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INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD, is a retained consultant for MAQUET. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Controlling Diabetic Neuropathic Pain

ABSTRACT & COMMENTARY

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: *Three common medications — amitriptyline, duloxetine, and pregabalin — all appear equally efficacious in treating neuropathic pain from diabetic neuropathy.*

Source: Boyle J, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain. *Diabetes Care* 2012; Sept 18 (Epub ahead of print. http://www.ncbi.nlm.nih.gov/pubmed/22991449).

Among the 246 million diabetics worldwide, approximately 20-30 million are at risk for polyneuropathy. More than 80% of patients with diabetic polyneuropathy have the distal, symmetric form, which is painful in 16%, unreported in 12.5%, and untreated in 39%. Relief is desperately sought. Which agent works best?

Type 1 and type 2 diabetics who were ≥ 18 years of age and had neuropathic pain manifested by lower extremity allodynia, dysesthesiae, hyperalgesia, and burning or lancinating pain were recruited to participate in a double-blind, randomized, placebo-controlled, parallel group trial of low-dose, followed by higher-dose, pregabalin, amitriptyline, and duloxetine. Low doses comprised amitriptyline 25 mg bid, duloxetine 60 mg qd, and pregabalin 150 mg bid, whereas high doses comprised amitriptyline 25 mg qAM and 50 mg qhs, duloxetine 60 mg bid, and pregabalin 300 mg bid. Diagnosis of painful neuropathy was confirmed with a score of > 12 on the Leeds Assessment of Neuropathic Symptoms and Signs, and exclusionary criteria included drug abuse, pregnancy, breastfeeding, recent cardiac or cerebral ischemic events, recurrent hypoglycemic episodes requiring third-party assistance, or end-stage disease of a major organ system. Subjective pain, assessed by the Brief Pain Inventory, was the primary outcome measure. Secondary outcomes measures, including quality of life, measured by the short-form, 36-item general health survey, and

VOLUME 31 • NUMBER 3 • NOVEMBER 2012 • PAGES 17-24

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subjective sleep, mood, and daytime sleepiness, assessed by the Leeds Sleep Evaluation Questionnaire, the Linear Analog Rating Scale, and the Karolinska Sleepiness Scale. Daytime functioning was evaluated during a 2-day inpatient period using a psychometric test battery including continuous tracking, choice reaction time, central nervous system arousal and information processing, Stroop task, digit symbol substitution testing, and working and explicit memory tasks. Statistical analysis comprised a preplanned statistical analysis plan, with statistical significance set at $P < 0.05$.

Among 83 patients enrolled and randomized between February 2007 and March 2009, 65 completed all treatment periods, with 27 randomized to pregabalin and 28 each to amitriptyline and duloxetine. No significant difference between treatment groups was found for the primary outcome of subjective pain. Pregabalin facilitated falling asleep and improved sleep continuity, but no significant differences between treatments were appreciated for any of the sleep components. Duloxetine significantly reduced sleep time and increased wake time, but nevertheless enhanced central nervous system (CNS) arousal and performance on sensory motor tasks. Duloxetine (60 and 120 mg) was associated with a small but significant decrease in nocturnal blood glucose, whereas pregabalin (600 mg only) was associated with a small but significant increase in nocturnal blood glucose. No serious adverse events were felt to be due to the study medication. Pregabalin, amitriptyline, and duloxetine are equally efficacious in reducing diabetic neuropathic pain, but sleep is improved with pregabalin.

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
VICE PRESIDENT AND GROUP PUBLISHER: Donald R. Johnston

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.coplin@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

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■ **COMMENTARY**

Microgliosis denotes the process whereby microglia, the CNS macrophages, respond to pathogens or injury by proliferating and altering their surface proteins, gene expression, and morphology. When peripheral nerves are injured, microgliosis occurs within the dorsal and ventral horns of the spinal cord, where these nerves terminate, as well as in the thalamus, hypothalamus, rostral ventromedial medulla, and periaqueductal grey. Mediators such as neuregulin-1, MMP-9, CCL2, and fractalkine induce this microglia transformation, as may tissue injury products including ATP, misfolded proteins or nuclear factors, complement components, and reactive oxygen species. These mechanisms, in part, explain chronic pain as a consequence of peripheral nerve injury, and blocking the microglial response can prevent injury-induced hypersensitivity in animal models. However, not all models of peripheral neuropathic pain evoke such a significant immune response in the CNS, and the extent to which CNS inflammation occurs in human peripheral neuropathic pain remains to be elucidated.[1] ■

Reference

1. Calvo M, et al. The role of the immune system in the generation of neuropathic pain. *Lancet Neurology* 2012;11:629-642.

Should Patients with Multiple Sclerosis Avoid IVF?

