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Neurology
[ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

How Helpful Is Bevacizumab in Recurrent Glioblastoma?

By Rajiv S. Magge, MD

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Dr. Magge reports no financial relationships relevant to this field of study.

SYNOPSIS: In a randomized Phase III trial, the addition of bevacizumab to lomustine did not improve overall survival in patients with recurrent glioblastoma compared to lomustine alone.

SOURCE: Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. *N Engl J Med* 2017;377:1954-1963.

Glioblastoma (GBM) continues to be one of the deadliest forms of cancer, and although generally rare, it is one of the most common primary brain tumors. Standard treatment includes maximal safe surgical resection followed by concurrent radiation therapy with temozolomide chemotherapy, as well as subsequent adjuvant chemotherapy. Unfortunately, these tumors invariably progress after chemoradiation, and although significant advances have been made (especially with molecular diagnostics and tumor genetic profiling), treatments for recurrent disease are few with only limited efficacy. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), is FDA-approved for recurrent GBM. Lomustine, an alkylating nitrosourea with good blood-brain barrier penetration, is an older oral chemotherapy with a similar mechanism of action to temozolomide. The BELOB trial was a multicenter, Phase II study that evaluated the efficacy of single-agent bevacizumab or lomustine vs. the combination of both drugs in progressive GBM. The authors of this study noted potential improved survival with the combination treatment compared to either drug alone, setting the stage for a subsequent Phase III trial that was reported recently in *The New England Journal of Medicine*.

In this randomized, Phase III trial supported by the European Organisation for Research and Treatment

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of Cancer, Wick et al randomly assigned patients with initially recurrent GBM after chemoradiation in a 2:1 ratio to receive combination lomustine/bevacizumab or lomustine alone. The trial's primary endpoint was overall survival, but other indicators, including MGMT promoter methylation status, quality of life, and neurocognitive function, also were assessed.

A total of 288 patients were randomized into the combination group, while 149 patients received lomustine monotherapy. Patients on both drugs received a median of three 6-week cycles, while a median of one cycle of lomustine was given in the monotherapy arm. Although progression-free survival was 2.7 months longer in the combination group, median overall survival was not significantly different (9.1 months with combination bevacizumab/lomustine vs. 8.6 months with lomustine alone). Severe adverse events were more common with the combination treatment (63.6% vs. 38.1% with monotherapy). Importantly, the addition of bevacizumab did not seem to improve health-related quality of life or neurocognitive function. As expected, patients whose tumors had MGMT promoter methylation (a positive prognostic indicator in GBM that is associated with better response to temozolomide chemotherapy) had better progression-free and overall survival compared to those with unmethylated MGMT promoters (13.5 vs. 8.0 months). However, like the general study population, adding bevacizumab to lomustine did not increase overall survival in the MGMT-methylated group.

■ COMMENTARY

This international study is impressive in its size and scope, but unfortunately did not demonstrate any improved overall survival with the addition of bevacizumab to lomustine. The results are consistent with the general presumption that although bevacizumab may delay progression, it does not appear to significantly improve overall survival. This is a difficult point for the neuro-oncology community, as bevacizumab remains one of the few FDA-approved therapies for recurrent GBM (data from large studies including AVAglio and RTOG 0825 do not support the use of bevacizumab up-front in newly diagnosed tumors). As an anti-angiogenic agent, bevacizumab contributes to decreased enhancing disease and edema, potentially allowing for tapering of steroids and avoidance of significant steroid-related side effects. However, the addition of bevacizumab did not lead to reduced use of glucocorticoids or improve health-related quality of life in the present study. Further, there was a higher rate of more serious adverse effects with combination treatment, although this could be related to a longer duration of treatment in this group (patients in the lomustine monotherapy arm only received a median of one treatment cycle).

[Unfortunately, this international study did not demonstrate any improved overall survival with the addition of bevacizumab to lomustine for patients with glioblastoma.]

