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INSIDE

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PBT2 for the Treatment of Alzheimer's Disease

ABSTRACT & COMMENTARY

By Norman R. Relkin, MD, PhD

Director, Memory Disorders Program, and Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Relkin reports that he receives grant/research support from Baxter Bioscience, and is a consultant to Eisai, Pfizer, Myriad, and Smart Genetics.

Synopsis: *This novel agent, which inhibits interactions between beta amyloid (Aβ) and metal ions, holds promise as a therapeutic agent for Alzheimer's disease.*

Source: Lannfelt L, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting Aβ as a modifying therapy for Alzheimer's disease: A phase IIa, double-blind, randomized, placebo-controlled trial. *Lancet Neurology* 2008;7:779-786.

Results of a phase II clinical study of PBT-2, an orally administered anti-amyloid agent, suggest that altering the interaction of beta amyloid (Aβ) with the metal ions may be a viable way to treat Alzheimer's disease (AD). PBT2 is a second-generation metal-protein attenuating compound (MPAC) that is designed to reduce Aβ aggregation and toxicity by interfering with the association of the Aβ peptide with ions such as zinc and copper. PBT2 is a successor to clioquinol, a now defunct antifungal agent that was the first MPAC to be tested as a potential AD therapeutic. Clioquinol is neurotoxic at high doses and caused optic neuropathy, whereas PBT2 was designed to be more easily synthesized, safer, and improved in its metal-peptide attenuating effects.

This Phase IIa study of PBT2 was a double-blind, placebo-controlled trial in 78 patients with mild AD (mini-mental score = 20–26) who were given either placebo or one of two oral, daily doses of PBT2 (50 mg or 250 mg) for 12 weeks. There were no serious adverse events in this study. Patients treated with PBT2 had reduced CSF Aβ42 concentrations compared with those treated with placebo, but no differences in the concentrations of plasma amyloid or

serum zinc and copper. Among several tests of cognition administered, outcomes favoring the 250mg dose of PBT2 were found on two executive function subtests of the Neuropsychological Test Battery (NTB), namely Category Fluency and Trail-Making part B.

The investigators interpreted the changes in cerebrospinal fluid (CSF), but not plasma amyloid levels, after treatment, to indicate a specific effect on central processing of Aβ42. They concluded that the safety and tolerability of PBT2 were good and its further development as a potential AD treatment is warranted.

■ COMMENTARY

The concept that Aβ–metal interactions may be relevant to AD is less well known nor as widely accepted as the amyloid hypothesis itself. Zinc and copper ions are present in increased concentration in brain synapses, where they play important roles in neurotransmission and other functions. Binding of zinc or copper to Aβ makes these metal ions less available for physiologic functions and also fosters the formation of potentially toxic Aβ aggregates. PBT-2 is not a metal chelator but does function as an ionophore, making copper and zinc more available for normal neuronal function. By attenuating the interaction of Aβ with metals, it also reduces the formation of soluble and potentially toxic aggregates. These novel mechanisms of action distinguish PBT-2 from other anti-amyloid therapies now under development.

The stated primary goal of this Phase II study was to assess PBT-2's safety in treating mild AD. In that regard, this study was positive. In the PBT-2 Phase II trial, there were no serious side effects and no visual disturbances resembling the demyelinating optic neuropathy associated with its predecessor, clioquinol. Larger clinical trials will be needed to establish its safety.

PBT2 treatment also brought about changes in CSF Aβ consistent with an amyloid-related mechanism of action. No attempt was made to correlate the observed biomarker changes with clinical outcomes, leaving unresolved the question of whether changes in CSF amyloid brought about by PBT-2 are relevant to any therapeutic effect.

In the aftermath of the failure of the first two anti-amyloid agents to complete Phase 3 trials (tramiprosate and tarenflurbil), better outcome on two tests of executive function in a 12-week trial with multiple other cognitive measures is modestly encouraging. However, this trial was too short and involved an inadequate number of subjects to draw conclusions about clinical efficacy. Given PBT2's novel mechanisms of action, oral dosing, excellent tolerability, and the changes it invoked in CSF Aβ42 levels, this is an agent that could well find a place in future AD therapeutics if larger, longer-term trials prove positive. ■

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Gingko for Preventing Alzheimer's? Forget It

ABSTRACT & COMMENTARY

By Norman R. Relkin, MD, PhD

Director, Memory Disorders Program; Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Relkin reports that he receives grant/research support from Baxter Bioscience, and is a consultant to Eisai, Pfizer, Myriad, and Smart Genetics.