ABSTRACT & COMMENTARY

By Susan Gauthier, MS, DO

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Gauthier reports she receives research support from EMD Serono, Biogen Idec, and Novartis Pharmaceuticals, and is on the speakers bureau for Biogen Idec and Teva Neurosciences.

Synopsis: *Multiple sclerosis (MS) relapse rates were found to increase post in vitro fertilization (IVF) in a small population of MS patients. The risk for relapse was highest in the first 3 months post-IVF.*

Source: Michel L, et al. Increased risk of multiple sclerosis relapse after in vitro fertilization. *J Neurol Neurosurg Psychiatry* 2012;83:796-802.

A HORMONAL INFLUENCE OVER DISEASE ACTIVITY IN PATIENTS with multiple sclerosis (MS) has been best demonstrated through a relative protective effect of pregnancy, which is then followed by an increase in relapse rate in

the months following delivery. In light of this observation and that assisted reproductive technology (ART), specifically in vitro fertilization (IVF), has become more widely available, the question of how IVF may affect MS is a legitimate concern. Michel et al recently reported on the first comprehensive study to address the potential effect of IVF on MS disease activity.

This retrospective study of 32 women recruited from either the French public hospital database or through private referrals from local neurologists analyzed two main outcomes: 1) the difference between the number of relapses before and after the IVF procedure during two similar time intervals (i.e., 3 months pre-IVF compared to 3 months post-IVF), and 2) the association between IVF and the time between two relapses (i.e., a multivariate analysis to determine the effect of IVF on relapses when controlling for all relapse time intervals experienced throughout the disease course). The two pools of patients were well matched to prevent selection bias and, importantly, the recruitment procedure was controlled for in all statistical models. The majority of the patients had never received treatment for their MS, their mean age was 26.3 years, and disease duration was relatively low, at a mean of 6.6 years. The annualized relapse rate (ARR) was significantly increased to 1.6 at 3 months post-IVF compared to the 3-month pre-IVF period (0.80). For those patients who had a relapse, the mean time to a relapse post-IVF was 42.2 days. If the time was extended to 6 months post-IVF, the ARR was increased as compared to the corresponding time pre-IVF but was no longer significant. Importantly, in the multivariate analysis, when controlling for all relapse time intervals (throughout the course of each patient's disease), there remained a risk of a relapse with IVF (relative risk [RR] = 1.18); however, it was no longer significant. Of the 70 total IVF procedures, 49 failed and 21 resulted in pregnancy. There was a significant risk of post-IVF relapse (RR = 1.67) in patients with a failed outcome; however, these patients had higher pre-IVF ARR (0.98) compared to the pre-IVF ARR in those with success (0.38). Patients who were treated with GnRH agonists had a higher post-IVF ARR (1.6) as compared to those treated with GnRH antagonist (0.84). However, the type of GnRH treatment was not found to be significant in the multivariate analysis.

■ COMMENTARY

This is the first study to investigate the effect of IVF on MS disease activity. Although there are some obvious methodological limitations to the study, specifically the low patient number and a retrospective analysis, the statistical methods used were well thought out and appropriately applied. As clinicians caring for women with MS, the question of child-bearing is one that is often discussed and is rarely discouraged; however, there are obstacles that must be considered. One such obstacle is breastfeeding vs restarting treatment after delivery and the second obstacle concerns treatment options while attempting to conceive. The majority of women with MS discontinue therapy while attempting to conceive, which, depending on the patient, can be time-sensitive and anxiety provoking. ART, such as IVF, allows patients struggling with infertility to get pregnant and to resume MS treatment more quickly. This study suggests that clinicians should caution their patients regarding the possible risk of relapse associated with IVF. However, these results should be interpreted with caution. The risk of a relapse with IVF exposure was not found to be significant in the multivariate analysis after controlling for all relapse intervals. In addition, the effect of GnRH treatments failed to remain significant in the multivariate analysis; therefore, changing protocols would not be warranted by these data. Interestingly, IVF failures had a much higher pre- and post-IVF ARR, which suggests that active patients are more likely to fail IVF. All of the observations reported in this small study suggest that a larger, prospective study should be organized to further investigate the effects of IVF. In conclusion, MS patients who are stable and without a recent relapse can still safely consider IVF, but those with more active disease should achieve disease stabilization before proceeding. ■

BG-12: New Oral Medication for Relapsing-remitting MS

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal is a consultant for Biogen Idec and Genzyme, and is on the speakers bureau for Teva and Biogen Idec.

Synopsis: *Two recently reported Phase 3 trials for BG-12 demonstrated efficacy and safety in the treatment of relapsing-remitting multiple sclerosis.*

Sources: Gold et al, for the DEFINE Study Investigators. Placebo-controlled Phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098-1107.