If clinical trials are not available, lomustine monotherapy may be a good option for recurrent disease, especially in tumors with MGMT promoter methylation, which theoretically are more likely to respond to alkylating agents. There does not appear to be any disadvantage in withholding bevacizumab on initial recurrence, especially if there is no significant tumor-related edema.

As with many GBM clinical trials, the negative results of this study highlight the lack of effective options for this deadly disease. There have been great advancements in the molecular characterization of gliomas, but this has not yet translated into improved treatment outcomes (except in cases of IDH1 mutation and 1p/19q codeletion). The greater oncology community has demonstrated fantastic results with immunotherapy (such as checkpoint inhibitors) — sadly, preliminary data indicate only limited efficacy in GBM, which may be related to its lower somatic mutational load and immunosuppressive tumor microenvironment. The success of future treatments may hinge on developing novel preclinical models that are more representative of in vivo human tumors. For patients with this horrible disease, these innovations cannot come soon enough. ■

ABSTRACT & COMMENTARY

The Incidence of Dementia May Be Declining

By Makoto Ishii, MD, PhD

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Dr. Ishii reports no financial relationships relevant to this field of study.

SYNOPSIS: In community-dwelling people from Bronx County, New York, there was a sharp decrease in dementia incidence in those born after mid-1929, which could not be readily explained by changes in the prevalence of cardiovascular diseases, higher education, or increased racial/ethnic diversity.

SOURCE: Derby CA, Katz MJ, Lipton RB, Hall CB. Trends in dementia incidence in a birth cohort analysis of the Einstein Aging Study. *JAMA Neurol* 2017;74:1345-1351.

With an increasingly aging population and no cure or vaccine for Alzheimer's disease (AD) or age-related dementias, dementia is poised to become a medical epidemic. Surprisingly, investigators recently have found that for unclear reasons, there may be a decrease in dementia incidence. Identifying the underlying causes for any such decrease would be critical for developing effective dementia prevention strategies. In this study, investigators from the Einstein Aging Study sought to determine whether there was evidence of a decrease in dementia incidence across sequential birth cohorts. As evidence mounts supporting the role of cardiovascular disease as a significant contributor to dementia, Derby et al also sought to determine whether trends in cardiovascular disease could explain any observed dementia trends.

The Einstein Aging Study is an ongoing study that has been recruiting noninstitutionalized individuals from Bronx County, New York, since 1993. Eligibility criteria were age 70 years or older, fluent in English, and no dementia at study entry. Each study participant had an annual follow-up assessment that included a clinical neurological examination, comprehensive neuropsychological assessments, medical history, blood pressure, anthropometrics, and psychosocial assessments. Self-report of physician diagnosis was used to determine the prevalence of myocardial infarction, stroke, or diabetes. Global cognitive performance was assessed using the Blessed Information Memory Concentration (BIMC) test, while depression was assessed using the Geriatric Depression Scale. Diagnosis of dementia was based on standardized clinical criteria from DSM-IV and assigned at consensus case conference. There were 1,348 participants in the study after excluding those who died or were unavailable for follow-up before their first annual visit.

Using crude dementia incidence rates as a function of age and dates of birth, the overall trend of increasing dementia incidence with increasing age was seen as expected. When the investigators fit locally weighted scatter plot smoothing (LOESS) functions using generalized additive models, there was a consistent pattern within each age range of decreasing incidence with sequential birth years and an accelerated decrease in those born in the middle to late 1920s. Investigators next identified birth years when there was a significant change in incidence rates by fitting Poisson regression models with change points. After adjusting for age, sex, race, and education level, a significant change point was found for individuals born after July 1929. Investigators then examined whether decreasing rates of cardiovascular disease affected the dementia incidence rates. While the age-specific prevalence of myocardial infarction and stroke decreased in the cohort across sequential birth cohorts, there was an increase in diabetes prevalence in later birth cohorts. However, adjusting for changes in prevalence of cardiovascular diseases did not change the results. Additionally, in the more recent birth cohort, there was a higher proportion of African-American and Hispanic individuals, as well as higher years of education and baseline cognitive status. None of these changes explained the decreased dementia incidence.