Synopsis: *Gingko biloba does not prevent Alzheimer's disease.*

Source: Dekosky S, Williamson JD, Fitzpatrick AL,et al. Ginkgo biloba for prevention of dementia: A randomized controlled trial. *JAMA* 2008;300:2253-2262.

TAKING GINGKO BILOBA EXTRACT DOES NOT PREVENT the development of dementia, according to a federally funded, prospective clinical trial involving more than 3,000 subjects. The U.S. multicenter Ginkgo Evaluation of Memory (GEM) trial recruited 3,069 community-dwelling volunteers age 75 years or older who were either cognitively normal or in a state of mild cognitive impairment at baseline. The subjects were randomly

assigned to receive either 120 mg of gingko biloba extract EGb 761 (Schwabe Pharmaceuticals) or an identical-appearing placebo twice a day. Participants received follow-up evaluations that included cognitive testing every 6 months for a median of 6.1 years.

There was a low overall drop-out rate from the study (6.3%) and no difference in discontinuations or side effects between the gingko-treated and placebo groups. A total of 523 subjects developed dementia over the course of the study — in most cases (92%), Alzheimer's disease (AD). There was no significant difference in the incidence of AD or other dementias among patients who took gingko (3.3 per 100 person years) versus those who took placebo (2.9 per 100 person years). There was no observed benefit associated with EGb 761, whether subjects tested normal initially or had mild cognitive impairment at baseline.

In an exploratory analysis, individuals taking gingko extract who had pre-existing cerebrovascular disease had a 56% increased risk of AD relative to patients given placebo. However, the authors caution that the study was not powered to examine interactions with cerebrovascular disease, and as such, that particular finding should not be considered conclusive.

In all, no evidence was found to support the use of gingko biloba extract EGb 761 for the prevention of dementia in individuals age 75 or older.

■ COMMENTS

Gingko biloba extract is a natural herbal derivative that has been purported to act as a memory enhancer and/or dementia preventative. The GEM study is the largest prospective trial to date of gingko biloba extract for dementia prevention, and its results are unequivocally negative. The study employed a well-characterized gingko biloba preparation (EGb 761) that contains known amounts of flavonoids and terpene lactones, substances that preclinical studies suggested might be beneficial in combating AD and other forms of dementia. While it could be argued that another preparation might still prove beneficial, EGb 761 is one of the few standardized formulations available. In addition, EGb 761 was used in previous studies that suggested gingko biloba has beneficial effects on memory loss.

The GEM study involved a large number of subjects, had excellent retention, and employed a sufficiently lengthy follow-up period to adequately test ginkgo's effects on dementia incidence. The selection of patients older than 75 years of age was a necessary expedient to obtain an adequate number of incident dementia cases. If longer use or younger populations are needed to observe benefits, it's unlikely that there will be sufficient enthusiasm to carry out such a study after the negative outcome of the GEM trial. Another large study (GuidAge) of EGb 761 for prevention of AD is currently being completed in France. The GuidAge study is also a placebo-controlled study of EGB 761 at a slightly higher dose (240 mg twice a day) in elderly subjects (mean age approximately 77) with initial memory complaints.

This initial GEM study report focuses on EGb761's effects on dementia incidence and does not further describe the cognitive outcomes. It is unlikely, but still possible, that gingko exerts beneficial effects on memory without affecting overall dementia incidence. Additional reports from the GEM and GuidAge studies can be anticipated that should clarify this issue. Based on the currently available findings, however, physicians should not recommend gingko biloba for dementia prevention. ■

A New Monoclonal Antibody in the Fight Against Multiple Sclerosis: Alemtuzumab

ABSTRACT & COMMENTARY

By Nancy Nealon, MD

Assistant Professor, General Neurology, Weill Cornell Medical College; Judith Jaffe Multiple Sclerosis Center, New York, NY.