Fox et al, for the CONFRIM Study Investigators. Placebo-controlled Phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;367:1087-1097.

BG-12, AN ORAL IMMUNOMODULATING AGENT, IS A FUMARIC acid ester, the active compound of which is dimethyl-

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, *MD, Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

A Simple Score Can Predict Outcome after Ischemic Stroke

Source: O'Donnell MJ, et al, for the Investigators of the Registry of the Canadian Stroke Network. The PLAN Score: A bedside prediction rule for death and severe disability following acute ischemic stroke. *Arch Intern Med* 2012;1-9. doi:10.1001/archinternmed.2013.30.

The investigators analyzed data from 9847 patients (4943 in the derivation cohort and 4904 in the validation cohort) hospitalized with acute ischemic stroke and included in the Registry of the Canadian Stroke Network from 2003 to 2008. Overall 30-day mortality was 11.5% in the derivation cohort and 13.5% in the validation cohort. In a multivariate model, nine clinical variables were identified as preadmission comorbidities and given a score (preadmission dependence = 1.5, cancer = 1.5, congestive heart failure = 1, atrial fibrillation = 1); reduced level of consciousness was given a score = 5, age was given 1 point/decade, and neurological deficit was scored as significant weakness of the leg = 2, significant weakness of the arm = 2, aphasia or neglect = 1. The maximum score was 25.

The PLAN score (preadmission comorbidities, level of consciousness, age, and neurologic deficit) identified patients who will have a poor outcome after hospitalization for acute ischemic stroke. In the validation cohort, the PLAN score predicted 30-day mortality (C statistic, 0.87), death or severe dependence at discharge (0.88), and 1-year mortality (0.84). The PLAN score also predicted good outcome (modified Rankin, 0-2) at discharge (C statistic, 0.80). ■

Mismatch Between Perfusion and Diffusion on MRI Can Identify Good Candidates for Endovascular Reperfusion Therapy

Source: Lansberg MG, et al, for the DEFUSE 2 study investigators. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): A prospective study. *Lancet Neurology* 2012;11:860-867.

There is a paucity of data from randomized, placebo-controlled trials of endovascular therapy (ET) in ischemic stroke resulting in uncertainty regarding its efficacy. In a prospective cohort study, the DEFUSE investigators, at eight centers in the United States and one in Austria, consecutively enrolled 138 patients scheduled to have ET within 12 hours of ischemic stroke onset. A

fumarate. Fumaric acid esters have been used for many years in Germany for the treatment of psoriasis. Although the exact mechanism of action is unclear, BG-12 is believed to have anti-inflammatory and antioxidative effects. After potential benefits in preclinical experiments and subsequent clinical trials in multiple sclerosis (MS), BG-12 underwent investigation in two large Phase 3 trials.

DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS Study) was a 2-year, placebo-controlled, double-blind, multicenter trial in which 1237 patients were randomized to BG-12 240 mg twice a day, BG-12 240 mg three times a day, or placebo in a 1:1:1 fashion. The study population was relapsing-remitting MS patients between the ages of 18 and 55 years who met the inclusion/exclusion criteria. The primary endpoint was the proportion of patients who had a relapse by 2 years. Twenty-seven percent of the patients in the BG-12 twice daily group and 26% in the BG-12 three times daily group had a relapse at 2 years compared to 46% in the placebo group ($P < 0.001$ for both comparisons). BG-12 met several secondary endpoints as well. The relative risk reduction for disability progression compared to placebo was 38% for the BG-12 twice daily group and 34% for BG-12 three times a day group, respectively. Both BG-12 groups were significantly superior to placebo in all the MRI endpoints, including new or enlarging T2-weighted lesions and number of gadolinium-enhancing lesions at 2 years.

CONFRIM (Comparator and Oral Fumarate in Relapsing-Remitting Multiple Sclerosis) was a 2-year multicenter, double-blind trial where patients were randomized in a 1:1:1:1 manner to BG-12 240 mg twice a day, BG-12 240 mg three times a day, glatiramer acetate 20 mg SQ once a day, or placebo. The glatiramer acetate arm was a reference comparator and the study was not designed to show a superiority or noninferiority of BG-12 over glatiramer acetate. In this study, 1430 patients were randomized and the primary endpoint was the annualized relapse rate (ARR) over 2 years. The ARR was 0.22 in the BG-12 twice daily, 0.20 in the BG-12 three times a

baseline MRI was performed within 90 minutes of the endovascular procedure and included diffusion and perfusion measurements using a standardized quantitative imaging analysis program, and patients were divided into those who had a diffusion/perfusion mismatch and those who did not have a mismatch. Reperfusion was assessed with a repeat MRI 12 hours after ET, and reperfusion was defined as a 50% reduction in the perfusion volume compared to baseline. The primary outcome measure was favorable clinical response, defined as improvement in the NIH Stroke Scale of ≥ 8. Secondary outcome was good functional outcome as assessed by the modified Rankin scale score of ≤ 2 at day 90.

