their analysis included patients with MS who received a diagnosis of MS between 2001 and 2016, had at least 1 year of history available before the MS diagnosis, and had no history of treated depression. The researchers matched these patients with as many as 10 patients without MS by age, sex, general practice, record history length, and no history of treated depression. Treated depression was defined as a diagnosis code for depression and a prescription for an antidepressant treatment within 90 days. They used Byar's method to estimate incidence rates and incidence rate ratios, the Kaplan-Meier method to generate cumulative incidence curves, and a log-rank test to compare the curves.

Neil Minton, MD

In all, 5,456 patients with MS and 45,712 matched patients without MS were included in the study. Patients' median age was 42 years; 65% were female. Compared with patients without MS, patients with MS were more likely to have a history of untreated depression (9.6% vs. 7.5%) and to have received an antidepressant treatment for any indication before cohort entry (28.0% vs. 15.5%). Diagnoses for other psychiatric conditions were similar between the groups.

Incidence rates of treated depression were higher among women with MS, compared with men with MS—241 versus 202 per 10,000 person-years. Compared with patients without MS, however, men with MS had a higher relative risk of treated depression (2.40 vs. 1.73).

The incidence rate ratios were similar in sensitivity analyses that excluded patients with a history of any psychiatric disorder at cohort entry and that did not require treatment to confirm a depression diagnosis.

The study was funded by a grant from Celgene. **NR**

—Jake Remaly

NEWSROUNDUP

Aducanumab Alzheimer's disease trials stopped

The ENGAGE and EMERGE trials, which were designed to test the efficacy and safety of aducanumab in patients with mild cognitive impairment caused by Alzheimer's disease and mild Alzheimer's disease dementia, are being discontinued, Biogen and Eisai announced.

Aducanumab is a human monoclonal antibody derived from B cells collected from healthy elderly subjects with no or unusually slow cognitive decline. The companies plan to present data from the phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials at future medical meetings.

A futility analysis by an independent data monitoring committee indicated that the drug would not meet the trials' primary endpoint, which was the slowing of cognitive and functional impairment as measured by changes in Clinical Dementia Rating-Sum of Boxes score.

FDA warns companies that illegally sell supplements for Alzheimer's disease

The FDA has issued warning letters to 12 companies and advisory letters to 5 companies illegally selling more than 58 products claiming to treat Alzheimer's disease.

The products, many of which are marketed as dietary supplements, include tablets, capsules, and oils that are unapproved or mislabeled and claim to prevent, treat, or cure Alzheimer's disease and other conditions in violation of the Federal Food, Drug, and Cosmetic Act, the agency said.

"Alzheimer's [disease] is a challenging disease that, unfortunately, has no cure. Any products making unproven drug claims could mislead consumers to believe that such therapies exist and keep them from accessing therapies that are known to help support the symptoms of the disease, or worse, as some fraudulent treatments can cause serious or even fatal injuries," FDA Commissioner Scott Gottlieb, MD, said in a press release.

Neurologists grappling with patients who embrace stem cell tourism

The unethical practice of offering unproven cellular preparations to patients with multiple sclerosis is increasing.

DALLAS—Stem cell tourism, the unethical practice of offering unproven cellular preparations to patients for various conditions, is increasingly sought by patients with incurable conditions such as multiple sclerosis (MS) and amyotrophic lateral sclerosis, results from a novel survey suggest.

In fact, most academic neurologists have been approached by patients with incurable conditions who ask them about stem cell therapy, while about two-thirds have had at least one patient who has undergone stem cell therapy.

> Approximately 73% of neurologists said that it would be helpful to have an evidence-based patient education tool about stem cell therapy.

"It's really scary," Wijdan Rai, MBBS, the study's lead author, said in an interview at the 2019 ACTRIMS Forum. "This is a more prevalent issue than we think, and the complication rates are higher than we think."

According to the study's senior author, Jaime Imitola, MD, who directs the Progressive Multiple Sclerosis Multidisciplinary Clinic and Translational Research Program at the Ohio State University (OSU) Wexner Medical Center, Columbus, the results "call for the creation of a nationwide registry where neurologists can document adverse reactions to stem cell procedures and further support dedicated patient and neurologist education as we have proposed before."

A survey of academic neurologists

To understand the experiences and attitudes of academic neurologists regarding stem cell tourism and patient-reported complications, the researchers developed a 25-question survey disseminated via Synapse, a web tool from the American Academy of Neurology. Respondents were asked about demographic information, frequency of patient questioning, perception of physician competence, patient complications and experiences, and attitudes toward increased physician education.

Dr. Rai, who is a senior neurology resident at the medical center, presented findings from 204 neurologist respondents, of whom 31% identified themselves as MS specialists. Nearly all respondents (91%) said they have been approached by patients with incurable conditions seeking information about stem cells (37% of whom had a diagnosis of MS). In addition, 65% have had at least one patient who has undergone "stem cell therapy," and 73% said it would be "helpful" or "very helpful" to have an evidence-based patient education tool on the topic. "Patients most often wanted general information," Dr. Rai said. "However, 50% requested permission to undergo a stem cell procedure, and 31% approached their neurologist after the procedure."

Wijdan Rai, MBBS

Survey respondents reported that 33% of the stem cell interventions were performed in the United States and 22% abroad, while 37% reported both in the U.S. and abroad. Patients underwent the procedures in China, Germany, the Bahamas, Mexico, Russia, and Costa Rica. Three-quarters of respondents (75%) indicated no patient experiencing complications from the stem cell interventions. However, 25% reported patients experiencing various complications from the procedures, including strokes, meningoencephalitis, quadriparesis, MS deterioration, sepsis, hepatitis C, seizures, meningitis from intrathecal cell injections, infections, and spinal cord tumors. "At least three respondents had a patient who died as a direct complication from stem cell therapy," Dr. Rai said.

An approach to patient education

In their poster, the researchers recommended a "multipronged approach to improve education of MS patients and engaging multiple stakeholders in the field, including MS academic societies, licensing boards, and legislative bodies. Specifically, we call for the creation of evidence-based education for both neurologists and patients, including physical resources that neurologists can use when discussing stem cell interventions with patients, and videos on proper counseling during these visits."

The researchers' colleagues from OSU's Laboratory for Neural Stem Cells and Functional Neurogenetics contributed to this work. The researchers reported having no financial disclosures.

NR

—Doug Brunk

Suggested Reading

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Julian K, Yuhasz N, Hollingsworth E, Imitola J. The "growing" reality of the neurological complications of global "stem cell tourism". *Semin Neurol.* 2018;38(2):176-181.

Injectable nimodipine does not improve outcomes of subarachnoid hemorrhage

EG-1962 significantly reduces the rate of angiographic vasospasm, compared with the standard of care, but does not alter disability at day 90.

HONOLULU—EG-1962, a sustained-release microparticle formulation of nimodipine, does not significantly improve outcomes of aneurysmal subarachnoid hemorrhage, compared with standard of care, according to a study presented at the International Stroke Conference sponsored by the American Heart Association. However, the treatment does reduce the rate of angiographic vasospasm significantly and does not raise significant safety concerns.

> **Approximately 46% of patients who received EG-1962 had a favorable outcome, compared with 43% of patients who received oral nimodipine.**

Approximately 70% of patients with subarachnoid hemorrhage develop vasospasm, which can in turn cause delayed cerebral ischemia. The only evidence-based treatment for ischemia of the brain resulting from vasospasm is nimodipine, which has been the standard of care for more than a decade.

EG-1962 was developed to deliver higher amounts of nimodipine to the CNS and spastic vessels than oral nimodipine. The formulation contains 50-µm particles of nimodipine combined with a biodegradable polymer. Pharmacokinetic studies indicate that EG-1962 successfully delivers higher amounts of nimodipine to the CNS than the oral formulation does.

A multisite, phase 3 trial

Stephan A. Mayer, MD, William T. Gossett Endowed Chair of Neurology at the Henry Ford Health System in Detroit, presented the trial results. He and his colleagues conducted NEWTON2, a phase 3 trial, to evaluate the safety and efficacy of a single 600-mg intraventricular dose of EG-1962 in patients with aneurysmal subarachnoid hemorrhage, compared with those of oral nimodipine. Eligible participants had a World Federation of Neurosurgeons Score (WFNS) of 2-4, Glasgow Coma Scale scores of 7-14, and an indication for placement of an external ventricular drain (such as hydrocephalus). All patients had their aneurysms clipped or coiled.

On the first day after the operation, the investigators randomized patients in equal groups to EG-1962 plus oral placebo or oral nimodipine plus placebo injection. Patients in the EG-1962 arm received a 600-mg injection of nimodipine into the ventricular system. The primary endpoint was the proportion of subjects with an extended Glasgow Outcome Scale (eGOS) score of 6-8 (that is, minimal or mild disability) at day 90. The main secondary endpoint was the proportion of subjects with a Montreal Cognitive Assessment (MOCA) score of 26 or greater (indicating no important cognitive disability) at day 90. Safety outcomes included cerebral infarction, hypotension, and ventriculitis.

Dr. Mayer and his colleagues conducted the study at 65 centers in 11 countries. They planned to enroll 374 patients and conduct an interim analysis after the first 210 participants had their 90-day follow-up. An independent data monitoring committee reviewed the safety data as it was collected. The investigators stopped the study for futility after the preplanned interim analysis was completed.

The challenge of identifying responders

The two study arms were well matched on age and gender. The proportion of patients with poor WFNS was 45% in the EG-1962 arm and 53% in the oral nimodipine arm.

The rate of any vasospasm (such as symptomatic or by imaging) was 56% in the intervention group and 70% in the oral nimodipine group, a statistically significant difference. Follow-up angiography showed vasospasm in 50% of the intervention group, compared with 63% of the oral nimodipine group, which was also statistically significant.

When the investigators examined the primary endpoint, they found that 46% of patients who received EG-1962 had a favorable outcome, compared with 43% of patients who received oral nimodipine, a nonsignificant difference. If the investigators had defined a favorable outcome as an eGOS score of 4 or greater, "there would have been a more favorable effect," said Dr. Mayer. The investigators found no difference between groups in MOCA score at day 90.

Subgroup analyses produced "puzzling" results, said Dr. Mayer. For example, more patients with poor-grade WFNS had a favorable outcome at 3 months in the EG-1962 group than in the nimodipine group, but fewer patients with good-grade WFNS had a favorable outcome at 3 months in the EG-1962 group than in the nimodipine group. In addition, the treatment effect was more evident in the United States than abroad.

Stephan A. Mayer, MD

The safety analysis indicated a trend toward less rescue therapy, defined as hypertensive therapy or any interventional approach, in the EG-1962 group (27%), compared with the oral nimodipine group (35%). The rate of hypotension was slightly lower in the EG-1962 group. The rates of treatment-emergent serious adverse events and hydrocephalus were not significantly different between groups.

The results may encourage neurologists to treat "extremely sick patients with highly refractory vasospasms," said Dr. Mayer. "We have a biologically active agent. The problem is, though, that it's very hard ... to prove efficacy in trials, because we do not fully understand who the responders were going to be."

Dr. Mayer reported receiving consulting fees from Edge Therapeutics, the company that developed EG-1962, in the past for activities unrelated to this study. Other investigators are employees of Edge Therapeutics. **NR**

—Erik Greb

Endarterectomy and stenting have similar efficacy in carotid stenosis

An analysis indicates that the procedures have similar rates of composite procedural complications and 4-year ipsilateral stroke.

HONOLULU—Carotid endarterectomy and carotid artery stenting with embolic protection have comparable efficacy and safety for asymptomatic patients with severe carotid artery stenosis, according to a pooled analysis presented at the International Stroke Conference sponsored by the American Heart Association. The treatments have similar rates of procedural complications and 4-year ipsilateral stroke, said Jon S. Matsumura, MD, chairman of the division of vascular surgery at the University of Wisconsin in Madison.

Asymptomatic severe carotid stenosis is the most common indication for carotid operations in the United States. Data support carotid endarterectomy in selected asymptomatic patients. Carotid artery stenting with embolic protection is a newer treatment option. Two of the five most recent large, randomized trials—CREST and ACT I—compared carotid stenting with endarterectomy in asymptomatic patients. Dr. Matsumura and his colleagues conducted a pooled analysis of these two trials to help inform the choice of treatment.