Dr. Nealon reports that she serves on the speaker's bureau for Biogen Idec.

Synopsis: *The monoclonal antibody alemtuzumab, that targets the CD52 receptor on lymphocytes, reduced acute exacerbations and early disability by 70%.*

Source: The CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008:359:1786-801

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system of unknown etiology, with both genetic and environmental risk factors. Current disease-modifying therapies decrease the acute inflammatory activity, decrease relapses, and slow short-term disability progression. But all patients do not respond to the currently approved medications, and most patients develop disability over time. Better understanding of the disease process and more effective medications are needed.

Alemtuzumab is a monoclonal antibody that targets the

CD52 receptor on lymphocytes and monocytes. Annual IV administration depletes T lymphocyte counts for more than a year. B lymphocytes begin to recover about three months after the infusion. Early reconstitution of B lymphocytes may be the mechanism that explains new autoimmunity side-effects described with this drug.

The CAMMS223 trial investigators reported the results of a phase 2, randomized, controlled trial, that enrolled 334 treatment-naïve MS patients. The subjects were recently diagnosed patients with disease duration of less than three years and Expanded Disability Status Scale (EDSS) < 3. One third of patients received 12 mg of alemtuzumab, once yearly; one third received 24 mg, once yearly; and one third received interferon beta 1a, 44 micrograms, subcutaneous, three times per week for 36 weeks. The interferon arm is the current standard of care for early relapsing–remitting patients. Co-primary outcome measures of efficacy were time to sustained development of disability and relapse rate. Patients receiving either dose of alemtuzumab had the same response and side-effect profile, so the two groups were combined. Alemtuzumab decreased the risk of sustained disability by 71% and reduced the risk of relapse by 74%, compared to high-dose interferon beta 1a. Secondary end points included MRI measures of lesion burden measured by T2-weighted MRI scans, and showed a reduced lesion burden in the alemtuzumab group compared to the interferon-treated patients. A dramatic finding was the change in brain volume between treatment groups. Patients on alemtuzumab had an increase in brain volume on T1 images in scans from month 12 to month 36, while brain volume decreased in patients treated with beta interferon.

Serious toxicity occurred from new autoimmunity disorders. Twenty-five percent (25%) of patients on alemtuzumab developed thyroid antibodies and hyperthyroidism Four patients needed thyroid ablation by radioactive iodine, and 24 required antithyroid medications. Three percent (3%) of patients on alemtuzumab developed idiopathic thrombocytopenic purpura (ITP), and one had a fatal cerebral hemorrhage. The other patients with ITP recovered after steroid therapy and one, after treatment with rituximab. No serious opportunistic infections occurred during the trial.

■ **COMMENTARY:**

The study design of the CAMMS223 trial was developed from earlier use of alemtuzumab in small groups of secondary progressive and relapsing–remitting patients. MS is a chronic disease with an early relapsing–remitting phase causing minimal disability in 85% of patients. However, most patients enter a secondary progressive phase with increasing disability, and by 15–20 years after onset of disease, 50% of patients need a cane to ambulate. Axonal injury and loss causes long-term disability in these patients. Brain atrophy measurements are used as a surrogate marker for axonal loss, and disability in MS correlates better with brain atrophy than T-2 lesion load. Newer MRI techniques (MR spectroscopy, diffusion tensor imaging, functional imaging) and optical coherence tomography of the optic disc document axonal loss early in the disease process.

Current disease-modifying agents have decreased inflammation and relapse rate by one third, but the relationship to axonal loss and long-term disability is unknown.