Of the total group, 99 had all imaging and clinical data and could be fully evaluated according to the protocol. Reperfusion was successful in 46 of 78 (59%) with target mismatch and in 12 of 21 (57%) patients without target mismatch. The odds ratio (OR) for favorable clinical response to reperfusion was 8.8 (95% confidence interval [CI], 2.7-29.0) in the target mismatch group and 0.2 (0.0-1.6) in the no target mismatch group (P = 0.003). Reperfusion was associated with good functional outcome at 90 days (OR, 4.0; 95% CI, 1.3-12.2) in the target mismatch group, but not in the no target mismatch group. The study results strongly support the hypothesis that diffusion/perfusion target mismatch on MRI predicts a more favorable clinical outcome in patients with ischemic stroke who undergo endovascular reperfusion therapy. ■

Cerebral Microbleeds May Be Associated with Elevated Vascular Endothelial Growth Factor

Source: Dassam P, et al. Association of cerebral microbleeds in acute ischemic stroke with high serum levels of vascular endothelial growth factor. *Arch Neurol* 2012;69:1186-1189.

Cerebral microbleeds are found in about 30% of patients with acute ischemic infarcts, often in areas remote from the region of infarction. Histologically, they are found adjacent to small vessels affected by hypertension or amyloid angiopathy. One mechanism for their formation could be a more widespread microangiopathy with leakage of the blood-brain barrier, and vascular endothelial growth factor (VEGF) has been implicated in such a mechanism. The authors measured serum VEGF within 24 hours of acute ischemic stroke in 20 patients. The median levels of VEGF in the entire group of stroke patients was significantly higher than in a non-stroke control group. Five of the 20 ischemic patients had cerebral microbleeds on MRI, and median VEGF level in those patients was significantly higher than in the group without cerebral microbleeds (P = 0.003). This study raises several issues regarding the possible role of VEGF in the genesis of intracerebral hemorrhage, both spontaneous and in the setting of thrombolytic therapies. ■

day group, 0.29 in the glatiramer acetate group, and 0.40 in the placebo group. The ARR reduction was statistically significant for all treatment arms when compared to placebo (P < 0.001). The reduction in disability progression was not statistically significant in this study. All the treatment groups had a significantly reduced number of new or enlarging T2-weighted lesions, odds of having more gadolinium enhancing lesions, and new T1-weighted lesions on MRI when compared to placebo.

The overall incidence of adverse events was similar in the treatment arms and placebo in both studies. Adverse events that were more frequent with BG-12 were predominantly flushing and gastrointestinal symptoms including diarrhea, nausea, and abdominal pain seen in about 40% of patients on BG-12. The incidence of these events was highest in the first month with a significant decrease after that. There were no instances of life-threatening or opportunistic infections or malignancies. There was a mean drop in white blood cell counts and lymphocyte count in the BG-12 groups that plateaued at first year, but the mean values remained within the normal range. There was also an increased incidence of elevated liver enzymes within the first 6 months of starting BG-12.

■ COMMENTARY

BG-12 is an oral agent that has continued to demonstrate significant efficacy in the treatment of relapsing-remitting MS. There were no major safety concerns and no life-threatening or opportunistic infections or malignancies. BG-12 appears to have a good benefits-risk profile. As an oral medication, it also offers ease of administration and potentially increased adherence to recommended dosing. However, the incidence of flushing and gastrointestinal symptoms was about 40%, so tolerability within the first few weeks of use would need to be considered. Measures to mitigate the frequency and severity of flushing and gastrointestinal symptoms associated with its use are being explored. Overall, BG-12 has demonstrated a good safety profile, shows significant efficacy in relapsing-remitting MS, and will be an exciting new addition to the

armamentarium. It is currently under FDA review and is expected to be available by early 2013. ■

Predictors of Outcome in SCN1A-positive Dravet Syndrome

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD

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

Synopsis: *Early seizures and EEG abnormalities as well as status epilepticus predicts worse outcome in SCN1A-positve Dravet syndrome in this new, large cohort of patients.*

Source: Brunklaus A, et al. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. *Brain* 2012;135(Pt 8):2329-2336.