The investigators analyzed data from the CREST and ACT I studies, which had many similarities. The researchers in these trials carefully selected the surgeons and the interventionalists who participated in them. Each trial used single carotid stent systems, and both trials used routine, distally placed embolic protection. The trials had independent neurologic assessment, routine cardiac enzyme screening, and central clinical and adjudication committees.

Dr. Matsumura and his colleagues decided to conduct a patient-level pooled analysis and defined the primary endpoint as a composite of death, stroke, and myocardial infarction in the periprocedural period and any ipsilateral stroke within 4 years of randomization. They included in their analysis all randomized, asymptomatic patients who were younger than 80 years.

The analysis comprised 2,544 patients, 1,637 of whom were randomized to stenting, and 907 of whom were randomized to endarterectomy. The population included more than 1,000 patients with 3-year follow-up and more than 500 with 4-year follow-up. Patients randomized to stenting were slightly younger, but the percentage of patients older than age 65 was similar between groups. Current cigarette smoking was slightly more common among patients randomized to stenting. The groups were well balanced by sex, race, and risk factors such as hypertension, hyperlipidemia, and diabetes.

The rate of primary endpoint events was 5.3% in the stenting arm and 5.1%

Endarterectomy and stenting have similar efficacy in carotid stenosis

in the endarterectomy arm (hazard ratio with stenting, 1.02; 95% confidence interval, 0.7-1.5; $P = 0.91$). The rate of periprocedural stroke was 2.7% in the stenting arm and 1.5% in the endarterectomy arm ($P = 0.07$). The rate of periprocedural myocardial infarction was 0.6% in the stenting arm and 1.7% in the endarterectomy arm ($P = 0.01$). The rate of periprocedural stroke and death was 2.7% in the stenting arm and 1.6% in the endarterectomy arm ($P = 0.07$). The rate of 4-year ipsilateral stroke was 2.3% in the stenting arm and 2.2% in the endarterectomy arm ($P = 0.97$).

A secondary analysis indicated that the cumulative, 4-year rate of stroke-free survival was 93.2% in the stenting arm and 95.1% in the endarterectomy arm ($P = 0.10$). "Almost all this difference is the initial periprocedural hazard difference," said Dr. Matsumura. The rate of cumulative 4-year survival was 91% in the stenting arm and 90.2% in the endarterectomy arm.

Among the sponsors of the analysis were the University of Wisconsin, Massachusetts General Hospital, the Medical University of South Carolina, the University of Alabama at Birmingham, Cardiovascular Associates, and the Mayo Clinic Jacksonville. **NR**

—Erik Greb

Trigger zone resection increases likelihood of seizure freedom in temporal lobe epilepsy

The findings, if confirmed in prospective interventional trials, could have important implications for surgery and drug development.

Resection of a brain area implicated in seizure modulation improves the odds of seizure freedom in patients with temporal lobe epilepsy, according to results of a recent multicenter analysis.

Patients with long-term postoperative freedom from seizures had a larger proportion of the piriform cortex resected versus patients who were not seizure-free. Removing at least half the piriform cortex was associated with a 1,500% increase in odds of seizure freedom, first author Marian Galovic, MD, of the department of clinical and experimental epilepsy at the University College London's Queen Square Institute of Neurology and his colleagues reported online ahead of print March 11 in *JAMA Neurology*.

The area tempestas in the piriform cortex has been identified as an epileptic trigger zone in animal studies, but to date, evidence of a human epileptic trigger zone in this area remains limited, according to the investigators. To evaluate the impact of resection in this area, Dr. Galovic and his colleagues examined 107 patients with temporal lobe epilepsy from an ongoing, single-center, prospective study and validated their findings with 31 patients from two other independent cohorts.

Of the 107 patients in the main cohort, 46% were completely seizure-free for a median of 5 years after epilepsy surgery. Voxel-based morphometry showed that those patients had a more pronounced loss of gray matter in the ipsilateral piriform cortex, compared with non–seizure-free patients. The seizure-free patients had a median of 83% of the piriform cortex resected, compared with 52% for the non–seizure-free patients ($P < 0.001$), results of a volumetric analysis confirmed.

Anxiety or psychosis outcomes were not influenced by the extent of piriform cortex resection, the investigators wrote. Poor verbal memory outcome was linked to the extent of resection of other brain regions, but not the piriform cortex.

Dr. Galovic reported receiving a grant from the Medical Research Council. His coauthors reported disclosures with the Medical Research Council, Wellcome Trust, Medtronic, Neuropace, Nevro, Eisai, UCB, and Mallinckrodt, among other entities. **NR**

—Andrew D. Bowser

Suggested Reading

Galovic M, Baudracco I, Wright-Goff E, et al. Association of piriform cortex resection with surgical outcomes in patients with temporal lobe epilepsy. *JAMA Neurol.* 2019 Mar 11 [Epub ahead of print].

Phase 3 studies of antiamyloid Alzheimer's drug crenezumab stopped

The molecule will continue to be tested in a study of familial Alzheimer's disease in Colombia.

After a disappointing interim analysis, Roche and its collaborator AC Immune are halting two phase 3 trials of the antiamyloid antibody crenezumab.

CREAD 1 and CREAD 2 enrolled patients with prodromal-to-mild sporadic Alzheimer's disease. The preplanned interim safety and efficacy analysis determined that neither study was likely to meet the primary end point of change from baseline on the Clinical Dementia Rating-sum of boxes score.

There were no unexpected safety signals associated with the drug, despite a quadrupling of the phase 3 dose from that used in phase 2. In a press release, the company said that it will continue to conduct the Autosomal Dominant Alzheimer's Disease (ADAD) trial as part of the Alzheimer's Prevention Initiative (API). ADAD is a large South American trial of crenezumab in Colombian families with familial Alzheimer's disease caused by mutations in the presenilin-1 gene (*PSEN1*). Roche did not release any data, but said that the trial results will be discussed at an upcoming scientific meeting.

Potential for a different indication

The decision was not a surprise to researchers who have followed the antibody's development. It advanced into phase 3 with lackluster phase 2 cognitive, imaging, and biomarker data. Its selection as the therapeutic agent for the ADAD trial was a key driver in its continued development, securing Roche $100 million in federal funds to help launch ADAD, the first-ever Alzheimer's primary prevention study.

Despite its failure in sporadic Alzheimer's disease, there is still some hope that crenezumab might benefit people with the *PSEN1* mutation, said Richard Caselli, MD, professor of neurology at the Mayo Clinic Arizona in Scottsdale and associate director and clinical core director of the Arizona Alzheimer's Disease Center.

"The Colombian trial is aimed at dominantly inherited Alzheimer's disease due to a *PSEN1* mutation, so it is different enough to imagine it still might make a difference in patients in whom amyloid metabolism is actually defective due to functionally altered amyloid precursor protein or gamma secretase," he said in an interview. "Possibly, some might argue that many of the patients in the crenezumab trial likely had additional pathologies, so that even if the Alzheimer's disease component responded, the overall clinical picture might not reflect it, due to the other components. That would be interesting if proven and could even argue against equating young-onset with late-onset Alzheimer's disease, at least for clinical purposes, as is currently envisioned."

But not everyone shares this perspective. "Although amyloid-beta [Abeta] production is not necessarily altered in sporadic Alzheimer's disease, there is essentially the same pathology, presentation, and progression with familial and sporadic Alzheimer's disease, suggesting a common molecular mechanism," said Michael Wolfe, PhD, the Mathias P. Mertes Professor of Medicinal Chemistry at the University of Kansas, Lawrence. "It's hard to say Abeta is the pathogenic species in familial, but not sporadic, Alzheimer's disease.

"To me, the failures of the antiamyloid approaches are because the drugs are given too late, are targeting the wrong form of Abeta, or are targeting an enzyme [for example, beta secretase1] that has other important functions. Most likely, it's a combination of these reasons. One could argue that even if some form of Abeta is the pathogenic entity, it is not a practical target because intervention may need to be initiated many years before the onset of symptoms."

The future of antiamyloid antibodies

Despite the long string of failed antiamyloid antibody trials, it's not yet time to give up on the approach, said James Kupiec, MD, chief medical officer at ProMIS Neurosciences of Toronto. "I understand where the pessimism is coming from, and I also understand the enthusiasm from these companies to pursue them," said Dr. Kupiec, who formerly headed Pfizer's neuroscience research unit. "Targeting plaque is clearly not going to do the job. But in my opinion, the deeper pathophysiologic questions have not been adequately addressed. I'm not willing to throw in the towel. The correct molecular species [of amyloid] has not been appropriately or adequately tested in studies with monoclonal antibodies."

The antibodies that have been failing for 5 years now were designed in the early 2000s, Dr. Kupiec pointed out, when knowledge of the various amyloid species was more limited. Newer candidates can target specific conformations of the protein—monomers and oligomers—before they aggregate into insoluble sheets. "Solanezumab was the first of these, paving the way for this new generation of antibodies," Dr. Kupiec said.

Because they target soluble Abeta, not amyloid plaques, these domain-specific antibodies are less likely to elicit amyloid-related imaging abnormalities (ARIA), the inflammatory reaction that has been associated with plaque dissolution in other antibody trials. ARIA has been a dose-limiting factor for antiamyloid antibodies: one that conformationally targeted antibodies could avoid, Dr. Kupiec said.

"There may be some limited success with the these, and there may be enough of a treatment effect to secure approval," he said. "The question is whether we can generate a higher effect size with an antibody that is more selective to the toxic forms of Abeta."

PMN310 is ProMIS's attempt to thread this needle. In preclinical studies, the antibody did not bind to amyloid monomers, plaques, or vascular Abeta aggregates. The company expects to study this antibody in phase 1 trials later this year.

"If we have a molecule that doesn't bind to monomers or to plaques, but only to the toxic oligomer, then that is something well worth testing in the clinic," Dr. Kupiec said.

Dr. Caselli and Dr. Wolfe have no financial disclosures. **NR**

—Michele G. Sullivan

We must keep our eyes on the prize

On behalf of the millions of people living with Alzheimer's disease and their families that we serve and represent, the Alzheimer's Association is disappointed to learn that these trials have been stopped.

We learn something from every Alzheimer's clinical trial. The Alzheimer's Association looks forward to hearing details of these studies at an upcoming scientific meeting.

More important, we must redouble our efforts to better understand the causes of the disease and to discover additional therapeutic targets. No stone can be left unturned in the pursuit of better treatments and effective preventions.

The Alzheimer's Association is investing in research looking at a variety of novel targets for treatment and prevention, including brain inflammation, the life and death cycle of brain cells, how brain cells use different energy sources, and the impact of lifestyle. Lifestyle interventions include leading the U.S. POINTER Study. To further the study of blood pressure control on reducing risk of mild cognitive impairment and dementia, the Alzheimer's Association recently announced seed funding of SPRINT MIND 2.0. The Part the Cloud Translational Research Program fills a gap in Alzheimer's disease drug development by supporting more than 30 early phase clinical studies. The Association is also funding research into the causes of the disease.

The emotional and financial cost of Alzheimer's disease is enormous. At the Alzheimer's Association, we will not stop. We will not slow down in our fight against this terrible disease.

—Maria Carrillo, PhD
Chief Science Officer, Alzheimer's Association, Chicago

Stroke endovascular therapy: The more you do, the better you do

Centers performing more endovascular thrombectomies produced better patient outcomes.

HONOLULU—The well-documented link between higher procedure volumes and better procedure efficacy applies to endovascular thrombectomy for acute ischemic stroke.

Centers that performed more endovascular stroke therapy (EST) procedures produced better outcomes for patients in an analysis of data from two U.S. sources: the National Inpatient Sample (NIS) and the state of Florida, Sunil A. Sheth, MD, said at the International Stroke Conference sponsored by the American Heart Association.

The finding raises questions about how best to triage patients with an acute ischemic stroke, suggesting that, in at least some situations, patients might be better served by being taken to a higher-volume center, even if it is not the closest center, noted Dr. Sheth. The results also suggest that the findings in the trials conducted primarily at large, tertiary care referral centers that proved the value of EST might not be generalizable to all centers that start an endovascular program.

Sunil A. Sheth, MD

The number of procedures performed has increased

The investigators examined data collected during 2006-2016 in Florida and during 2012-2016 in the NIS and found that in both databases, the rate of EST procedures performed increased steadily over time. The increase in the number of centers performing EST was sharp in 2015. Each of the two data sets also showed that better discharge outcomes occurred in patients treated at centers with the highest procedural volumes.