■ COMMENTARY

Although earlier studies found no significant changes in dementia incidence for cohorts followed before 1990, the major findings from this study are consistent with more recent studies that also found decreased dementia incidence, particularly in the United States and Western Europe. Of note, the analytic approach of this study differs from other recent studies by examining incidence of dementia according to year of birth, as opposed to dementia rates in specified age brackets enrolled during different periods. This should allow for more precise separation of age and cohort effects. Another strength of this study is the use of standardized diagnostic criteria applied to all participants across the study period in a community-based sample. Also, there was a high concordance with the clinical diagnosis and pathological changes found in the subset of subjects who received autopsy, giving confidence to the accuracy of the clinical diagnosis.

A significant limitation is the small number of dementia cases for the more recent birth cohorts. This is important as the largest effect in decreased dementia incidence was seen in this cohort. In addition, Derby et al could not distinguish between Alzheimer's disease and other age-related dementias. Furthermore, while the authors attempted to address whether improved cardiovascular risk factors contributed to the decreased dementia incidence, they used self-reported diagnosis as opposed to more direct measures such as hemoglobin A1c levels, which may lead to errors or bias in the data. The authors also did not address other factors that may be important in more recent birth cohorts, such as improved infection control and treatment, better nutrition, and other societal changes.

Additional studies clearly are needed to replicate these findings and, importantly, to identify any potential factors that contribute to decreasing dementia incidence. Moreover, it is unknown if this trend will continue, as a significant increase in the prevalence of obesity and related cardiovascular diseases in more recent birth cohorts may reverse any gains made. Although this study shows promise that dementia incidence may be decreasing, caution should be exercised before declaring any victory against the still rising tide of a dementia epidemic. ■

ABSTRACT & COMMENTARY

Blockade of CGRP for Migraine Prevention: Promising, but Not a Cure

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports no financial relationships relevant to this field of study.

SYNOPSIS: Blockade of calcitonin gene-related peptide in patients with chronic or episodic migraine results in the prevention of about two headache days a month compared to placebo.

SOURCES: Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med* 2017;377:2113-2122.

Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017;377:2123-2132.

Two papers, published simultaneously in *The New England Journal of Medicine*, evaluated two randomized, double-blind, placebo-controlled, parallel-group, industry-funded trials of monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) in the prevention of chronic or episodic migraine, using the molecule antagonist fremanezumab (Teva Pharmaceuticals) or the receptor antagonist erenumab (Amgen and Novartis), respectively.

In the paper authored by Silberstein et al, the two active fremanezumab treatment arms were either a one-time set of three injections of 225 mg per 1.5 mL at baseline or the baseline three injections followed by one injection of 225 mg at each week 4 and week 8. Up to 30% of patients could continue on a stable dose of one migraine-preventive medication. Of the 1,130 patients who were randomly assigned to fremanezumab quarterly (376), fremanezumab monthly (379), and placebo (375), 91-93% completed the trial. The mean change (± SE) in the average number of headache days per month within the 12-week intervention period compared to the baseline 28-day preintervention period was a decrease of 4.3 ± 0.3 days in the fremanezumab quarterly group, 4.6 ± 0.3 days in the fremanezumab-monthly group, and 2.5 ± 0.3 days in the placebo group ($P < 0.001$ for both comparisons with placebo). For the 12 weeks of the intervention, patients receiving placebo had an average of 10.4 ± 6.4 headache days compared to 8.5 ± 6.3 days for those receiving fremanezumab quarterly and 8.0 ± 6.3 days for those receiving fremanezumab monthly. There was a significant reduction in the average number of migraine days per month and in the use of acute medication, as well as a significant increase in patients who had a reduction of at least 50% in the average number of headache days per month. Evidence of hepatic dysfunction, including elevation of liver enzyme levels to three or more times the upper limit of the normal range, occurred in three patients in the placebo group (< 1%) and five patients in each of the fremanezumab groups (1%) ($P = 0.73$ for each fremanezumab group vs. placebo, and $P = 0.56$ for the combined fremanezumab groups vs. placebo). The levels reverted to normal without discontinuation of the intervention.