Severe myoclonic epilepsy in infancy (Dravet syndrome) represents approximately 5% of epilepsy syndromes that begin in infancy and is strongly associated with mutations in the sodium channel alpha 1 subunit gene (SCN1A). However, not all patients with SCN1A mutations have Dravet. Dravet syndrome is currently defined by the International League Against Epilepsy to have the following criteria: family history of seizures; normal development before onset; seizures that begin during the first year of life as generalized or unilateral febrile clonic seizures followed by later onset of myoclonic jerks and also often other partial, generalized and absence seizures; and EEG with generalized spike-waves and polyspike-waves, with early photosensitivity and focal abnormalities. In addition, the seizures in Dravet syndrome tend to be highly refractory to medication, status epilepticus is common, seizures exacerbate with hyperthermia, ataxia and pyramidal signs are common, and most children eventually will develop moderate to profound learning disabilities.

This study identified 355 Dravet cases pooled from a total of 1023 patients referred for SCNA1 testing. Patient information was obtained from a structured form submitted by the referring clinician. Of the children meeting criteria for Dravet, 241 (68%) had an SCN1A mutation and were included in further analysis. The authors estimate an incidence of 1 in 40,000 births in the United Kingdom. Missense mutations were the most common (46%), followed by nonsense (19%), and frameshift (8%). Twenty-nine percent had a family history positive for seizures. De novo mutations accounted for 104/115 (90%) of cases with parental data. Status epilepticus was noted in 80% and 72% had an episode of febrile seizures lasting longer than 10 minutes. The incidence of identified seizure types included generalized tonic-clonic seizures (94%), hemiclonic (72%), myoclonic (61%), complex partial (61%), and atypical absence (51%). The first seizure was precipitated by fever or illness in 58%, vaccination in 7%, bath in 2%, and 33% had no obvious precipitant.

Only 8/47 (17%) EEGs performed during the first 6 months of life were abnormal. In contrast, 30/38 patients (79%) had an abnormal EEG during the third year of life. Photosensitivity was present in 16% of all patients. The MRIs were normal in 89%. MRI abnormalities were mostly non-specific atrophy and temporal lobe changes. Valproate was most commonly reported to reduce seizure frequency (51%), followed by clobazam or clonazepam (34%) and topiramate (28%). Carbamazepine (60%) and lamotragine (43%) were reported to increase seizure frequency.

As expected, behavioral problems and developmental delay were common. Nearly all infants were classified as normal during infancy, and the median age at which developmental delay was first noted was 18 months. At the fifth year of life, however, only 10% of patients had normal development, and 70% had moderate or profound disability. By 15 years of age nearly all patients had, at minimum, moderate disability (15%) with the rest having severe (65%) or profound (20%) learning disability.

Using logistic regression, the authors found that the following clinical features predicted a worse developmental outcome: status epilepticus, interictal EEG abnormalities found during the first year of life, presence of a motor disorder, and early focal seizures with impairment of awareness. Mutation class, seizure precipitant, or MRI abnormalities did not contribute to predicting outcome.

■ COMMENTARY

Previous reports of prognostic information in Dravet syndrome have been relatively small with somewhat contradictory findings. Although limited by the reliance on structured referral forms as the main source of data, this study provides useful new information, particularly that status epilepticus, earlier seizures, and EEG abnormalities predict worse outcomes. Mutations in the sodium channel encoded by the SCN1A gene may be directly responsible for the cognitive dysfunction.[1] Thus, it still is not clear whether seizures are causative for encephalopathy or merely a marker of a more severe phenotype. In absence of other approaches, however, aggressive prevention and treatment of seizures in Dravet is warranted. In addi-

tion, this study adds yet more weight to using valproate as first-line therapy, although it is important to note that only stiripentol has been validated (as add-on therapy to valproate and clobazam) for use in Dravet in blinded, placebo-controlled studies.

Mutation type did not predict outcome, which is consistent with other studies that failed to show any genotype/phenotype correlations and is evidence of other genetic or environmental disease-modifying factors. Gene mutations besides SCN1A, for example protocadherin 19, also can cause Dravet syndrome, and it is likely that many more genetic causes of Dravet and other epileptic encephalopathy syndromes will be discovered. ■

Reference

1. Bender AC, et al. SCN1A mutations in Dravet syndrome: Impact of interneuron dysfunction on neural networks and cognitive outcome. *Epilepsy Behav* 2012;23:177-186.

Antibodies to Clustered Acetylcholine Receptor in Myasthenia Gravis

ABSTRACT AND COMMENTARY

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience, Director of the Peripheral Neuropathy Center, Weill Cornell Medical College

Dr. Latov has served a consultant to Grifols, Novartis, CSL Behring, Pfizer, Baxter Biotherapeutics, Elan Pharmaceuticals, and Eisai Inc. He owns stock in Therapath LLC, and is the beneficiary of a licensing agreement between Cornell University and Teva Pharmaceuticals.