In the nationwide NIS data, for every 10 additional patients a center treated with EST annually, the incidence of a good hospital-discharge outcome (defined as either discharge home or to an acute rehabilitation hospital) rose by 30%, compared with lower-volume centers in a multivariate regression analysis. This relationship was statistically significant, said Dr. Sheth, a neurologist at the University of Texas, Houston. This volume-outcome relationship held fairly constant through volumes up to about 50 EST cases annually. "The more, the better," he observed.

Other factors contribute to good outcomes

"The data suggest that EST outcomes are not always the same," but most emergency medical service systems do not take EST case volume into account when deciding where to take an acute stroke patient, Dr. Sheth said in an interview. But he cautioned against an oversimplified focus on EST case volume.

A link between volume and better outcomes "is easy to understand and not surprising. We see this relationship for a variety of procedures. The data suggest we need to consider procedure volumes. But volume is only part of what makes for good outcomes; it's not the only factor," he stressed.

Dr. Sheth and his associates used data collected by the Florida Agency for Health Care Administration for 3,890 acute ischemic stroke patients treated with EST at 56 Florida hospitals and for 42,505 such patients in the NIS database treated at 2,260 U.S. hospitals. During the 11-year period for Florida data collection, the number of centers performing EST in the state rose steadily at an average of about four per year. Although the number of EST procedures performed also rose sharply, in general, a higher percentage of patients underwent treatment at lower-volume centers over time. Similar patterns were observed in the national data. The Florida data showed a statistically significant 10% improvement in good discharge outcomes for every 10 additional EST patients whom a center treated per year, consistent with the NIS data.

> For every 10 additional patients a center treated with EST per year, the incidence of a good hospital-discharge outcome increased by 30%, compared with lower-volume centers.

Dr. Sheth's results were published in the March issue of *Stroke*. Dr. Sheth reported no disclosures.

—*Mitchel L. Zoler*

Suggested Reading

Saber H, Navi BB, Grotta JC, et al. Real-world treatment trends in endovascular stroke therapy. *Stroke*. 2019;50(3):683-689.

Volume concerns should not limit access

Bruce Ovbiagele, MD

The idea that when centers perform more of a procedure, such as endovascular thrombectomy for acute ischemic stroke, they more often do it better is intuitively plausible, which helps makes these findings believable. It's also a relationship we've already seen for other types of endovascular therapies. What this study did not address were other factors beyond case volume that might also make important contributions to outcome, such as the speed of treatment delivery.

It's been only 4 years since endovascular thrombectomy became standard of care in early 2015 for treating selected patients with an acute ischemic stroke. Since then, the focus of stroke clinicians has largely been on increasing the number of locations where patients could receive this important treatment. There remains a shortage of endovascular availability in many rural U.S. regions. The precedent clearly exists from other types of endovascular interventions for professional societies to set volume minimums that can sometimes be a surrogate marker of a center having and maintaining an optimal level of competence. But I don't believe that we currently have adequate availability of endovascular stroke therapy to take this step. If we set a volume minimum now, it could deny treatment access to a significant number of patients.

Volume thresholds for endovascular stroke programs will come eventually, but for the time being, our focus should be on insuring wide access to endovascular treatment.

—Bruce Ovbiagele, MD, a neurologist and chief of staff for the San Francisco Veterans Affairs Health Care System, made these comments in an interview. He reported no disclosures.

Second-generation hydrogel coil surpasses platinum for brain aneurysm closure

Brain aneurysm embolization with a next-generation hydrogel coil led to fewer recurrences than bare platinum wire.

HONOLULU—A second-generation hydrogel coil that is already approved for U.S. marketing proved superior to bare platinum wire for durably embolizing brain aneurysms in a multicenter, randomized trial with 600 patients.

For the study's primary endpoint of recurrent intracranial aneurysm during 18-24 months of follow-up, the 297 patients treated with the hydrogel coil had a rate of 4%, compared with 15% among patients treated with platinum wire, Bernard R. Bendok, MD, said at the International Stroke Conference sponsored by the American Heart Association. The hydrogel coil materials were also relatively easy to use—much easier than the first-generation hydrogel materials, according to Dr. Bendok—and the adverse event rate using the hydrogel coils was similar to the rate using platinum wire, the standard material for brain aneurysm embolization.

> The study results may soon change the way that neurologists treat brain aneurysms.

Given the similar safety, ease of use, and superior efficacy, clinicians treating brain aneurysms may increasingly use hydrogel coil. "I think these results will change practice. It's compelling data," Dr. Bendok predicted in an interview. "The problem with platinum is that it is not conducive to healing." When an aneurysm is closed by insertion of platinum wire, most of the space within the aneurysm remains unfilled by metal. In contrast, animal models suggest that when hydrogel fills an aneurysm, it forms a matrix for collagen deposition that further fills the aneurysm space in a wound-healing process, thereby making recurrence less likely, said Dr. Bendok, professor and chair of neurosurgery at the Mayo Clinic in Phoenix.

The HEAT (Hydrogel Endovascular Aneurysm Treatment) trial enrolled patients at 46 centers in the United States and Canada during June 2012–January 2016. Enrolled patients had a ruptured or unruptured brain aneurysm of 3-14 mm in diameter and averaged 57 years old. A blinded core laboratory reviewed brain scans to identify recurrent aneurysms. Of the 297 patients randomized to hydrogel coil treatment, 254 underwent

The hydrogel coil was associated with a reduced risk of recurrent intracranial aneurysm

follow-up at 3-12 months, and 222 had additional follow-up at 18-24 months, the study's prespecified time for the primary endpoint. Among 303 patients treated with platinum, 258 had follow-up after 3-12 months, and 231 had follow-up at 18-24 months.

Among patients who entered the study with an unruptured aneurysm (nearly three-quarters of enrolled patients), the recurrence rate was 12% with platinum and 3% with hydrogel. Among the patients with a ruptured aneurysm, the recurrence rate was 24% with platinum and 8% with hydrogel. Adverse events occurred in 25% of those treated with platinum and 22% of those treated with hydrogel coil. Mortality during follow-up was 3% in the platinum arm and 2% in the hydrogel coil arm. The two groups also had similar outcomes, as measured by the modified Rankin Scale and by quality-of-life measures.

Bernard R. Bendok, MD

The HEAT trial was sponsored by MicroVention, the company that markets the hydrogel coil that the researchers investigated. Dr. Bendok had no personal disclosures. **NR**

—Mitchel L. Zoler

New data bolster latitude's association with MS prevalence

continued from page 1

study. The estimates were log-transformed and weighted with the inverse of the variance. Random-effects meta-regression models adjusted for prevalence year and method of case ascertainment.

They identified 126 new studies, 94 of which met inclusion criteria. The new studies yielded 230 additional prevalence points, predominantly in Scandinavia, France, and the Middle East.

Latitude was consistently and significantly associated with MS prevalence in all analyses, increasing in magnitude on adjustment and persisting on age-standardization.

Strong and significant positive gradients continue to exist in Australasia, the United Kingdom and Ireland, and North America. A significant inverse gradient continues to exist in the Italian region, which may relate to the frequency of an MS-related *HLA-DRB1* allele there. A negative gradient in the Scandinavian and North Atlantic region in the original meta-analysis, considered potentially related to dietary differences, was "markedly reduced" and no longer statistically significant in the updated meta-analysis.

"These results and the relative consistency across the whole of the globe continue to provide indirect evidence in support of the role of sun and vitamin D in MS etiology," Dr. Simpson and his colleagues concluded. **NR**

—Jake Remaly

Which comorbidities most diminish quality of life in patients with MS?

Systemic lupus erythematosus, depression, and hyperthyroidism may have large effects on health-related quality of life.

DALLAS—Systemic lupus erythematosus, depression, hyperthyroidism, and anxiety are among the comorbidities that most affect health-related quality of life in patients with multiple sclerosis (MS), according to an analysis presented at the 2019 ACTRIMS Forum. Comorbidities account for about 18% of the variance in health-related quality of life; a higher number of comorbidities correlates with lower health-related quality of life in a "clear dose–response" manner, the researchers said.

The "magnitude of effect emphasizes the need for recognition and appropriate management of comorbidities," said presenting author Lara Marie Pangan Lo, a researcher at Menzies Institute for Medical Research at the University of Tasmania, Australia, and her research colleagues. "The individual effect sizes may assist with the prioritizing of comorbidities that require more or less aggressive treatment in order to minimize" their impact.

Prior studies have found that patients with MS have lower health-related quality of life, compared with the general population, and that comorbidities affect patients' quality of life, but few studies have looked at the effects of individual comorbidities on quality of life. To examine the total impact and relative importance of comorbidities on psychosocial, physical, and overall health-related quality of life in people with MS, the investigators analyzed survey data from 902 participants in the survey-based Australian MS Longitudinal Study. They used linear regression and dominance analysis to assess relationships between comorbidities and participants' Assessment of Quality of Life-8 Dimensions scores, which can range from 0 (death) to 1 (perfect health).

The predicted health-related quality of life for patients without comorbidities was 0.74. After adjusting for age, sex, and education, the researchers found that systemic lupus erythematosus (reported by 1.56% of patients), depression (41.25%), hyperthyroidism (3.01%), and anxiety (38.35%) were associated with the greatest estimated decreases in health-related quality of life (–0.16, –0.15, –0.12, and –0.11, respectively). Depression and anxiety had the largest effect on psychosocial health–related quality of life, whereas systemic lupus erythematosus, rheumatoid arthritis, and hyperthyroidism had the largest impact on physical health–related quality of life. Other comorbidities that significantly correlated with quality of life included osteoporosis, type 2 diabetes, migraine, and inflammatory bowel disease. **NR**

—Jake Remaly

Large survey reveals that few MS patients have long-term care insurance

The findings suggest that clinical care teams should initiate early discussions of possible long-term needs with their patients.

DALLAS—A number of sociodemographic factors may influence health and disability insurance access by individuals with multiple sclerosis (MS), including employment, age, gender, disease duration, marital status, and ethnicity, results from a large survey suggest.

"The last similar work was conducted over 10 years ago, and so much has happened in the meantime, including the Great Recession and the introduction of the Affordable Care Act that offers protection for health care, but not for other important types of insurance (short- and long-term disability, long-term care, and life)," lead study author Sarah Planchon, PhD, said in an interview in advance of the 2019 ACTRIMS Forum. "MS is one of the most costly chronic diseases today. That is not only because of the cost of disease-modifying therapies, but also because of lost employment and income. We wanted to better understand the insurance landscape so that we could in turn educate patients and professionals about the protection these insurance [policies] offer and advise them on how to obtain these policies."

Most respondents had health insurance

In an effort to evaluate factors that affect insurance access for patients with MS, Dr. Planchon, a project scientist at the Mellen Center for Multiple Sclerosis at the Cleveland Clinic, and her colleagues used the North American Research Committee on MS (NARCOMS), iConquerMS, and the National MS Society to survey 2,507 individuals with the disease regarding insurance, demographic, health, disability, and employment status. They used covariate-adjusted nominal logistic regression to estimate odds ratios for the likelihood of having or not having a type of insurance.

The majority of respondents (83%) were female, their mean age was 54 years, 91% were white, 65% were currently married, and their mean disease duration at the time of the survey was 16 years. In addition, 43% were employed full or part time, and 29% were not employed or retired because of disability. Nearly all respondents (96%) reported having health insurance, while 59% had life insurance, 29% had private long-term disability insurance, 18% had short-term disability insurance, and 10% had long-term care insurance.

The researchers found that employment status had the greatest impact on insurance coverage. Of those with health insurance, 33% were employed full time, compared with 89% of those with short-term disability insurance, 42% of those with private long-term disability insurance, 44% of those with long-term care insurance, and 41% of those with life insurance. Logistic regression analyses indicated that respondents employed part time were significantly more likely to have short-term disability insurance if they were currently married (odds ratio [OR], 4.4). Short-term disability insurance was significantly more likely among fully employed patients with disease duration of 5–10 years versus more than 20 years (OR, 2.0). Private long-term disability insurance was significantly associated with female gender (OR, 1.6), age 50–59 years versus younger than 40 (OR, 1.6), full-time vs. part-time employment (OR, 2.3), and shorter disease duration (ORs, 1.4–1.6 for 6-10 years, 11–15 years, and 16–20 years' duration). Long-term care insurance was associated with older age (ORs, 2.5 and 4.3, respectively, for those aged 50-59 years and 60–65 years versus those younger than 40), and having excellent or good general health status vs. fair or poor health status (OR, 1.8). Life insurance was associated with non-Hispanic ethnicity (OR, 1.6), full-time versus part-time employment (OR, 2.4), older age (ORs, 1.6–1.7 for ages 40–49 years and 50–59 years vs. younger than 40 years), and marital status (currently or previously married, ORs, 1.6–2.6). Considering the high rate of survey respondents with health insurance, covariate-adjusted modeling was not applicable.