The results described in the report by Goadsby et al are from the screening (≤ 3 weeks of initial screening and a four-week baseline phase) and the treatment phase with a subcutaneous injection of either erenumab, at a dose of 70 mg or 140 mg, or placebo monthly (24 weeks). Although the initial protocol did not permit patients to take a migraine-preventive medication, an amendment

during the enrollment period allowed the concomitant use of one migraine-preventive medication. The mean number of migraine days per month at baseline was 8.3 in the overall episodic migraine population. Of the total of 955 patients who underwent randomization (317 to the 70 g erenumab group, 319 to the 140 mg erenumab group, and 319 to the placebo group), 89.8% completed the six-month, double-blind treatment phase population. The primary endpoint of change from baseline to months four through six in the mean number of migraine days per month was reduced by 3.2 in the 70 mg erenumab group and by 3.7 in the 140 mg group, compared with a reduction of 1.8 days in the placebo group ($P < 0.001$ for each dose vs. placebo). A 50% or greater reduction in the mean number of migraine days per month was achieved for 43.3% of patients in the 70 mg erenumab group and 50.0% of patients in the 140 mg group, compared with 26.6% in the placebo group ($P < 0.001$ for each dose vs. placebo). The number of days of use of acute migraine-specific medication was reduced by 1.1 days in the 70 mg erenumab group and by 1.6 days in the 140 mg group compared with a reduction of 0.2 days in the placebo group ($P < 0.001$ for each dose vs. placebo). There was significant improvement in physical impairment scores with treatment. There were no safety or trial completion differences between those treated and on placebo.

■ COMMENTARY

CGRP, an endogenous vasoactive neuropeptide, plays a key role in migraine pathophysiology, and has been studied as a treatment target for over a decade. CGRP receptors are found on first and second order trigeminal neurons and on smooth muscle cells in meningeal vessels. Levels of CGRP are increased in the blood of patients with a migraine, and injection of CGRP can induce a migraine-like headache. Initially, CGRP antagonists were studied to provide acute migraine relief, and in 2008, a large Phase III trial demonstrated the benefit of an oral CGRP antagonist for acute abortive treatment; however, use of the specific oral antagonist to prevent episodic migraine was associated with significant liver toxicity.[1] Now, the research focus is on blocking the CGRP molecule or receptor as a parenteral migraine preventive treatment. In 2014, published results of a trial of eptinezumab showed a significant decrease in migraine days after one infusion of the CGRP molecular antagonist.[2] Further clinical trials are ongoing. These currently reviewed trials of subcutaneous treatment with monoclonal antibodies to either the CGRP molecule or its receptor found a mean reduction of about two migraine days a month compared to placebo treatment.

However, CGRP receptors are ubiquitous, and CGRP, in its alpha and beta forms, appears to modulate a wide variety of physiological functions in multiple major organ systems. Although the trajectory of research into CRGP antagonism is showing improving results, the long-term effects and benefits of potentially decades of this migraine-preventive treatment in a population that is predominantly women of childbearing age will take years to determine. The patients recruited into these clinical trials appeared to have migraines refractory to usual preventive therapy. The mean benefit of the parenteral treatment, while significant, was not overwhelming and likely varies considerably over the wide range of migraineurs. Each individual migraine sufferer, and her insurance company, will have to decide if intermittent subcutaneous injections of CGRP is a treatment to be initiated early in the stepwise trials of preventive therapy or is treatment to be tried when other proven therapies fail. Like onabotulinum injections, cost probably will restrict insurance-covered use to those who have failed other therapies. Because so many individuals suffer from migraines, there will be a large population of potential therapeutic candidates, if CGRP antagonism becomes an approved preventive treatment in the near future. ■

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2. Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: A randomised, double-blind, placebo-controlled, exploratory phase 2 trial. *Lancet Neurol* 2014;13:1100-1107.

ABSTRACT & COMMENTARY

TBI in Prodromal Parkinson's Disease

By Harini Sarva, MD

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Dr. Sarva reports no financial relationships relevant to this field of study.