Synopsis: *Up to 50% of patients with seronegative ocular myasthenia gravis have antibodies to clustered acetylcholine receptor antibodies that can fix complement and passively transfer disease to experimental mice.*

Source: Jacob S, et al. Presence and pathogenic relevance of antibodies to clustered acetylcholine receptor in ocular and generalized myasthenia gravis. *Arch Neurol* 2012;69:994-1001.

IN GENERALIZED MYASTHENIA GRAVIS, 80-85% OF THE PATIENTS have antibodies to the acetylcholine receptor (AChR) detected by the standard radio immunoprecipitation assay, and an additional 5-8% have antimuscle specific kinase (MuSK) antibodies. The remainder, approximately 10%, are considered to be seronegative. In ocular myasthenia, approximately 10% are seronegative or have no detectable

United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Neurology Alert	0 7 4 1 – 4 2 3 4	10/1/12
4. Issue Frequency	**5. Number of Issues Published Annually**	**6. Annual Subscription Price**
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Robin Salet; Telephone: 404-262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*: James Still, President and CEO, AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and complete mailing address)*: Leslie Coplin, same as above

Managing Editor *(Name and complete mailing address)*: Neill Kimball, same as above

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12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526,** October 1999 *(See Instructions on Reverse)*

13. Publication Title: Neurology Alert			14. Issue Date for Circulation Data Below: September 2012	
15.		Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a.		Total Number of Copies *(Net press run)*	840	797
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	(2)	Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
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h.		Copies not Distributed	127	130
i.		Total *(Sum of 15g. and h.)* ▶	840	797
j.		Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*	94%	94%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2012 issue of this publication. ☐ Publication not required.

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autoantibody activity. Proposed mechanisms included differential expression of fetal AChRs in the extraocular muscles or the presence of low-affinity antibodies that cannot be detected by the standard assay.

Using a newly developed immunofluorescence assay for detecting antibodies to clustered AChR on the surface of human embryonic kidney cells, the authors detected anticlustered AChR in 50% of previously seronegative patients with ocular myasthenia. The cells were transfected with recombinant AChR subunits in association with the clustering protein rapsyn, resulting in the expression of high-density AChR clusters, as occurs at the neuromuscular junction. This allowed for detection of antibodies with lower intrinsic affinities, whose apparent affinity would be enhanced by formation of stable bonds by both F(ab)s with neighboring AChR on the cell membrane.

Antibodies to AChR can bind, block, or modulate the receptor on skeletal muscle.[1] The anticlustered AChR antibodies were of the IgG1 subtype and were capable of activating complement. IgG binding and complement deposition correlated with the mean consecutive difference (jitter) on single-fiber electromyography, and passive transfer of purified IgG from two patients with clustered AChR antibodies into wild type or complement regulator-deficient mice reduced miniature end-plate potential amplitudes, with complement deposition at the end plates, providing further support for their pathogenicity.

In addition to providing a potentially more sensitive assay for anti-AChR for diagnosing ocular myasthenia gravis, these studies indicate that the anticlustered anti-AChR receptor antibodies are similar to non-clustered AChR antibodies that are typically present in patients with generalized myasthenia gravis, and they act by similar mechanisms. The anticlustered anti-AChR antibodies react with the adult form of the AChR rather than the fetal form, making it unlikely that differential expression of the fetal form of AChR plays a role. The studies also support a role for complement activation in the disease process, providing a rationale for testing novel agents that inhibit the complement cascade[2] as potential therapies. ■

References

1. Howard FM Jr, et al. Clinical correlations of antibodies that bind, block, or modulate human acetylcholine receptors in myasthenia gravis. *Ann NY Acad Sci* 1987;505:526-538.
2. Soltys J, et al. Novel complement inhibitor limits severity of experimental myasthenia gravis. *Ann Neurol* 2009;65:67-75.

CME Questions

1. In double-blind, placebo-controlled trials, which agent best controls pain in diabetic peripheral neuropathy?
a. Pregabalin
b. Amitriptyline
c. Duloxetine
d. All are equally efficacious in controlling the pain of diabetic peripheral neuropathy.
e. Pregabalin and amitriptyline are better than duloxetine in controlling the pain of diabetic peripheral neuropathy.

2. A higher post-IVF relapse rate was found in patients:
a. with IVF failure.
b. with longer disease duration.
c. given GnRH antagonists for IVF.
d. not on previous therapy for MS.
e. with IVF success.

3. Which of the following statements is *not* true regarding BG-12?
a. BG-12 is an oral medication for multiple sclerosis.
b. BG-12 has been shown to reduce long-term disability in multiple sclerosis patients.
c. BG-12 reduces the incidence of relapses compared to placebo.
d. BG-12 has anti-inflammatory properties.
e. BG-12 causes flushing and gastrointestinal upset.