Sarah Planchon, PhD

Many patients with MS will need long-term care

"The number of people with MS who do not have long-term care insurance was surprisingly high," Dr. Planchon said. "Although the recently improved treatment climate may decrease the long-term disability levels, we do not yet know this with certainty. A large number of people with MS are likely to need long-term care in the future, which often is a significant financial burden to families." The findings suggest that clinical care teams "need to initiate early discussions of possible long-term needs with their patients," she continued. "Incorporation of social work teams, who are familiar with the needs of people with MS and insurance options available to them, within MS specialty practices will bolster the comprehensive care of patients and their families."

She acknowledged certain limitations of the study, including the low proportion of respondents who were Hispanic or Latino and African American (about 4% each). "The insurance landscape may differ in these groups, compared to the majority Caucasian population who responded to this survey," Dr. Planchon said.

The National MS Society funded the study. Dr. Planchon reported having no relevant financial disclosures. **NR**

—Doug Brunk

Suggested Reading

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Ublituximab depletes B cells in phase 2 trial

The investigational therapy may allow for lower doses and shorter infusion times, compared with available anti-CD20 treatments.

DALLAS—Ublituximab, a novel anti-CD20 antibody, rapidly and robustly depletes B cells in patients with relapsing forms of multiple sclerosis (MS), according to phase 2 trial results presented at the 2019 ACTRIMS Forum. Patients treated with the investigational therapy had reduced MRI activity and relapse rates during the 48-week trial, and the treatment was well tolerated, researchers said.

The monoclonal antibody targets a unique epitope on the CD20 antigen and is glycoengineered for enhanced B-cell targeting through antibody-dependent cellular cytotoxicity, said presenting author Edward Fox, MD, PhD, director of the MS Clinic of Central Texas, Round Rock. Ublituximab's potency "may offer a benefit over currently available anti-CD20s in terms of lower doses and shorter infusion times," Dr. Fox and his research colleagues said.

To assess the optimal dose, infusion time, safety, and tolerability of ublituximab in relapsing MS, investigators conducted a phase 2, multicenter study. The trial included 48 patients with relapsing MS; 65% were female. Patients' average age was 40 years and average disease duration was 7.7 years. The researchers included patients with one or more confirmed relapse in the past year, two relapses in the past 2 years, or at least one active gadolinium-enhancing T1 lesion. The primary endpoint was the percentage of patients with at least a 95% reduction in peripheral CD19+ B cells within 2 weeks after the second infusion on day 15.

For their first infusions, patients received 150 mg of ublituximab over an infusion time of 1, 2, 3, or 4 hours. On day 15, patients received 450 mg or 600 mg of ublituximab over an infusion time of 1, 1.5, or 3 hours. At week 24, patients received 450 mg or 650 mg of ublituximab infused over 1 hour or 1.5 hours.

All patients met the primary endpoint of greater than 95% B-cell depletion between baseline and week 4. Median B-cell depletion was 99% at week 4, and this effect was maintained at weeks 24 and 48.

The researchers detected no T1 gadolinium-enhancing lesions at week 24 or week 48, and total T2 lesion volume decreased by 10.6% between baseline and week 48.

The most frequent adverse events were infusion-related reactions, which occurred in 48% of patients and were more common with the first infusion, particularly when the infusion time was less than 4 hours. All of the infusion-related reactions were grade 1 or 2. One grade 3 serious adverse event of fatigue was considered possibly related to ublituximab. No patients withdrew from the study because of drug-related adverse events. At week 48, 93% of the patients were relapse free, 7% had 24-week confirmed disability progression, and 17% had confirmed disability improvement.

TG Therapeutics, the company developing ublituximab, is evaluating the therapy in phase 3 trials known as ULTIMATE I and II. The phase 3 trials are using the 450-mg dose with a first dose of 150 mg delivered over 4 hours.

Dr. Fox has disclosed research support from TG Therapeutics and other pharmaceutical companies and working as a consultant and speaker for TG Therapeutics and other companies. **NR**

—Jake Remaly

Can technology automate assessments of patients with MS in the clinic?

An iPad-based series of neuroperformance tests and patient-reported outcomes may facilitate the evaluation of patients with multiple sclerosis.

DALLAS—An iPad-based series of neuroperformance tests and patient-reported outcomes, along with automated MRI analysis, may facilitate the clinical evaluation of patients with multiple sclerosis (MS), according to research described at the 2019 ACTRIMS Forum.

An analysis of data collected using these methods found that patient-reported outcomes and MRI measures correlate with neuroperformance test results, said Laura Baldassari, MD, a clinical neuroimmunology fellow at the Mellen Center for Multiple Sclerosis at the Cleveland Clinic. Such assessments "could potentially enable us to better tune in to disability worsening and treatment response in our patients," she said.

The Multiple Sclerosis Performance Test (MSPT), which collects patient-reported outcomes and tests processing speed, contrast sensitivity, dexterity, and walking speed, has been "incorporated into routine clinical care at the Mellen Center," Dr. Baldassari said. Before seeing their provider, patients complete the MSPT with a biomedical assistant, which usually takes 30–40 minutes. The scores are available during the clinical visit.

Dr. Baldassari and her research colleagues analyzed associations between the neuroperformance metrics, patient-reported outcome measures, and MRI. The analysis included 976 patients who completed the MSPT between December 2015 and December 2017 and had an MRI within 3 months of a clinical encounter. T2 lesion volume, normalized whole brain volume or whole brain fraction, thalamic volume, and cross-sectional upper cervical spinal cord area at the level of C2 on MRI were calculated using a fully automated method.

Patient-reported outcomes included Quality of Life in Neurological Disorders (Neuro-QoL) upper and lower extremity function, Patient-Reported Outcomes Measurement Information System (PROMIS) physical, and Patient Determined Disease Steps (PDDS).

The researchers used Spearman correlation coefficients to examine the relationships between each neuroperformance test, patient-reported outcome, and MRI measure. Linear regression models determined which outcomes and characteristics predicted neuroperformance test results.

Patients had a mean age of about 48 years, and the population was predominantly female and white with relapsing remitting MS.

"There were significant correlations between all neuroperformance tests and all patient-reported outcomes except for the contrast sensitivity test and PROMIS physical," Dr. Baldassari said. "The processing speed test was most strongly correlated with the PDDS as well as the Neuro-QoL lower extremity." Neuro-QoL lower extremity also correlated with contrast sensitivity. The manual dexterity test correlated with PDDS and Neuro-QoL upper and lower extremity, and the walking speed test correlated with PDDS and Neuro-QoL lower extremity.

"With worsening self-reported functions, these neuroperformance test results demonstrated impairment as well," Dr. Baldassari said.

The neuroperformance tests and all MRI metrics had significant, moderate correlations.

The MSPT was developed by the Cleveland Clinic in partnership with Biogen. Dr. Baldassari reported receiving funding through the National Multiple Sclerosis Society and fees for serving on a scientific advisory board for Teva. Her coauthors' disclosures included the contribution of intellectual property to the MSPT, for which they could receive royalties. **NR**

—Jake Remaly

Migraine is associated with more severe disability in patients with MS

Traditional migraine risk factors such as obesity, anxiety, and depression also may be overrepresented among patients with MS and migraine.

DALLAS—In a cohort of patients with multiple sclerosis (MS), a history of migraine was associated with more severe disability and significantly slower walking speeds, researchers reported at the 2019 ACTRIMS Forum.

"Traditional migraine risk factors such as obesity, anxiety, and depression were also overrepresented in our cohort" of patients with MS and migraine, said Anne M. Damian, MD, of Johns Hopkins University, Baltimore, and her research colleagues.

> Migraine also was associated with significantly slower walking speeds.

Migraine is common in patients with MS, but whether migraine plays a role in MS disease course or MS symptom severity is unknown. Dr. Damian and her colleagues conducted an observational study to examine the associations between migraine history, disability, and neurologic function in patients with MS and whether migraine tends to occur with other comorbid conditions in MS.

They analyzed data from 289 patients with MS (79% female; mean age, 49.2 years) who completed the Multiple Sclerosis Performance Test (MSPT), an iPad version of the MS Functional Composite. MS outcome measures included disability (such as the Patient Determined Disease Steps) and objective neurologic outcomes (such as walking speed, manual dexterity, and processing speed). Patients also completed a questionnaire about comorbidities, including history of physician-diagnosed migraine, diabetes, hypertension, hypercholesterolemia, heart disease, sleep apnea, depression, and anxiety.

Dr. Damian and colleagues used generalized linear models adjusted for age, sex, MS subtype, MS duration, years of education, and body mass index to evaluate the association between history of migraine and MS outcomes.

Compared with patients with MS without migraine, migraineurs (n = 65) tended to be younger (mean age, 44.3 years vs. 50.4 years) and were more likely to be overweight or obese (73.9% vs. 51.6%). In addition, patients with MS and migraine were more likely to have a history of depression (46.2% vs. 24.2%), anxiety (30.8% vs. 18.8%), and severe rather than mild disability (odds ratio, 3.08; 95% confidence interval, 1.04–9.20). Migraine also was associated with significantly slower walking speeds (9.08% slower; 95% CI, 0.82%–18.77%). Migraine was not associated with processing speed or manual dexterity, however.

If an association between migraine history and worse MS disability is confirmed, migraine history may be a factor that neurologists could consider when making MS treatment decisions, Dr. Damian said. The researchers noted that migraine was reported by patients and not detected using a validated questionnaire. Future studies should investigate whether MS lesions on MRI differ in migraineurs and whether migraine predicts future neurologic disability in patients with MS, she said.

Collection of the MSPT outcomes was sponsored by Biogen. **NR**

—Jake Remaly

Evaluations for possible MS often find one of its many mimics

At two multiple sclerosis centers, 74% of patients referred for a possible diagnosis of MS did not have the disease.

DALLAS—Of 95 patients referred to two multiple sclerosis (MS) centers for a possible diagnosis of MS, 74% did not have MS, according to a study presented at ACTRIMS Forum 2019. A majority had clinical syndromes or imaging findings that are atypical for MS, which "underscores the importance of familiarity with typical MS clinical and imaging findings in avoiding misdiagnosis," said Marwa Kaisey, MD, and her research colleagues. Dr. Kaisey is a neurologist at Cedars-Sinai Medical Center in Los Angeles.

> In all, the referred patients received 28 diagnoses other than MS, most commonly migraine and anxiety or conversion disorder.

Physicians often refer patients to academic MS centers to determine whether patients have MS or one of its many mimics. To study the characteristics and final diagnoses of patients referred to MS centers for evaluation of possible MS, the investigators reviewed electronic medical records and MRI from all new patient evaluations at the Cedars-Sinai Medical Center and University of California, Los Angeles MS clinics between July 2016 and June 2017. The researchers excluded patients referred with a previously established diagnosis of MS.

There were 366 new patients evaluated, including 236 patients with previously established MS diagnoses and 35 patients whose evaluations were not related to MS. Of the 95 patients referred for a question of MS diagnosis, 60% had clinical syndromes that were atypical for MS, 22% had normal neurologic exams, and a third had pain or sensory changes that were not localizable to the CNS.

Sixty-seven percent had an MRI that was atypical for MS, and nearly half of the patients without MS had nonspecific MRI changes. "Often, these MRI changes alone prompted referral for an MS evaluation," Dr. Kaisey and colleagues reported. "This suggests that novel, specific imaging tools may increase diagnostic confidence in the clinical setting."

In all, the referred patients received 28 diagnoses other than MS, most commonly migraine (10 patients), anxiety or conversion disorder (9), postinfectious or idiopathic transverse myelitis (8), compression myelopathy or spondylopathy (8), and peripheral neuropathy or radiculopathy (7).

The researchers did not have any relevant disclosures. **NR**

—Jake Remaly

Glyceryl trinitrate does not improve outcomes of ischemic stroke

Although treatment reduced blood pressure, it did not reduce disability at 90 days, compared with sham.

HONOLULU—Administering glyceryl trinitrate (GTN) early after onset of ischemic stroke or transient ischemic attack (TIA) does not improve outcomes, according to data presented at the International Stroke Conference sponsored by the American Heart Association. Results suggest that GTN causes adverse effects in patients with intracerebral hemorrhage (ICH), but this observation is not definitive, according to the researchers. Study results were published online ahead of print Feb. 6 in the *Lancet*.