SYNOPSIS: This population-based study using Medicare data demonstrated that in the five years prior to diagnosis of Parkinson's disease (PD), when compared with age-matched controls, those who were diagnosed with PD had a higher incidence of traumatic brain injury (TBI). The TBI was rated as mild and concussive and was most often related to falls.

SOURCE: Camacho-Soto A, Warden MN, Searles Nielsen S, et al. Traumatic brain injury in the prodromal period of Parkinson's disease: A large epidemiological study using Medicare data. *Ann Neurol* 2017;82:744-754.

The authors of this population-based study assessed Medicare data for patients aged 66 to 90 years from 2004 to 2009. Longitudinal data were gathered to determine the frequency of traumatic brain injury (TBI) in those with prodromal Parkinson's disease (PD) (i.e., the period prior to diagnosis of PD vs. age-matched controls). Incident PD cases were those with the ICD-9 code 332.0. Atypical Parkinsonism was excluded based on individual ICD-9 codes. The ICD-9 code for TBI (V15.52) was used to determine the number of TBI cases in both groups during this period, and those incidents of TBI prior to this period were excluded. The primary endpoint was TBI up until PD diagnosis or control reference date. TBI was graded as mild or concussive and moderate/severe, and mechanisms of TBI included falls, motor vehicle accidents, and other mechanisms. PD patients (n = 89,790) were older than the control group, less likely to be smokers, more likely to be men, and had more comorbidities. In the five years preceding the first recorded PD diagnosis, there were 24,421 TBIs, with 18.6% occurring in those eventually diagnosed with PD and 6.52% occurring in controls. Of all the TBIs in both groups, 84% were characterized as mild/concussive. The most common cause of TBI in both groups (82% in those with PD and 74.4% in controls) was a fall followed by motor vehicle accidents. PD patients during the five-year prodromal period were at increased risk for TBI regardless of age and gender. Hazard ratios for TBI increased as time approached PD diagnosis, and the highest hazard ratios were in the year prior to diagnosis of PD.

■ COMMENTARY

Patients with PD have a higher risk of falls compared to age-matched controls. Having reliable predictors of falls can reduce morbidity and mortality in these patients. TBI as a prodromal PD marker may lead to more aggressive earlier treatment of PD with medical and physical therapies. Although the study was well powered and contained a considerable amount of demographic data, there are some important considerations. The time-frame of five years prior to the diagnosis of PD is not always reliable, as prodromal symptoms are not always accurately reported and none of the prodromal symptoms have a high enough sensitivity or specificity to individually predict PD. Also, we do not know if prodromal symptoms with higher sensitivities and specificities, such as rapid eye movement sleep behavior disorder, were ascertained during this five-year period to help determine if it is a true prodromal period. Next, as noted by the authors, some of these cases may be misdiagnosed as PD. They may have been atypical Parkinsonism, such as progressive supranuclear palsy, which in its early stages can appear quite similar to PD and is associated with early falls. Finally, PD is a clinical diagnosis based on motor features. If these features are subtle, those with PD may not have been diagnosed, thus misclassifying them as controls. Despite these limitations mainly derived from the use of ICD-9 data, the study demonstrates the importance of asking about early falls even in the most obvious cases, with the goal of reducing morbidity and mortality. ■

ABSTRACT & COMMENTARY

Isolated Amyloid Myopathy

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: Isolated amyloid myopathy is a rare disorder that can be distinguished from systemic amyloidosis with myopathy by clinical, biochemical, and muscle biopsy histologic criteria.

SOURCE: Liewluck T, Milone M. Characterization of isolated amyloid myopathy. *Eur J Neurol* 2017;24:1437-1445.