If axons degenerate as a result of earlier inflammatory activity, early aggressive suppression of inflammation may prevent disease progression. If inflammatory activity and axonal loss are independent disease mechanisms, decreasing inflammation may slow the disease course but will not change the secondary progressive phase. Alemtuzumab suppressed inflammation in secondary progressive patients in a study by Coles.[1] It also reduced new gadolinium lesions by 90% over a period of 18 months, but failed to prevent progression of brain atrophy or disability as measured by the EDSS. Open-label use of alemtuzumab in 25 relapsing–remitting patients suggested disease stabilization. The idea that suppressing inflammation closer to disease onset might prevent progression led to the use of intense immunosuppression in newly diagnosed patients. In the CAMMS223 trial, alemtuzumab suppressed inflammatory activity and relapse rate in recently diagnosed patients with MS by 70% compared to high-dose interferon. Disability did not progress as measured by EDSS. More importantly, cerebral volume increased from months 12–36 in patients treated with alemtuzumab but not with beta interferon. This implies that early aggressive treatment of the inflammatory component of the disease may prevent axonal loss later on. These findings support the hypothesis that the early inflammatory lesions in MS may result in secondary axonal degeneration. Treating patients with intense immunosuppression at disease onset may be necessary to prevent later degeneration.

However, treating patients early with more potent monoclonal antibodies like alemtuzumab exposes active young patients to more serious, potentially life-threatening toxicity. Patients need to be aware of the risk/benefit ratios involved in these treatments. Longer follow-up will show whether this early treatment retains its efficacy. Continued surveillance is necessary for opportunistic infections, other autoimmune problems, and malignancy risk. ■

Reference

1. Coles AJ. The window of therapeutic opportunity in multiple sclerosis. *J Neurol* 2006:98-108.

IV Immunoglobulin in MS Patients with Corticosteroid Refractory Optic Neuritis

ABSTRACT & COMMENTARY

By Erik J. Kobylarz, MD, PhD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College, Cornell University

Dr. Kobylarz reports no financial relationship relevant to this field of study.

Synopsis: *The use of sustained pulsed dosing of intravenous immunoglobulin (IVIG) may be useful for treating multiple sclerosis (MS) patients with corticosteroid refractory optic neuritis.*

Source: Tselis A, Perumal J, Caon C, et al. Treatment of corticosteroid refractory optic neuritis in multiple sclerosis patients with intravenous immunoglobulin. *Eur J Neurol* 2008;15:1163-1167. Epub 2008 Aug 21.

PATIENTS WITH SEVERE VISUAL LOSS DUE TO OPTIC NEUritis (ON) that does not respond to conventional intravenous methyprednisolone (IVMP) treatment have limited therapeutic options. Tselis and colleagues performed an open-label, non-randomized, controlled prospective IVIG treatment trial of MS patients with corticosteroid refractory ON. They compared the treatment group to control patients who received only corticosteroids.

Twenty-three patients who received IVIG treatment were compared with 24 matched patients not receiving this medication. All patients had visual acuity of 20/400 or worse in the affected eyes. IVMP was administered to both groups for five days without oral prednisone taper. IVIG was administered between 60 and 90 days after the onset of ON after the patients were deemed to be IVMP failures. IVIG was administered for five days followed by once-monthly infusions for five months. There was significant improvement in the IVIG group with 18/23 (78%) subjects achieving near normal vision (20/30 or better). Only 3/24 (12.5%) from the control group responded similarly. In addition, there was improvement of the P100 latency in five patients in the IVIG treated group in whom the visual evoked potential test was repeated at one year after onset. In contrast, there was no improvement in the P100 latency of six patients in the control group one year after onset. The afferent papillary defect resolved one year after onset of ON in 19 of 23 (82%) IVIG patients, but in only four of 24 (17%) control patients. The investigators concluded that the use of IVIG with pulsed dosing, following corticosteroids, may be useful for treating IVMP refractory ON patients.

■ COMMENTARY

IVIG is an established therapy for demyelinating diseases of the peripheral nervous system. IVIG has been shown to promote remyelination in a mouse model of inflammatory demyelinating disease.[1] A meta-analysis of the four double-blind IVIG trials demonstrated that this treatment reduces the relapse rate and, possibly, disease progression in relapsing–remitting MS.[2] Pöhlau et al concluded from their study that monthly IVIG infusion could delay progression of disease in patients with primary–progressive MS, and that there was a trend in favor of IVIG treatment in patients with secondary–progressive MS.[3] Okada and colleagues found that intermittent IVIG successfully prevented relapses in their patients with neuromyelitis optica.[4] However, Roed et al found no effect of IVIG on long-term visual function six months following the onset of acute ON.[5] Fazekas et al demonstrated no significant benefit versus placebo in their multinational, randomized, double-blind, placebo-controlled, phase II trial of IVIG in patients with relapsing-remitting MS (RRMS).[6] Therefore, the efficacy of IVIG in ON and RRMS remains uncertain at present.