4. Which of the following is *not* correlated with worse outcome in SCN1A-positive Dravet syndrome?
a. Early onset of developmental delay
b. MRI abnormalities
c. Status epilepticus
d. Motor dysfunction

5. Antibodies that are associated with myasthenia gravis include:
a. acetylcholine receptor (AChR) antibodies.
b. anti-muscle specific kinase (MuSK) antibodies.
c. anti-clustered anti-AChR antibodies.
d. All of the above

6. Clinical features of acute ischemic stroke upon hospital admission can predict long-term outcome.
a. True
b. False

7. Diffusion/perfusion mismatch on MRI does not predict good clinical outcomes after interventional reperfusion therapies.
a. True
b. False

8. Cerebral microbleeds are commonly seen on MRI after ischemic stroke.
a. True
b. False

In Future Issues:

Update on Epilepsy

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Volume 17, Number 11 Pages 21-22 November 2012

Secondary Prevention of Lacunar Stroke

Source: SPS3 Investigators. *N Engl J Med* 2012;367:817-825.

Lacunar strokes (L-CVA) are small subcortical brain infarctions that may comprise as many as 25% of ischemic strokes. Aspirin (ASA) monotherapy is already established as appropriate treatment for secondary prevention of ischemic stroke, as is clopidogrel (CLOP) monotherapy. In the CAPRIE trial, CLOP provided a *marginal* advantage over ASA for major adverse cardiovascular events (absolute risk reduction = 0.5%) in the overall study population, leading some to advocate clopidogrel routinely over ASA. It is often underrecognized that in the CAPRIE trial, study subjects who enrolled specifically because of previous stroke did *not* experience any statistically significant stroke reduction with CLOP compared to ASA; the outcomes were the same.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the first published trial to compare the efficacy of ASA monotherapy vs ASA + CLOP in reference to L-CVA. The study population included more than 30% Hispanics, concordant with the observation that L-CVA is more common in Hispanics.

At the conclusion of the trial (3.4 years mean), ASA + CLOP was *not* more effective than ASA alone in preventing L-CVA. Among the study population (n = 3020 adults with prior L-CVA), most new strokes were L-CVA (71%).

Unfortunately, as has been seen in other studies of combined ASA + CLOP, bleeding risk was significantly increased compared to ASA alone, as was all-cause mortality. Two prior trials in vasculopathic populations (MATCH, CHARISMA) have arrived at similar conclusions: For persons with stable non-acute vascular disease, ASA + CLOP is not more beneficial than ASA alone, but incurs greater bleeding risk. ■

Quality-of-life Effects of PSA Screening

Source: Heijnsdijk EA, et al. *N Engl J Med* 2012;367:595-605.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a clinical trial in which adult men (n = 162,243) were randomized to prostate-specific antigen (PSA) screening or no screening. While this trial did find a statistically significant reduction in prostate cancer deaths, overall mortality was not affected, supporting the current recommendations by the United States Preventive Services Task Force (USPSTF) that PSA screening be abandoned. Although the USPSTF decision was based on the "hard" data about mortality, there is likely also substantial quality-of-life (QOL) burden engendered from PSA screening, since many — indeed, the vast majority of — men diagnosed with prostate cancer through PSA screening will die with, not from, their prostate cancer. Additionally, adverse effects of intervention for (the mostly) early prostate cancer detected through screening are not uncommon, and include erectile dysfunction and incontinence. Finally, even in men who elect not to have a surgical intervention in response to prostate cancer detected as a result of PSA screening, it would take little imagination to envision substantial ongoing concerns/anxieties referable to that diagnosis.

Heijnsdijk et al report that per 1000 men screened by PSA, nine fewer prostate-cancer related deaths would occur and 73 life-years would be gained. After adjustment for overdiagnosis and overtreatment of prostate cancer subsequent to PSA screening, these benefits were reduced by almost one-fourth. In an era when PSA screening is no longer supported because of an insufficiently favorable risk:benefit ratio, recognition of the negative QOL impact of PSA screening may help clinicians (and their patients) better come to terms with the now well-recognized limitations of PSA screening. ■

PSA Elevations After Prostate Cancer Radiotherapy

Source: Crook JM, et al. *N Engl J Med* 2012;367:895-903.

Since prostate cancer (PCA) is often androgen-dependent, PCA recurrences after radiotherapy are often treated with androgen deprivation by means of regimens consisting of continuous luteinizing hormone-releasing hormone agonists (LHRHa) combined with antiandrogens. Unfortunately, such treatment is associated with hot flashes, decreased libido, urinary symptoms, and fatigue. Might intermittent androgen deprivation be equally effective, but less problematic as far as adverse effects?