Amyloid myopathy is a rare and underdiagnosed disorder, unless muscle biopsy specimens are stained Congo red and evaluated with fluorescence optics. It is seen most often (75%) in patients with light-chain (AL) immunoglobulin amyloidosis, whether they have multiple myeloma, and presents with proximal weakness and elevated serum creatine kinase (CK) with or without dysphagia, myalgia, macroglossia, and enlarged muscles. Amyloid myopathy is also seen in familial amyloidosis with transthyretin and gelsolin mutations, whereas isolated amyloid myopathy occurs in limb-girdle muscular dystrophy type 2B (dysferlinopathy) and 2L (anoctaminopathy-5). Can isolated amyloid myopathy be differentiated from amyloid myopathy seen with systemic amyloidosis?

Patients seen at the Mayo Clinic between Jan. 1, 1998, and Sept. 20, 2016, and diagnosed with amyloid myopathy, defined by the presence of amyloid in intramuscular connective tissue or blood vessels on Congo red staining, were identified through the Mayo Clinic muscle biopsy database. They were classified as isolated

amyloid myopathy or systemic amyloidosis-associated myopathy, based on the absence or presence, respectively, of monoclonal gammopathy, extra-muscular amyloid deposition, organomegaly by examination or computerized tomography, and peripheral neuropathy, clinically or electrodiagnostically. Patients were excluded if they had a coexisting independent myopathy. Statistical analysis comprised the Fisher exact test to compare frequencies of findings, and the Mann-Whitney U-test to compare continuous variables between the two groups.

Among 52 patients included in the study, 14 had isolated amyloid myopathy and 38 had systemic amyloidosis, the former including eight anoctaminopathy-5, two dysferlinopathy, and four genetically unknown cases, and the latter comprising 32 immunoglobulin AL amyloidosis, four familial amyloid polyneuropathy (three due to transthyretin-encoding gene mutations and one gelsolin-encoding gene mutation), and two senile systemic amyloidosis cases. Compared to those with systemic amyloidosis, patients with isolated amyloid myopathy had a younger age of onset (median 41.5 vs. 65 years) and a longer duration of symptoms until diagnosis (median 60 vs. 17.5 months). Although muscle strength was similar in both groups, with proximal weakness being the most common pattern, muscle atrophy, particularly of the calf muscles, was seen only in those with isolated amyloid myopathy, who also had no dysphagia or weight loss (vs. 26% in systemic amyloidosis group). Compared to systemic amyloidosis, isolated amyloid myopathy patients demonstrated small collections of inflammatory cells on muscle biopsy (43% vs. 0%) and had CK elevation at onset (100% vs. 29%). CK elevation < 2.5 times the upper limit of normal was seen only in systemic amyloidosis-associated myopathy. Among patients with amyloid myopathy, 27% are isolated to muscle, are usually due to anoctaminopathy-5, and may be differentiated clinically from amyloid myopathy seen with systemic amyloidosis.

■ COMMENTARY

Caused by a point mutation of the transthyretin gene, of which almost 100 mutations have been identified,

Continued on page 40

Neurology [ALERT®]

Stroke Alert

By Matthew E. Fink, MD

Thrombectomy Is Effective Up to 24 Hours After Stroke – the DAWN Trial

SOURCE: Nogueira RG, Jadhav AP, Haussen DC, et al; for the DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2017; Nov. 11. doi: 10.1056/NEJMoa1706442. [Epub ahead of print].

At the International Stroke Conference in 2015, five separate randomized trials were reported and simultaneously published that definitively showed that endovascular thrombectomy with a stent retriever had a clinical benefit when it was performed within six hours after onset of stroke symptoms, with diminishing benefit as the interval between time of onset and thrombectomy increased. In the recently published DAWN trial, researchers studied a group of patients who had onset of symptoms more than six hours and up to 24 hours before enrollment and had a mismatch between neurological deficit and infarct size, using a novel imaging approach to determining mismatch. Many of these patients were so-called "wakeup strokes." Patients were enrolled and divided into two groups, < 80 years or ≥ 80 years of age, and were assigned randomly to thrombectomy plus standard care or to standard care alone. The primary endpoints were the mean score for disability on a utility-weighted modified-Rankin scale, which ranges from 0 (dead) to 10 (no symptoms or disability), and the rate of functional independence using the modified-Rankin scale at 90 days.