The results of this small study by Tselis et al suggest that there may be a beneficial effect of IVIG in MS patients with ON. However, the authors correctly note several limitations of their study. The open-label, non-randomized design introduces unavoidable bias. In addition, the population is skewed, since the patients selected were those without any improvement of their visual acuity at three months after treatment with IVMP, which is atypical for most patients who experience ON. Lastly, visual acuity was used as a measure of afferent visual function, which is likely not the best outcome measure for studying therapeutic effects in ON. Contrast sensitivity, color vision, visual fields, and possibly optical coherence tomography would be better indicators of optic nerve recovery.

As the authors note, a large-scale, double-blind, placebo-controlled, prospective trial is indicated to confirm these results and to help determine which specific patients with severe ON may benefit from IVIG treatment. Such a study should be performed, since the previous studies yielded mixed results and treatment with IVIG is quite costly. Further experimental data in com-

bination with clinical experience will assist in defining the specific mechanisms by which IVIG suppresses the central nervous system demyelination disease process and will clarify any future indications for IVIG treatment in ON and MS. ■

References

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Can Denture Cream Cause Neurological Disorders?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

Dr. Safdieh reported that he received grant/research support from the American Academy of Neurology.

Synopsis: *Excessive use of denture cream, which contains high concentrations of zinc, may cause copper deficiency nervous system syndromes.*

Source: Nations SP, Boyer PJ, Love LA, et al. Denture cream: An unusual source of excess zinc, leading to hypocupremia and neurological disease. *Neurology* 2008;71:639-643.

Over the past few years, copper deficiency has been reported as a cause of various neurological syndromes, most commonly a myelopathy with or without neuropathy, similar to subacute combined degeneration. Other syndromes reported with copper deficiency include optic neuritis and motor neuron disease-like syndromes. The most commonly reported causes of copper deficiency include dietary deficiency, gastrointestinal surgery and malabsorption syndromes.

Excessive ingestion of zinc has also been reported to cause copper deficiency. An elevated level of intestinal zinc induces upregulation of metallothionen, a copper binding protein. Copper is then sequestered in the intestine, not absorbed, and is excreted in the stool. As clinicians, we take advantage of this process by treating Wilson disease with zinc sulfate to treat copper overload.

The authors of this study report four patients with various neurological syndromes who all used excessive amounts of denture cream. The syndromes demonstrated by the patients included myeloneuropathy with poor cognition, motor neuron disease-like illness, and dorsal column myelopathy with and without neuropathy. All of these patients demonstrated significantly decreased serum copper and ceruloplasmin levels as well as elevated serum levels of zinc. All patients had normal serum B12 levels and no intramedullary spinal cord abnormalities on MRI. All patients used two or more tubes of dental cream per week, which is much higher than should be used if following the product labeling. All patients were treated with copper supplementation. The three patients who demonstrated some degree of improvement also stopped using denture cream. One patient continued to use denture cream and did not improve.

The authors also performed metallurgic analysis of major brands of denture cream to determine the concentration of zinc, and determined that there were indeed very high levels of zinc in the creams. They calculated that the affected patients were exposed to approximately 330 mg of zinc per day, much higher than the recommended allowance of 8–11mg per day. They hypothesize that the high zinc exposure caused the copper deficiency syndromes. They noted that a direct toxic effect of zinc could not be excluded, but was unlikely.

■ COMMENTARY

This paper should interest the general neurologist encountering patients with myelopathy or myeloneuropathy when no identifiable cause, such as B12 deficiency or a demyelinating disorder, is found. Patients presenting with these syndromes should be asked about their use of denture creams. The authors note that a standard tube of denture cream should last 3–10 weeks with

recommended use. If patients are using significantly more than that amount, they should be screened with serum copper, zinc, and ceruloplasmin levels. It is not known if excess zinc ingestion may also cause cognitive impairment in the elderly, since this group uses denture cream very commonly. This condition is likely rare, but it is quite important for neurologists to be familiar with as it is treatable and potentially reversible with cessation of denture cream use and copper supplementation. ■

Amyloidosis and Neuropathy

ABSTRACT & COMMENTARY

By Michael Rubin, MD, FRCP(C)

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Dr. Rubin reports that he receives grant/research support from Pfizer and is on the speaker's bureau of Athena Diagnostics.