Nitric oxide is a regulatory molecule that has vasoactive effects and promotes blood pressure reduction. Vascular levels of nitric oxide are low in stroke, which suggests that the molecule may be a target for stroke treatment. GTN, a nitric oxide donor, lowered blood pressure and improved functional outcome among patients with acute stroke in the phase 2 Rapid Intervention with GTN in Hypertensive Stroke Trial (RIGHT).

> **At 1 hour after treatment initiation, systolic blood pressure decreased by 6.2 mm Hg, and diastolic blood pressure decreased by 2.7 mm Hg, in patients who received GTN, compared with controls.**

The RIGHT-2 study

Philip Bath, MD, Stroke Association Professor of Stroke Medicine at the University of Nottingham (United Kingdom), and colleagues conducted the RIGHT-2 study to evaluate the safety and efficacy of GTN when administered early after onset of suspected stroke. Paramedics randomized patients in equal groups to a GTN patch or a sham patch in the ambulance. Three more patches were administered in the hospital on the following days. Active and sham patches looked similar and had no writing on them, thus ensuring effective blinding upon administration. Investigators followed up patients by telephone at 90 days to assess the modified Rankin Scale score and markers of disability, mood, cognition, and quality of life.

Eligible participants were adults who had dialed emergency services, independently or with assistance, because of a possible stroke. They had a Face, Arm, Speech, Time (FAST) score of 2 or 3, were within 4 hours of onset, and had a systolic blood pressure greater than 120 mm Hg. Patients from nursing homes, those with hypoglycemia, those who were unconscious, and those with a witnessed seizure were excluded.

Dr. Bath and colleagues planned to enroll 850 patients from five ambulance services in 30 hospitals across the United Kingdom. Data were to be examined through an intention-to-treat analysis. During the trial, however, the investigators observed that the rate of stroke mimics was 26%, rather than the 12% that they had anticipated. To ensure the proper power for the study, the investigators increased the sample size to 1,149 patients. They also changed the planned data analysis from intention-to-treat to hierarchical analysis. Specifically, the researchers planned to perform the primary analysis in patients with stroke or TIA. If the results were positive, then they would perform a standard intention-to-treat analysis.

Time to randomization affected outcome

More than 99% of patients received the first patch. Approximately 57% of the population received the first two patches. One reason for this decrease in adherence was that many patients were discharged from the hospital with a TIA or a stroke mimic. Participants' average age was 72. The median time from onset to randomization was 71 minutes, and the median time to treatment was 73 minutes. Participants' mean systolic blood pressure was 162 mm Hg. Approximately 60% of the patients had a FAST score of 3. About 50% of participants had ischemic stroke, 13% had ICH, 10% had TIA, and 26% had stroke mimics.

Philip Bath, MD

At 1 hour after treatment initiation, systolic blood pressure decreased by 6.2 mm Hg, and diastolic blood pressure decreased by 2.7 mm Hg among patients who received GTN, compared with controls. At one day, the differences were 5.2 mm Hg and 2.5 mm Hg, respectively, in treated patients, compared with controls. Blood pressure became similar between groups thereafter, "in part because of the tachyphylaxis that we know happens with GTN," said Dr. Bath.

The researchers found no evidence of an effect of GTN on functional outcome at 90 days in participants with stroke or transient ischemic attack. The adjusted common odds ratio of poor outcome was 1.25 in the GTN group, compared with the control group (95% confidence interval, 0.97–1.60; $P = 0.083$). "We were close to getting a negative trial," said Dr. Bath.

Subgroup analyses revealed differences in outcome according to the time to randomization. GTN had a negative effect in patients treated within 1 hour of onset. Results were neutral, but tended to be negative, in patients treated between 1 and 2 hours of onset. Results were neutral, but tended to be positive, among patients treated at more than 2 hours after onset. There was no difference between groups in the rate of mortality.

One of the study's limitations was its single-blind design. In addition, the trial was conducted in a single country, and the investigators changed the protocol after it was initiated. "We had a higher-than-expected [stroke] mimic rate, although I'm reassured by most experts that ... this is probably about right," said Dr. Bath.

A potential reason for the neutral results is the negative effect that GTN had among patients with ICH, said Dr. Bath. "In that very early first hour, we are of course breaking a law that we learned in medical school, which is that the first part of hemostasis is spasm. We gave an antispasmodic: a vasodilator," he added. "That is speculation."

The trial was funded by the British Heart Foundation. Dr. Bath declared a modest ownership interest in Platelet Solutions and consultant or advisory board positions with Moleac, DiaMedica, Phagenesis, Nestle, and ReNeu-

GTN impaired outcomes in patients treated within 1 hour of stroke onset

ron. The other investigators declared no conflicts of interest.

Prehospital trials pose particular challenges

The RIGHT-2 trial shows the limitations of a prehospital enrollment model, wrote Karen C. Johnston, MD, professor of neurology at the University of Virginia in Charlottesville, and Valerie L. Durkalski-Mauldin, PhD, professor of medicine at Medical University of South Carolina in Charleston, in an editorial accompanying the RIGHT-2 trial results. The rate of nonstroke diagnoses was so high that it would have reduced the study's power to assess the efficacy of glyceryl trinitrate (GTN), had the investigators not increased the sample size and changed the statistical analysis plan.

> Telemedicine in the ambulance could reduce the enrollment of patients with stroke mimics.

"Future prehospital trials need to consider the implications of enrolling, yet excluding, stroke mimics in the primary analysis," said Dr. Johnston and Dr. Durkalski-Mauldin. Using telemedicine in the ambulance to facilitate direct contact between the stroke provider and the patient and emergency medical services provider could reduce the enrollment of patients with stroke mimics in clinical trials, they added. "Improved tools to exclude stroke mimics in the field have been difficult to develop and validate. The absence of imaging in most ambulances will continue to limit field personnel from definitively determining ischemic stroke from intracerebral hemorrhage, which will limit hyperacute trials to interventions presumed safe in both populations."

In addition, the blood pressure reduction that GTN provided might not be clinically relevant, said Dr. Johnston and Dr. Durkalski-Mauldin. "The RIGHT-2 investigators report no difference in blood pressure at day 3 or day 4 of treatment, which might have been related to the very low adherence to study protocol by day 4.

"Regardless of these limitations, RIGHT-2 has provided high-level evidence that GTN given within 4 hours of onset does not significantly improve outcome in hyperacute patients presenting with possible stroke," the authors concluded.

Dr. Johnston and Dr. Durkalski-Mauldin declared no conflicts of interest. **NR**

—Erik Greb

Suggested Reading

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Can intraputamenal infusions of GDNF treat Parkinson's disease?

The investigational therapy, delivered through a skull-mounted port, was well tolerated in a randomized, controlled trial and an open-label extension study.

Intraputamenal infusions of glial cell line–derived neurotrophic factor (GDNF) every 4 weeks are feasible and may hold promise as a treatment for Parkinson's disease, researchers reported. The investigational therapy, delivered through a skull-mounted port, was well tolerated in a 40-week, randomized, controlled trial and a 40-week, open-label extension.

Neither study met its primary end point, but post hoc analyses suggest possible clinical benefits. In addition, PET imaging after the 40-week, randomized trial found significantly increased ^{18}F-DOPA uptake in patients who received GDNF. The randomized trial was published in the March 2019 issue of *Brain*; data from the open-label extension were published online ahead of print Feb. 26, 2019, in the *Journal of Parkinson's Disease*.

"The spatial and relative magnitude of the improvement in the brain scans is beyond anything seen previously in trials of surgically delivered growth-factor treatments for Parkinson's [disease]," said principal investigator Alan L. Whone, MBChB, PhD, of the University of Bristol (United Kingdom) and North Bristol National Health Service Trust. "This represents some of the most compelling evidence yet that we may have a means to possibly reawaken and restore the dopamine brain cells that are gradually destroyed in Parkinson's [disease]."

> The findings could have implications for other neurologic disorders as well.

Nevertheless, the trial did not confirm clinical benefits. The hypothesis that growth factors can benefit patients with Parkinson's disease may be incorrect, the researchers acknowledged. It also is possible that the hypothesis is valid and that a trial with a higher GDNF dose, longer treatment duration, patients with an earlier disease stage, or different outcome measures would yield positive results. GDNF warrants further study, they wrote.

The findings could have implications for other neurologic disorders as well.

"This trial has shown that we can safely and repeatedly infuse drugs directly into patients' brains over months or years. This is a significant breakthrough in our ability to treat neurologic conditions ... because most drugs that might work cannot cross from the bloodstream into the brain," said Steven Gill, MB, MS. Dr. Gill, of the North Bristol National Health Service Trust and the U.K.-based engineering firm Renishaw, designed the convection-enhanced delivery system used in the studies.

The GDNF delivery device.

CREDIT: MintMotion for Passionate Productions.

A neurotrophic protein

GDNF has neurorestorative and neuroprotective effects in animal models of Parkinson's disease. In open-label studies, continuous, low-rate intraputamenal administration of GDNF has shown signs of potential efficacy, but a placebo-controlled trial did not replicate clinical benefits. In the present studies, the researchers assessed intermittent GDNF administration using convection-enhanced delivery, which can achieve wider and more even distribution of GDNF, compared with the previous approach.

The researchers conducted a single-center, randomized, double-blind, placebo-controlled trial to study this novel administration approach. Patients were aged 35–75 years, had motor symptoms for at least 5 years, and had moderate disease severity in the off state (that is, Hoehn and Yahr stage 2–3 and Unified Parkinson's Disease Rating Scale motor score–part III [UPDRS-III] of 25–45).

In a pilot stage of the trial, six patients were randomized 2:1 to receive GDNF (120 µg per putamen) or placebo. In the primary stage, another 35 patients were randomized 1:1 to GDNF or placebo. The primary outcome was the percentage change from baseline to week 40 in the off-state UPDRS-III among patients from the primary stage of the trial. Further analyses included all 41 patients from the pilot and primary stages.

Patients in the primary analysis had a mean age of 56.4 years and mean disease duration of 10.9 years. About half were female.

Results on primary and secondary clinical end points did not significantly differ between the groups. Average off state UPDRS motor score decreased by 17.3 in the active treatment group, compared with 11.8 in the placebo group.

A post hoc analysis, however, found that nine patients (43%) in the active-treatment group had a large, clinically important motor improvement of 10 or more points in the off state, whereas no placebo patients did. These "10-point responders in the GDNF group are a potential focus of interest; however, as this is a post hoc finding we would not wish to overinterpret its meaning," Dr. Whone and his colleagues wrote. Among patients who received GDNF, PET imaging demonstrated significantly increased ^{18}F-DOPA uptake throughout the putamen, ranging from a 25% increase in the left anterior putamen to a 100% increase in both posterior putamena, whereas patients who received placebo did not have significantly increased uptake.

No drug-related serious adverse events were reported. "The majority of device-related adverse events were port site associated, most commonly local hypertrophic scarring or infections amenable to antibiotics," the investigators wrote. "The frequency of these declined during the trial as surgical and device handling experience improved."

Open-label extension

By week 80, when all participants had received GDNF, both groups showed moderate to large improvement in symptoms, compared with baseline. From baseline to week 80, percentage change in UPDRS motor score in the off state did not significantly differ between patients who received GDNF

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Can intraputamenal infusions of GDNF treat Parkinson's disease?

continued from page 42

for 80 weeks and patients who received placebo followed by GDNF (26.7% vs. 27.6%). Secondary end points also did not differ between the groups. Treatment compliance was 97.8%; no patients discontinued the study.

The trials were funded by Parkinson's UK with support from the Cure Parkinson's Trust and in association with the North Bristol NHS Trust. GDNF and additional resources and funding were provided by MedGenesis Therapeutix, which owns the license for GDNF and received funding from the Michael J. Fox Foundation for Parkinson's Research. Renishaw manufactured the convection-enhanced delivery device on behalf of North Bristol NHS Trust. The Gatsby Foundation provided a 3-T MRI scanner. Some study authors are employed by and have shares or share options with MedGenesis Therapeutix. Other authors are employees of Renishaw. Dr. Gill is Renishaw's medical director and may have a future royalty share from the drug delivery system that he invented. **NR**

—Jake Remaly

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Study hints at lacosamide's efficacy for small fiber neuropathy

The approved treatment for partial-onset seizures may benefit patients with $Na_v1.7$-related small fiber neuropathy.