Patients were eligible for inclusion if they had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both, on either CT angiography or MR angiography. In addition, they had to show a mismatch between the severity of the clinical deficit and infarct volume. In the group of patients ≥ 80 years of age, a score of 10 or higher on the NIH stroke scale and infarct volume of < 21 mL indicated mismatch. In those < 80 years of age, mismatch was defined as a score of 10 or higher on the NIH stroke scale, and an infarct volume of < 31 mL. Infarct volume was measured by either diffusion-weighted MRI or perfusion CT.

A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group. At 31 months, enrollment in the trial was stopped because a prespecified interim analysis demonstrated significant differences in outcome between the groups. In the thrombectomy group, the utility-weighted modified Rankin scale at 90 days was 5.5 compared to 3.4 in the control group, with high statistical significance. The rate of functional independence at 90 days was 49% in the thrombectomy group compared with 13% in the control group, also highly statistically significant. There was no significant difference in 90-day mortality (19% vs. 18%), and the rate of symptomatic hemorrhage did not differ significantly between the groups (6% in the thrombectomy group and 3% in the control group).

In conclusion, among a group of ischemic stroke patients last known to be well six to 24 hours earlier and who had a mismatch between clinical deficit and infarct size, outcomes regarding disability and functional independence were better if treated with mechanical thrombectomy, rather than standard care alone. ■

Continued from page 39

transthyretin familial amyloid neuropathy (TTR-FAP) is rare, but is the most disabling hereditary neuropathy of adult-onset, fatal if untreated, affecting sensorimotor and autonomic function, as well as the eyes, heart, kidneys, and other organ systems. Seen worldwide, there is considerable phenotypic variability and course severity, depending on the particular point mutation. Early initiation of the TTR stabilizer tafamidis delays neuropathy progression in early-onset Val30Met TTR-FAP, and is the first-line therapy for stage 1 disease. Phase III clinical trials are ongoing using TTR gene silencing, which affects both mutant and wild-type TTR production, with results expected soon. Further research to allow early diagnosis, and early intervention, remains crucial. ■

CME QUESTIONS

1. **Which of the following statements regarding glioblastoma is *false*?**
   a. Standard treatment includes surgical resection and radiation therapy.
   b. Temozolomide given concurrently with radiation improves survival.
   c. Adjuvant therapies, such as bevacizumab, improve survival.
   d. Epileptic seizures are common in patients with glioblastoma.
   e. Less than 10% of glioblastoma patients survive more than two years.
2. **In the study population from the Einstein Aging Study, which of the following was associated with a significant decrease in the incidence of dementia?**
   a. Higher mean years of education
   b. Lower prevalence of myocardial infarction and stroke
   c. Change in racial/ethnic diversity
   d. Birth after mid-1929
3. **Which of the following statements about blockade of calcitonin gene-related peptide (CGRP) is true?**
   a. CGRP blockade is restricted to receptor antagonism.
   b. CGRP antagonists decrease the number of headache days by about two a month compared to placebo.
   c. Both oral and parenteral agents show promise in migraine prevention.
   d. Because CGRP is a central nervous system-specific molecule, there are no potential systemic effects of its blockade.
4. **Which of the following is *not* true regarding the results of the study of Parkinson's disease (PD) and traumatic brain injury (TBI)?**
   a. Patients with PD were at a higher risk of falls when compared with controls.
   b. PD patients were older, more likely to be men, and less likely to be smokers.
   c. The most common mechanism of TBI was motor vehicle accidents.
   d. The highest hazard ratio for TBI was in the year preceding PD diagnosis.
5. **Compared to amyloid myopathy seen with systemic amyloidosis, patients with isolated amyloid myopathy:**
   a. have no dysphagia.
   b. have no weight loss.
   c. demonstrate small collections of inflammatory cells on muscle biopsy.
   d. All the above
   e. None of the above
6. **The DAWN trial showed that mechanical thrombectomy results in better functional outcomes after ischemic stroke than does intravenous thrombolysis.**
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

[IN FUTURE ISSUES]

Update on Multiple Sclerosis