Crook et al randomized patients who had undergone radiation treatment for PCA but had a post-treatment PSA > 3.0 ng/dL to continuous or intermittent androgen deprivation.

For overall mortality, intermittent androgen deprivation was non-inferior to continuous treatment. The time to development of castration-resistant disease (the stage at which androgen deprivation no longer represses disease progression) was significantly longer for intermittent treatment. Similarly, the adverse effects of hot flashes, libido, and urinary symptoms were all significantly fewer in the intermittent treatment group. In addition to necessitating a substantially reduced amount of medication (and of course, expense), intermittent androgen deprivation regimens are non-inferior for overall mortality, and are associated with superior quality of life. ■

Attenuated CV Benefits of Clopidogrel in Diabetes

Source: Andersson C, et al. *JAMA* 2012; 308:882-889.

There is no controversy over whether antiplatelet therapy (e.g., aspirin, clopidogrel, prasugrel) reduces cardiovascular (CV) events when used for secondary prevention (i.e., post-acute coronary syndrome, post-myocardial infarction [MI], post-stroke). It is equally apparent that risk reduction through antiplatelet therapy is not equal among all risk groups. For instance, although aspirin (ASA) consistently shows CV risk reduction in mixed populations post-MI, two clinical trials of ASA comprised solely of diabetics failed to show benefit. Diabetics are known to have greater platelet reactivity, and their platelets are relatively resistant to antiplatelet effects as measured by medication-induced platelet aggregation inhibition testing.

Comparative benefits of clopidogrel in diabetics vs non-diabetics have not been described well enough. To assess whether diabetics fare as well with clopidogrel post-MI as non-diabetics, Andersson et al reviewed data from the Danish nationwide administrative registries of patients discharged from the hospital post-MI (n = 58,851), of which 12% had diabetes.

One-year follow-up compared outcomes among all persons treated with clopidogrel. Although all groups did have CV risk reduction from clopidogrel treatment, there was a significant difference between diabetics and non-diabetics, favoring non-diabetics. For instance, the hazard ratio (HR) for all-cause mortality was more than twice as favorable for non-diabetics (HR = 0.75, a 25% reduction) than diabetics (HR = 0.89, an 11% reduction).

The obstacle of clopidogrel-resistant platelets can be overcome by dose intensification (i.e., more clopidogrel), combination therapy (i.e., clopidogrel + ASA), or consideration of another P2y12 agent (i.e., prasugrel). Unfortunately, however, each of these methods has been associated with an increased risk for bleeding. Optimization of antiplatelet therapy in diabetics remains somewhat elusive. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
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Is A1c Always the Best Game in Town to Monitor Type 2 Diabetes?

Source: Wright LAC, Hirsch IB. *Diabetes Spectrum* 2012;25:141-148.

Even as time-honored a metric as A1c has limitations. There are, for instance, situations in which A1c can markedly mis-estimate actual sustained glucose concentrations. Since A1c measurement requires hemoglobin to be exposed to excess glucose for the entire life of a red cell (90-120 days), anything that shortens red cell life (e.g., thalassemia, Hgb C, HbS, hemolysis) will *underestimate* actual sustained glucose levels (since red cells don't live long enough to become fully glycosylated). Hemoglobin F, which is persistent in a small percentage of adults, glycosylates so rapidly that even very modest elevations of glucose can induce marked elevations of A1c (A1c 12%-17% or greater), grossly *overestimating* sustained glucose levels.

Fructosamine is a composite measure of relatively short-lived serum proteins that have become converted into irreversible ketoamines, of which glycated albumin is the primary component (approximately 90%). Since this process occurs over a few weeks, red cell life span — shortened or not — has no impact. Similarly, however, the measurement of fructosamine only provides an observation window of the sustained glucose levels in the preceding 2-3 weeks. Any condition that alters serum protein turnover (eg, thyroid dysfunction, hypopoproteinemia, nephrotic syndrome) can invalidate fructosamine measurement.

Glycated albumin, the primary protein constituent of fructosamine, has been compared with A1c and fructosamine in patients with advanced chronic kidney disease, and found to be the most accurate marker in this population, although it is subject to the same perturbations as fructosamine mentioned above.

One other serum marker not used commonly in the United States, but widely used in Japan, is 1,5 anhydroglucitol (1,5-AG), which reflects sustained glucose over a 2-14 day period. Normally, 1,5-AG is reabsorbed by renal tubules; when plasma and urine glucose are high, they compete with 1,5-AG for reabsorption, resulting in loss of 1,5-AG in the urine, with a corresponding diminution in plasma 1,5-AG. This metric has been found to be particularly useful in measurement of postprandial glucose excesses.

For the time being, A1c will remain the metric of choice for most patients. When A1c and individual glucose measurements are discordant, consideration of another metric is appropriate. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■