As a treatment for small fiber neuropathy (SFN), lacosamide decreased pain and improved sleep quality in patients with mutations in the gene *SCN9A* that encodes the voltage-gated sodium channel $Na_v1.7$, according to a randomized, placebo-controlled, double-blind, crossover study published in *Brain*.

"Compared with placebo, lacosamide appeared to be safe to use and well tolerated," wrote Bianca T. A. de Greef, MD, of Maastricht University Medical Center, the Netherlands, and her coauthors.

Lacosamide (Vimpat), an approved treatment for partial-onset seizures, binds to $Na_v1.7$. The investigators randomized 25 Dutch patients with $Na_v1.7$-related SFN into the Lacosamide-Efficacy-'N'-Safety in SFN (LENSS) study to receive lacosamide followed by placebo, or vice versa. They recruited patients between November 2014 and July 2016; 1 patient dropped out before treatment and another after the first treatment period, leaving 24 patients who received lacosamide and 23 patients who received placebo. Patients completed a 3-week titration period, an 8-week treatment period, a 2-week tapering period, and a washout period of at least 2 weeks, after which they switched to the other treatment arm and repeated the same schedule.

Through the daily pain intensity numerical rating scale, the daily sleep interference scale (DSIS), and other questionnaires, the investigators sought to determine if lacosamide reduced pain and thereby improved sleep quality. More patients had a mean average pain decrease of at least 1 point during lacosamide treatment than during the placebo period (50.0% vs. 21.7%). In addition, 25.0% of the lacosamide group had at least a 2-point decrease in mean average pain versus 8.7% of the placebo group. Median DSIS value during the lacosamide period was 5.3, compared with 5.7 for the placebo period.

According to the patients' global impression of change questionnaire, 33.3% felt better while using lacosamide versus 4.3% who felt better while taking placebo. The most common adverse events included dizziness, headache, and nausea, all of which were comparable during the placebo and lacosamide periods.

The study was funded by the Prinses Beatrix Spierfonds. Some authors disclosed grants, fees, research funding, and honoraria from foundations, pharmaceutical companies, and the European Commission.

NR

—Steve Cimino

Suggested Reading

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Risks of MI and stroke increase after cancer diagnosis

During the first 30 days after a cancer diagnosis, the incidence of MI or stroke increased by nearly 500%.

HONOLULU—During the first month after a new cancer diagnosis, patients face a substantially elevated risk for an arterial thromboembolic event—an MI or stroke—consistent with the well-described increased risk that newly diagnosed cancer patients face from venous thromboembolism, based on findings from a prospective study of more than 4,000 people.

> Factors released by tumors could account for the increased risk of thromboembolic events in this population.

In the new study, 836 patients newly diagnosed with cancer had a 480% increased rate of a fatal or nonfatal MI or stroke during the 30 days following their diagnosis, compared with 3,339 matched people without cancer. The results were adjusted for baseline differences in demographics and cardiovascular risk factors, Babak B. Navi, MD, said while presenting a poster at the International Stroke Conference sponsored by the American Heart Association.

Reasons for increased risk are uncertain

An additional analysis that focused on 210 of the 836 patients with incident cancer who had any of seven of the cancers known to pose the highest risk of venous thromboembolism (i.e., lymphoma; gynecologic cancer; or cancer of the pancreas, stomach, lung, bladder, or testes) showed a 1,750% greater rate of incident MI or stroke during the first 30 days after diagnosis, compared with matched people without cancer, reported Dr. Navi, division chief of stroke and hospital neurology at Weill Cornell Medicine, New York.

In contrast, during both the period 1–3 months after the cancer diagnosis and more than 3 months after, the rate of MI or stroke among recently diagnosed cancer patients was not significantly different from the rate in comparator individuals, although the data showed modest trends toward more arterial thromboembolic events after a month. The lack of statistically significant differences may have been a question of the study's power, Dr. Navi suggested.

The reasons for this acutely increased risk for arterial thromboembolic events, as well as the early spike in venous thromboembolic events, are not completely clear, but it likely results from factors released by tumors, effects from the drugs that patients receive for cancer treatment, stress, and interruption of antithrombotic treatment. Dr. Navi hypothesized that cancer-induced hypercoagulability was likely the biggest culprit. It may now be reasonable to test the idea of treating newly diagnosed cancer patients with agents that could reduce their risk for MI or stroke, such as aspirin or statins, he said in an interview.

The REGARDS study

The new analysis used data collected in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, which during 2003-2007 enrolled more than 30,000 U.S. residents who were at least 45 years old. Dr. Navi and his associates used data collected from all REGARDS participants who developed incident cancer and had continuous Medicare coverage for at least 1 year before entering REGARDS, excluding those with cancer before enrollment. They used the Medicare records to identify the cancer diagnoses and matched each of these people with four similar but cancer-free people enrolled in the study. Follow-up continued through September 2015. The average age of this REGARDS subgroup at enrollment was 72 years, and nearly half were women. The incident cancers included solid tumor (640 patients), hematologic cancers (71 patients), brain tumors (13 patients), and unknown primary cancer site (112 patients).

Babak B. Navi, MD

Dr. Navi and his associates designed this study to validate previously reported findings of increased arterial thromboembolic events in newly diagnosed cancer patients from studies of insurance claims databases. Although the increased risk for venous thromboembolism in cancer patients is already well established, documenting a similar risk for arterial events is important because they are "generally more impactful for patients than venous thromboembolism," Dr. Navi said.

REGARDS has received no commercial funding. Dr. Navi reported no disclosures. **NR**

—Mitchel L. Zoler

MENTALFLOSS

Inhalation may be associated with improved cognitive function

Before you take a big test, someone might recommend a shot of espresso, a piece of chocolate, or a headstand. The best advice, however, could be to take a deep breath. People who inhaled when presented with a visuospatial task were better at completing it than those who exhaled in the same situation, according to research by Noam Sobel, PhD, of the Weizmann Institute of Science's Department of Neurobiology in Rehovot, Israel. The study, which was published online ahead of print March 11 in *Nature Human Behavior,* suggests that the olfactory system may have shaped the evolution of brain function far beyond the basic function of smelling.

The researchers designed an experiment in which they could measure the air flow through the nostrils of subjects and simultaneously present them with test problems (e.g., math problems, spatial visualization problems, and verbal tests) to solve. The subjects were asked to click a button once when they had answered a question and once again when they were ready for the next question. The researchers noted that as the subjects went through the problems, they took in air just before pressing the button for the question. The subjects were not aware that their inhalations were being monitored, and the researchers ruled out a scenario in which the button-pushing itself was the reason for inhaling, rather than preparation for the task.

Next, the team changed the format, giving subjects only spatial problems, but half were presented as the test-takers inhaled, half as they exhaled. Inhalation was significantly associated with successful completion of the test problems. During the experiment, the researchers measured the subjects' electric brain activity with EEG and found differences between inhaling and exhaling, especially with regard to connectivity between different parts of the brain. This finding was observed during rest periods, as well as in problem solving, with greater connectivity linked to inhaling. Moreover, the larger the gap between the two levels of connectivity, the more inhaling appeared to help the subjects solve problems.

"One might think that the brain associates inhaling with oxygenation and thus prepares itself to better focus on test questions, but the time frame does not fit," said Dr. Sobel. "Our results show that it is not only the olfactory system that is sensitive to inhalation and exhalation, it is the entire brain. We think that we could generalize and say that the brain works better with inhalation."

Perl O, Ravia A, Rubinson M, et al. Human non-olfactory cognition phase-locked with inhalation. *Nat Hum Behav*. 2019 Mar 11 [Epub ahead of print].

Hippocampal abnormalities in epilepsy subtypes may be congenital

Imaging studies of patients and unaffected siblings suggest that changes in hippocampal volume occur before birth and are not the result of seizures.

NEW ORLEANS—Abnormalities of hippocampal volume and morphology in children with temporal lobe or juvenile myoclonic epilepsy (JME) are also present in the brains of their unaffected siblings, although to a lesser extent, based on findings from two studies presented at the annual meeting of the American Epilepsy Society.

While the studies suggest an imaging endophenotype associated with these disorders, it's unclear if a larger degree of abnormality causes disease manifestation, or whether there are other predisposing actors at work.

> "What our study tells us is that hippocampal abnormalities can occur in the absence of seizure."

"What our study tells us is that hippocampal abnormalities can occur in the absence of seizure," Marian Galovic, MD, said in an interview. "It may be that, in some cases, hippocampal abnormalities could be the cause, rather than the consequence, of seizures."

Dr. Galovic, of University College London, first author Lili Long, MD, PhD, of the Xiangya Hospital of Central South University, Changsha, China, and their research colleagues conducted a study that included 18 sibling pairs in which the affected siblings had sporadic, nonlesional temporal lobe epilepsy (TLE). TLE involved the right lobe in 12 cases and the left lobe in 6. The patients, siblings, and 18 healthy, age-matched controls underwent clinical, electrophysiologic, and high-resolution structural neuroimaging.

The researchers compared overall hippocampal volumes between groups and determined the subregional extent of hippocampal abnormalities using shape analysis. They also looked at whole-brain differences in cortical thickness and folding complexity.

Patients, siblings, and healthy controls

As expected, median hippocampal volumes were larger in the healthy controls (left = 2.82 mL, right = 2.94 mL), and smaller in patients. Patients with left TLE had a median left hippocampal volume of 2.23 mL, while those with right TLE had a median right hippocampal volume of 1.92 mL.

However, volume in the unaffected siblings was a surprise. Like the patients, these subjects also had significant reductions in hippocampal volume, when compared with controls (left = 2.47 mL, right = 2.65 mL). "The atrophy was relatively similar in siblings and patients, although not as pronounced in siblings," Dr. Galovic said. "It was mostly unilateral in the siblings and bilateral in the patients, but it was still more pronounced on the side where the epilepsy of the affected sibling was coming from."

Patients and siblings also shared morphologic variations of the hippocampus, with atrophy more pronounced on the right than the left. The right lateral body and anterior head of the hippocampus were most affected, Dr. Galovic said, with reductions in the right cornu ammonis 1 subfield and subiculum.

Widespread cortical thinning was present in patients, including in the pericentral, frontal, and temporal areas. Unaffected siblings also showed cortical thinning, but this was mostly restricted to the right postcentral gyrus. Patients and siblings also demonstrated increased cortical folding complexity, but in different areas: predominantly frontal in patients, but predominantly parieto-occipital in siblings. Both were significantly different than healthy control subjects.

The study didn't examine any association with memory, which is often impaired in patients with TLE. However, Dr. Galovic said, "We have just submitted for publication a study in which we did find an association between focal hippocampal atrophy and memory performance."

Unusual activation patterns on functional MRI

A separate study by a team at University College London looked at hippocampal structure and function in patients with JME and their unaffected siblings. The imaging study, led by Lorenzo Caciagli, MD, comprised 37 patients with JME, 16 unaffected siblings, and 20 healthy controls. It employed multimodal MRI and neuropsychological measures to examine the form and function of the mesiotemporal lobe.

The subjects were matched for age, sex, handedness, and hemispheric dominance, which was assessed with language lateralization indices. This measures the number of active voxels on functional MRI, showing which hemisphere is dominant for language.

Both patients and their siblings showed reductions in left hippocampal volume on the order of 5%–8%, significantly smaller than the volumes seen in healthy controls. About half of patients and half of siblings also showed either unilateral or bilateral hippocampal malrotation. This was present in 15% of controls, another significant difference. The structural differences weren't associated with seizure control or age at disease onset, or with any impairments in verbal or visual memory. But when the investigators performed functional mapping, they found unusual patterns of hippocampal activation in both patients and siblings, pointing to a dysfunction of verbal encoding. In patients, there appeared to be distinct patterns of underactivation along the hippocampal long axis, regardless of whether malrotation was present. But among patients who had malrotation, the left posterior hippocampus showed more activation during visual memory.

The team concluded that the hippocampal abnormalities in volume, shape, and positioning in patients with JME and their siblings are related to functional reorganization. The abnormalities probably occur during prenatal neurodevelopment, they noted.

"Cosegregation of imaging patterns in patients and their siblings is suggestive of genetic imaging phenotypes and independent of disease activity," Dr. Caciagli and his coinvestigators wrote in their abstract.