Synopsis: *Generalized autonomic failure (GAF) in the presence of a sensory neuropathy strongly suggests amyloidosis.*

Source: Wang AK, Fealey RD, Gehrking TL, et al. Patterns of neuropathy and autonomic failure in patients with amyloidosis. *Mayo Clin Proc* 2008;83;1226-1230.

WHAT FORMS OF NEUROPATHY AND WHAT PATTERNS OF autonomic failure may result from amyloidosis? To answer these questions, a retrospective chart review was undertaken at Mayo Clinic, Rochester, of all patients seen between January 1, 1985 and December 31, 1997, who had biopsy-proven amyloidosis and also had undergone autonomic testing. Sixty-five patients were captured, including 45 men and 20 women, with a mean age of 63 years (range 32–79 years). Amyloidosis was biopsy-proven by tissue from nerve, fat, skin, liver, stomach, colon, or flexor retinaculum. Neuropathy was diagnosed and characterized as either polyneuropathy, defined as distal weakness with vibratory and deep tendon reflex loss, or small-fiber, characterized by distal burning pain, loss of temperature or pain sensation with spared deep tendon reflexes, and relatively intact vibratory and position sensation. Autonomic symptoms included pupillary, secretomotor, vasomotor, orthostatic, gastrointestinal, genitourinary, or sexual dysfunction. Autonomic testing comprised the autonomic reflex screen (ARS), encompassing adrenergic, cardiovagal, and sudomotor function, the results of which produced a composite autonomic severity score (CASS) ranging from 0 (normal) to 10 (severe autonomic failure). Tests included the quantitative sudomotor axon reflex test (QSART), heart response to deep breathing, the Valsalva maneuver, and tilt-table testing of blood pressure and heart rate response. Statistical analysis included the two-sided Wilcoxon rank sum tests and the Wilcoxon signed rank test, with $P<0.05$ considered significant.

Systemic light-chain amyloidosis was diagnosed in 43 (66%) and familial amyloid polyneuropathy (FAP) in 22 patients (34%). Other than one instance of concomitant B12 deficiency that did not improve with replacement therapy, no other cause of neuropathy or autonomic failure was identified in any patient. Autonomic symptoms most commonly comprised orthostatic (74%) and gastrointestinal symptoms (71%), and less often secretomotor (54%), genitourinary (39%), erectile (67% of men only), vasomotor (26%), or pupillary (25%). Four patients (6%) had no autonomic symptoms. Median CASS scores were 3 for adrenergic and cardiovagal testing and 2 for sudomotor testing. Axonal sensorimotor polyneuropathy was found on nerve conduction studies in 49 of 52 (94%) studied. Overall, five patterns of neuropathy and autonomic failure were disclosed: generalized autonomic failure (GAF) with polyneuropathy and pain (62%); GAF with polyneuropathy without pain (17%); GAF only (11%); polyneuropathy without GAF (6%); and GAF with small-fiber neuropathy (5%). Autonomic testing is warranted in patients with idiopathic polyneuropathy, as abnormal findings may be seen even in the absence of autonomic symptoms, leading to the early diagnosis and treatment of amyloidosis.

■ COMMENTARY

"All that glitters is not gold," and not all painful neuropathies with dysautonomia are due to amyloid, even in the presence of amyloid on biopsy.[1] Amyloid neuropathy was initially diagnosed in a 66-year-old woman with a 19-year history of progressive gait difficulties and painful distal paresthesiae. Bilateral Adie's pupils indicated autonomic involvement, but she denied dryness of the mouth or eyes, orthostatic hypotension, abnormal sweating, or other autonomic dysfunction. Periumbilical fat aspiration biopsy was positive for amyloid, resulting in initial misdiagnosis, but sural nerve biopsy ultimately ruled out an acquired amyloid neuropathy, and nucleotide sequencing demonstrated a Thr95Met mutation in the myelin protein zero (MPZ) gene, seen with CMT1B. Axonal MPZ gene mutations can perfectly mimic amyloid neuropathy. ■

Reference

1. Briani C, Adami F, Cavallaro T, et al. Axonal neuropathy due to myelin protein zero mutation misdiagnosed as amyloid neuropathy. *Muscle Nerve* 2008;38:921-923.