Funding for the TLE study came from the National Natural Science Foundation of China, the Ministry of Science and Technology of China, and Xiangya Hospital. Funding for the JME study came from various U.K. charities and government agencies. **NR**

—Michele G. Sullivan

Minimally invasive ICH lysis may safely help outcomes when clot adequately shrinks

In MISTIE III, surgeons' approach to clot lysis often fell short of aggressive goals.

HONOLULU—A minimally-invasive approach to lysing an intracerebral hemorrhage clot was safe but failed to produce a statistically significant improvement in long-term functional outcome when compared with usual medical management in a phase 3 randomized trial of 499 patients. However, the results also showed that when the procedure met its acute goal of cutting residual clot to a volume of 15 mL or less, it significantly increased the percentage of patients with a modified Rankin Scale score of 0–3 when assessed a year after treatment, Daniel F. Hanley Jr., MD, said at the International Stroke Conference sponsored by the American Heart Association.

"Improved function and increased survival was produced by surgical [clot] reduction to 15 mL or less," said Dr. Hanley, professor of neurology at Johns Hopkins University, Baltimore, and one of the organizers of the MISTIE III trial.

When assessed by another measure, treated patients showed significant, long-term functional improvement, compared with controls, when their clot burden decreased by at least 70% following the lytic procedure.

"This is the first description of specific thresholds of hematoma evacuation that impact functional outcomes in intracerebral hemorrhage surgery trials," said Issam A. Awad, MD, professor of surgery and director of neurovascular surgery at the University of Chicago and coprincipal investigator of the trial.

Daniel F. Hanley, MD

Issam A. Awad, MD

Aggressive treatment goals

The problem in the trial was that the surgeons who performed the interventions did not treat many patients aggressively enough to reach these thresholds. They achieved the prespecified goal of residual clot of 15 mL or less in 59% of patients, Dr. Hanley reported, even though the study protocol called for serial infusions of 1 mg of tissue plasminogen activator (Alteplase) into the clot via a catheter as many as nine times, administered at 8 hour intervals, with treatment to continue until patients reached the goal residual volume or until they had received all nine doses. In actual practice during the study, operators administered a median of four lytic doses.

"We showed that this goal was important, but not all sites embraced the goal," Dr. Hanley said. Even though the participating clinicians had a specific interest in intracerebral hemorrhage patients and in this procedure, several nonetheless "had a poor understanding of the goal," he said in an interview. He attributed the less-than-aggressive approach that many operators took to the safety concern that further doses of the lytic drug could trigger recurrent hemorrhage.

"I think they will embrace the [hematoma evacuation] goal when they see these data," Dr. Hanley predicted.

An as-treated analysis of the data that focused on the 145 of 246 patients who were treated with minimally invasive lysis, reached the target residual volume, and were functionally assessed a year later showed that the rate of patients with a modified Rankin Scale score of 0–3 was 53%, compared with 42% among the controls.

This shows "a large treatment effect. This is a big, transformative treatment," Dr. Hanley said. "Our data clearly show that more than half the patients had a positive outcome when their surgeons were more aggressive about clot removal." He cautioned that the trial was not just about the volume of clot removed, but was also about doing it in a gentle way with a minimum of tissue trauma. Other approaches to reducing hematoma volume may be faster or more complete, but they cannot match the record of safety and efficacy documented in MISTIE III for minimally invasive clot lysis, Dr. Hanley noted.

MISTIE III

MISTIE III (Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III) enrolled patients at 78 centers in the United States and several other countries during 2013–2017. Patients had to enroll 12–72 hours after onset and present with a hematoma volume of at least 30 mL. Participating neurosurgeons used image-guided neuronavigation to place a 4- to 6-mm cannula through the clot, ideally straight through the hematoma's long axis and with the tip placed within the largest clot segment. Among the 110 surgeons who performed this procedure dur-

COMMENTARY: Safety makes this an attractive option

Louise D. McCullough, MD, PhD

The MISTIE III results showed that this approach to clot lysis is safe and feasible for surgeons to perform even if they have had limited experience with the procedure. I think that based on these findings, minimally-invasive clot lysis will become widely adopted. It's pretty simple to perform in most patients. At my center in Houston, we already use it on a routine basis in patients like those enrolled in MISTIE III.

Some people may focus on the neutral primary end point result from the MISTIE III trial, but the study made two important findings. First, the results showed that we have improved medical management of patients who have an intracerebral hemorrhage. The 1-year functional outcomes of patients in the control group of the study, who had a 41% rate of scoring 0–3 on the modified Rankin Scale after 1 year, were much better than we have seen in these patients in the past. Second, the results gave a clear signal that the more clot an operator can lyse to get the residual clot to 15 mL or less, the better patients do. Faster clot lysis might also be important.

It's hard to call the minimally invasive approach used in MISTIE III the new standard-of-care approach for these patients, given the neutral primary end point of the study. On the other hand, if you have a treatment that poses little risk to patients and that you know could benefit them if it succeeds in minimizing residual clot volume, then it makes sense to try it. It's a low-risk treatment with reasonable potential for benefit. Its demonstrated safety is very important.

—Louise D. McCullough, MD, PhD, is a professor of neurology and chair of neurology at the University of Texas, Houston. She had no disclosures. She made these comments in an interview.

ing the study, 88% had never done it before, and operator and site experience was associated with better performance. No surgeon who had already performed four minimally invasive lytic cases, and no center that had already performed seven cases, had a subsequent patient with a residual volume that exceeded 30 mL, Dr. Awad said. The surgical experience during the trial showed that catheter repositioning and using a second catheter were safe ways to maximize evacuation of the hematoma, he added.

The trial's primary end point, the rate of patients with a modified Rankin Scale score of 0–3 at 1 year after treatment in a modified intention-to-treat analysis that included all patients regardless of the amount of hematoma evacuation they received, showed a 45% rate among the patients who underwent minimally invasive lysis and a 41% rate among those in the control arm, a difference that was not statistically significant. Safety assessments showed that patients treated with the investigational approach had significantly lower mortality 7 days after treatment: 0.8% compared with 4.0%. By 1 year after treatment, mortality was reduced by one-third in the minimally invasive patients, compared with the control patients, also a statistically significant difference. The rates of symptomatic bleeds and brain infections were similar in the two treatment groups, Dr. Hanley reported. Concurrently with his talk at the conference, a paper with the primary study results was published in *Lancet*.

> "This is the first description of specific thresholds of hematoma evacuation that impact functional outcomes in intracerebral hemorrhage surgery trials."

The MISTIE III trial was supported by the National Institute of Neurological Disorders and Stroke. The trial received no commercial support aside from free tissue plasminogen activator supplied by Genentech. Dr. Hanley has been a consultant to BrainScope, Neurotrope, Portola, and Op2Lysis, and he has served as an expert witness on behalf of Medtronic. Dr. Awad had no disclosures.

NR

—Mitchel L. Zoler

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Andexanet alfa effectively reverses factor Xa inhibition

continued from page 1

dexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study to evaluate the drug's safety and efficacy in patients with acute major bleeding associated with treatment with a factor Xa inhibitor. For participants to be eligible, their bleeding had to be life threatening with signs of hemodynamic compromise, be associated with a decrease in hemoglobin level of at least 2 g/dL, or occur in a critical organ such as the brain. An independent academic committee determined whether patients met these criteria.

> **The overall mortality rate was 13.9%. The rate of mortality resulting from ICH was 15%, and the rate of mortality resulting from gastrointestinal bleeding was 11%.**

The trial's primary efficacy outcomes were change from baseline in anti–factor Xa activity and the percentage of patients with excellent or good hemostatic efficacy at 12 hours. The primary safety end points were death, thrombotic events, and the development of neutralizing antibodies to andexanet or to native factor X and factor Xa. The efficacy population included patients with major bleeding and baseline anti–factor Xa activity of at least 75 ng/mL. The safety population included all patients who received a dose of andexanet. The independent committee adjudicated the efficacy and safety outcomes.

Hemostasis sustained for 12 hours

The investigators enrolled 352 participants into the study, all of whom received andexanet and were followed for at least 30 days or until death. The population's mean age was 77 years. "These were older and sicker patients with a significant amount of comorbid disease," said Dr. Milling. The primary indication for anticoagulation was atrial fibrillation in 80% of patients. The primary site of bleeding was intracranial in 64% of patients and gastrointestinal in 26% of patients. The remaining 10% of patients had bleeding affecting other areas (such as pericardial or intramuscular bleeding).

The investigators included 254 patients in the efficacy population. At the end of the administration of the andexanet bolus, the median value for anti–factor Xa activity decreased by 92% among participants receiving apixaban, 92% among participants receiving rivaroxaban, and 75% among patients receiving enoxaparin. Among patients receiving apixaban, the median value for anti–factor Xa activity was decreased by 32% at 4 hours, 34% at 8 hours, and 38% at 12 hours. Among patients receiving rivaroxaban, the median value for anti–factor Xa activity was decreased by 42% at 4 hours, 48% at 8 hours, and 62% at 12 hours.

Dr. Milling and his colleagues assessed hemostatic efficacy in 249 patients. Of this group, 82% achieved good or excellent hemostasis. Among participants with good or excellent hemostasis, 84% had excellent results, and 16% had good results. Subanalysis by factor Xa inhibitor, type of bleed, age, and dose of andexanet did not alter the findings significantly.

To determine whether hemostasis had been sustained sufficiently to prevent clinical deterioration, the investigators examined 71 patients with ICH and a single-compartment bleed. From 1 hour to 12 hours, one patient's outcome changed from excellent/good to poor/none, and one patient's outcome changed from excellent to good. For the majority of these patients, however, good hemostasis was sustained from 1 to 12 hours.

The rate of thromboembolic events was 9.7%, which is in the expected range for this population, said Dr. Milling. These events were distributed evenly among the 4 weeks of the study. Stroke and deep vein thrombosis accounted for most of these events, and pulmonary emboli and heart attacks occurred as well. "Once we restarted oral anticoagulation ... there were no more thrombotic events," said Dr. Milling. No patient developed neutralizing antibodies to factor X or factor Xa, nor did any patient develop neutralizing antibodies to andexanet.

Truman John Milling Jr, MD

The overall mortality rate was 13.9%. The rate of mortality resulting from ICH was 15%, and the rate of mortality resulting from gastrointestinal bleeding was 11%. These results are impressive, considering that patients had received anticoagulants, said Dr. Milling.

Portola Pharmaceuticals, the maker of andexanet alfa, funded the study. Dr. Milling reported receiving funding and honoraria from the Population Health Research Institute at McMasters University, Janssen, CSL Behring, and Octapharma. He also received a small research payment from Portola Pharmaceuticals. Several of the investigators reported receiving funding from Portola Pharmaceuticals. **NR**

—Erik Greb

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What happens when patients with relapsing-remitting MS discontinue their DMT?

Age of discontinuation may affect prognosis.

DALLAS—Patients with relapsing-remitting multiple sclerosis (RRMS) who discontinued treatment after a period of disease inactivity had a similar time to next event, compared with those who remained on treatment, results from a single-center study showed. In addition, being over the age of 45 years was associated with a better disease course after treatment discontinuation.

"Being clinically and radiologically stable for more than 2 years can be a potential milestone to regard the discontinuation of DMT [disease-modifying therapy] as a reasonable option in a subset of patients, especially patients who are nondisabled," lead study author Hajime Yano, MD, said in an interview at the 2019 ACTRIMS Forum.

> Clinical and radiological stability for more than 2 years can be a basis for considering the discontinuation of DMT.

According to Dr. Yano, a research fellow at the Ann Romney Center for Neurologic Diseases and Partners Multiple Sclerosis Center in Boston, RRMS patients without relapse for long periods on treatment may consider discontinuing DMT, but there is limited information regarding the impact of discontinuation, especially in terms of MRI activity.

Clinical and radiologic outcomes

In an effort to investigate the impact of DMT discontinuation on clinical and radiologic outcomes in patients with RRMS, he and his colleagues identified 70 patients from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) study, which was initiated in 2000 and has enrolled more than 2,400 patients cared for at the Partners Multiple Sclerosis Center. The treating neurologist evaluated relapse date, symptoms, and Expanded Disability Status Scale (EDSS) score at 6-month intervals for each patient during the time of clinic visits. Additionally, brain MRIs were performed annually.

Next, the researchers matched the patients with 70 patients who remained on DMT by age, sex, treatment, treatment duration, disease duration, and EDSS. They used univariate and multivariable Cox proportional hazard models to test the differences between DMT discontinuation status with time to clinical relapse, MRI event, disability progression, and any inflammatory event (either clinical relapse or MRI event).

The mean age of patients was 45 years, 87% were female, their mean disease duration was about 13 years, and they had been receiving treatment for a mean of about 6 years. In adjusted analyses, the 70 pairs of patients who discontinued DMT and patients who continued DMT had similar outcomes in time to clinical relapse (hazard ratio, 0.93; $P = 0.84$), MRI event (HR, 1.01; $P = 0.98$), disability progression (HR, 1.33; $P = 0.43$), and any inflammatory event (HR, 0.93; $P = 0.85$). In a subgroup analysis, which compared the impact of DMT discontinuation between patients over the age of 45 years and those aged 45 years and younger, the researchers observed a statistically significant difference in effect of discontinuation on time to clinical relapse ($P = .032$), time to MRI event ($P = .013$), and time to any inflammatory event ($P = .0005$), all favoring patients over the age of 45 years.

Hajime Yano, MD

Prognosis may differ by age

"This finding makes sense, since age has been reported as one of the factors that negatively impacts on the inflammatory activity in patients with RRMS," Dr. Yano said. "However, our study is the first study [to find] that the impact of discontinuing DMT on RRMS patient prognosis may differ based on the age at the discontinuation. In short, stopping DMT at a younger age has a statistically significant higher risk of inflammatory activities, compared to [stopping DMT at an] older age."

He acknowledged certain limitations of the study, including its small sample size and single-center design. However, Dr. Yano said that a key strength of the analysis was the inclusion of MRI activity prior to DMT as the definition of stable state, "which is an integral piece of information when physicians and patients consider DMT discontinuation in a 'real-world' clinical setting. We also used MRI activity as an outcome measure, which is lacking in prior discontinuation studies."

Dr. Yano reported that he has received a research grant from Yoshida Scholarship Foundation in Japan. His coauthors reported financial ties to industry.

NR

—Doug Brunk

Can higher MAP post cardiac arrest improve neurologic outcomes?

A higher-than-recommended mean arterial pressure appears safe, but might not improve neurologic outcomes.

CHICAGO—A European clinical trial that targeted a mean arterial blood pressure (MAP) after cardiac arrest that was higher than what guidelines recommend found that the approach was safe. The approach also improved blood flow and oxygen to the brain, helped patients recover more quickly, and reduced the number of adverse cardiac events. It did not, however, reduce the extent of anoxic brain damage or improve functional outcomes, the lead investigator reported at the American Heart Association scientific sessions.

The Neuroprotect trial randomly assigned 112 adult survivors of an out-of-hospital cardiac arrest who were unconscious upon admission to early goal-directed hemodynamic optimization (EGDHO) or standard care. For the former group, researchers used a targeted MAP of 85-100 mm Hg and mixed venous oxygen saturation between 65% and 75% during the first 36 hours after ICU admission. In the latter group, researchers used the guideline-recommended MAP target of 65 mm Hg, said Koen Ameloot, MD, of East Limburg Hospital in Genk, Belgium.

> "EGDHO clearly improved cerebral perfusion and oxygenation, thereby for the first time providing the proof of concept for this new hemodynamic target."

"EGDHO clearly improved cerebral perfusion and oxygenation, thereby for the first time providing the proof of concept for this new hemodynamic target," Dr. Ameloot said. "However, this did not result in the reduction of the extent of anoxic brain hemorrhage or effusion rate on MRI or an improvement in functional outcome at 180 days."

He noted that the trial was predicated on improving upon the so-called "two-hit" model of cardiac arrest sequelae. The first hit is the period of no or low flow before the restoration of spontaneous circulation. The second hit includes hypoperfusion and reperfusion injury during the ICU stay.

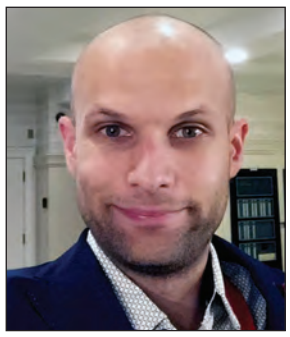
Norepinephrine improved cerebral oxygenation

In a previous study, Dr. Ameloot and colleagues found that patients with a MAP target of 65 mm Hg "experience a profound drop of cerebral oxygen saturation during the first 12 hours of ICU stay that may cause additional brain damage."

The researchers explored the question of what the optimal MAP is if a target of 65 mm Hg is too low, Dr. Ameloot said. "We showed that maximal brain oxygenation is achieved with a MAP of 100 mm Hg, while lower MAPs were associated with submaximal brain perfusion, and higher MAPs with excessive afterload, a reduction in stroke volume, and suboptimal cerebral oxygenation."

During the 36-hour intervention period, the EGDHO patients received higher doses of norepinephrine, Dr. Ameloot said. "This resulted in significant improvement of cerebral oxygenation during the first 12 hours and was paralleled by significantly higher cerebral perfusion in the subset of patients in whom Doppler measurements were performed," he said. "While patients allocated to the MAP 65-mm Hg target experienced a profound drop of cerebral oxygenation during the critical first 6-12 hours of ICU stay, cerebral oxygenation was maintained at 67% in patients assigned to EGDHO."

The rate of anoxic brain damage, however, measured as the percentage of irreversibly damaged anoxic voxels on diffusion-weighted MRI (the primary end point of the study), was higher in the EGDHO group (16% vs. 12%), Dr. Ameloot said. "The percentage of anoxic voxels was only a poor predictor of favorable neurological outcome at 180 days, questioning the validity of the primary end point," he said. He also noted that 23% of the trial participants did not have an MRI scan because of higher than expected 5-day rates of death.



Koen Ameloot, MD

ICU stay did not differ between groups

"The percentage of patients with favorable neurological outcome tended to be somewhat higher in the intervention arm, although this did not reach statistical significance at ICU discharge and at 180 days," Dr. Ameloot said. He noted that 42% of the intervention group and 33% of controls in the full-analysis set ($P = 0.30$) and 43% and 27%, respectively, in the per-protocol set ($P = 0.15$) had a favorable neurological outcome, as calculated using the Glasgow-Pittsburgh Cerebral Performance Category scores of 1 or 2, at 180 days.

The study did not reveal any noteworthy differences in ICU stay (7 vs. 8 days, $P = 0.13$) or days on mechanical ventilation (5 vs. 7, $P = 0.31$), although fewer patients in the EGDHO group required a tracheostomy (4% vs. 18%, $P = 0.02$). The intervention group also had lower rates of cardiac events, including recurrent cardiac arrest, limb ischemia, new atrial fibrillation, and pulmonary edema (13% vs. 33%; $P = 0.02$), Dr. Ameloot said.

Future post hoc analyses of the data will explore the hypothesis that higher blood pressure leads to improved coronary perfusion and reduced infarct size, thus improving prognosis, he added.

"Should this trial therefore be the definite end to the promising hypothesis that improving brain oxygenation might reduce the second hit in post–cardiac arrest patients? I don't think so," Dr. Ameloot said. He noted the following limits to the study: that the perfusion rate on MRI was a poor predictor of 180-day outcome, that more patients than expected entered the trial without receiving basic life support and with nonshockable rhythms, and that there was possibly less extensive brain damage among controls at baseline. "Only an adequately powered clinical trial can provide an answer about the effects of EGDHO in post–cardiac arrest patients," Dr. Ameloot said.

Dr. Ameloot had no financial relationships to disclose. **NR**

—Richard Mark Kirkner

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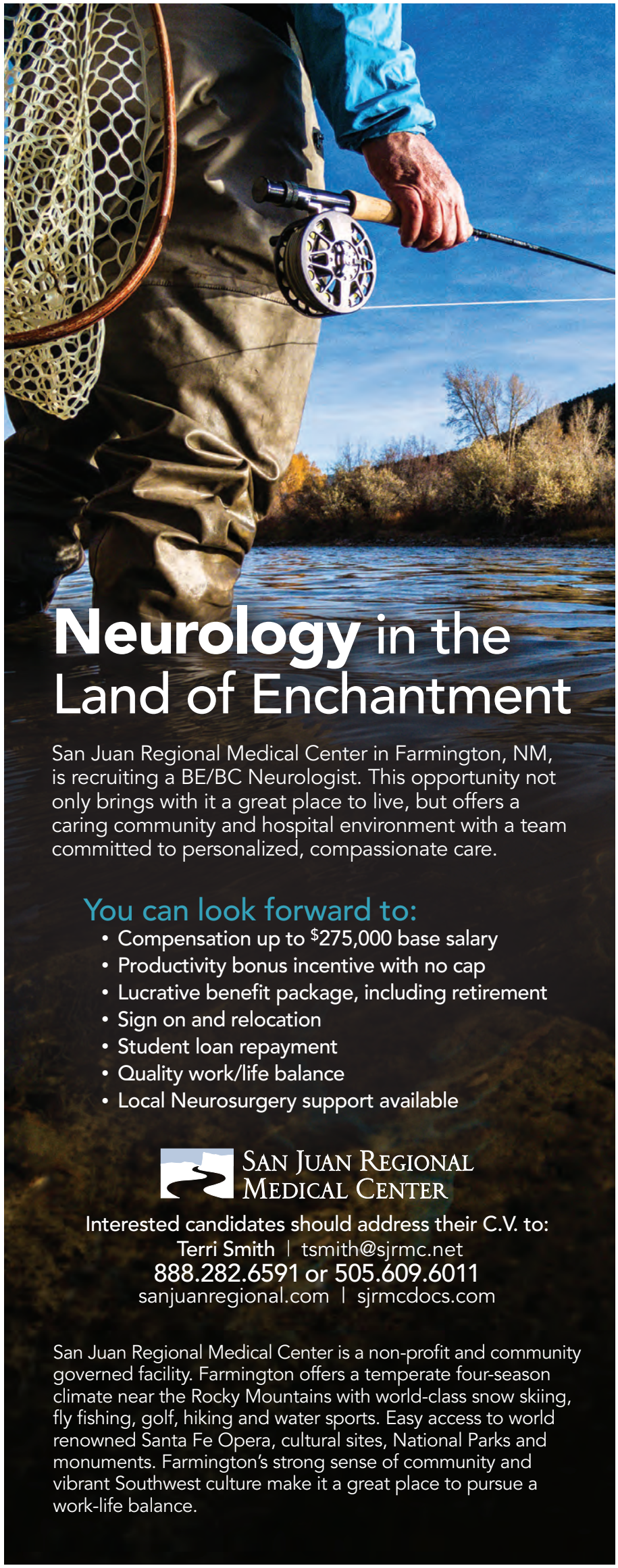

Genetic signature helps identify those at risk of MS

Molecular and cellular studies are becoming important in the effort to understand disease onset.

DALLAS—Genetic and molecular studies are coming closer to pinpointing just when multiple sclerosis (MS) really starts, Philip De Jager, MD, PhD, said at the 2019 ACTRIMS Forum.

"MS remains a diagnosis of exclusion.... But we're now beginning to understand a lot more about the earliest stages of the disease, and we're constantly redefining the disease in terms of when it starts, and what it consists of," said Dr. De Jager, professor of neurology and chief of neuroimmunology at Columbia University, New York, in an interview.

For example, physicians are now starting to treat asymptomatic individuals with radiologically isolated syndrome, he said. "Is that part of the disease? Well, a lot of us think so, and we're currently doing the studies to see whether treating them has an impact on long-term disability."

> Researchers are beginning to understand more about when multiple sclerosis starts and what its earliest stages are like.

"In this effort to redefine this disease and when it starts, these molecular and cellular studies are becoming very important," Dr. De Jager said. Individuals in the general population and high-risk individuals, such as family members of people with MS, will benefit from these research approaches, he said.

Right now, it's hard to know who could benefit most from future preventive therapies, or who should have the most rigorous surveillance.

Dr. De Jager pointed to a presentation by his collaborator, Nikolaos Patsopoulos, MD, PhD, of Brigham and Women's Hospital, Boston, who reported on the activities of the International MS Genetics Consortium. The consortium has collected and is nearing publication of data from more than 45,000 people with MS and 65,000 control participants to identify the genetic architecture of MS onset.

"We are going to be reporting that there are more than 234 genetic variations" that contribute to the onset of MS, Dr. De Jager said. "There are more to be found, but that's a large number," he said. The data point toward a genetic fingerprint similar to that of lupus, type 1 diabetes, and other inflammatory diseases. This shared genetic architecture means that there is overlapping susceptibility for many diseases in this spectrum. **NR**

—Kari Oakes