CME Questions

23. All of the following are true of PBT2 *except*:
a. It can act as a metal chelator.
b. It can reduce formation of toxic amyloid aggregates.
c. It can reduce CSF amyloid-42 levels.
d. It can make metal ions more available for synaptic function.

24. Ginkgo biloba is beneficial for:
a. Dementia prevention in normal elderly
b. Dementia prevention in mild cognitive impairment
c. Dementia prevention in patients with cerebrovascular disease
d. All of the above
e. None of the above

25. Alemtuzumab decreased relapse rate and disability progression in early MS patients compared to high-dose interferon by:
a. 10%
b. 30%
c. 70%

26. In Tselis et al, all of the following visual afferent indices significantly improved in the majority of patients after a severe episode of optic neuritis in the IVMP+IVIG treated group compared with those in the IVMP-alone treated group *except*:
a. Visual acuity
b. Relative afferent pupillary defect
c. Visual evoked potential P100 latency
d. Visual fields

27. Which of the following statements about denture cream is *incorrect*?
a. Denture cream contains high concentrations of zinc.
b. Normal use of denture cream (one tube every 3–10 weeks) is safe.
c. Zinc in denture cream is neurotoxic.
d. Excess zinc ingestion may cause copper deficiency.
e. Zinc excess/copper deficiency syndromes resemble B12 deficiency syndromes.

28. Patterns of neuropathy and autonomic failure in amyloidosis include:
a. Generalized autonomic failure with polyneuropathy and pain
b. Generalized autonomic failure with polyneuropathy without pain
c. Generalized autonomic failure only
d. Generalized autonomic failure with small-fiber neuropathy
e. All the above

Answers: 23. a; 24. e; 25.c; 26. d; 27. c; 28. e

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

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Update on Current Stroke Trials

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The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 14, NUMBER 1 PAGES 1-2 JANUARY 2009

Effective Combination Therapy for Acne

Source: Thiboutot D, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for once-daily treatment of moderate to severe acne vulgaris. *J Am Acad Dermatol* 2008;59:792-800.

TOPICAL AGENTS, BOTH AS MONOTHERapy and in combination, have shown efficacy in management of acne. Benzoyl peroxide (BPO) is one of the most commonly used agents, but despite excellent efficacy, the side effects of skin dryness, burning, erythema, and peeling are sometimes limiting effects of treatment.

Clinical trials of clindamycin phosphate (CMP) 1% + BPO have demonstrated that the combination is more effective than either agent alone, but traditional BPO concentrations (5%-10%) have been associated with dryness and irritation. Monotherapy comparisons of BPO 2.5% with BPO 5%-10% indicate similar efficacy, with better tolerability. Hence a clinical trial to establish the relative efficacy of CMP, BPO 2.5%, and the combination was a sensible next step.

Thiboutot et al randomized adolescents and adults (n = 2813) with moderate-to-severe acne to CMP 1%, BPO 2.5%, CMP + BPO, or placebo. Subjects were followed for 12 weeks. Outcomes included facial acne lesion counts as well as tolerability evaluation.

CMP + BPO was statistically significantly superior to CMP, BPO, and placebo at the conclusion of the trial. The tolerability of CMP + BPO was essentially the same as placebo (vehicle), and when adverse effects were reported, 97% were mild to moderate. My on-line search (Nov. 23, 2008) does not yet show availability of a CMP 1% + BMP 2.5% product, but FDA approval of this product (Acanya) occurred Nov. 20, 2008. ■

Genotypes associated with CRP elevations

Source: Zacho J, et al. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med* 2008; 359:1897-1908.

IT REMAINS UNCERTAIN WHETHER THE observed relationship between elevated CRP levels and adverse cardiovascular outcomes is causal. The question remains whether elevated CRP simply reflects the presence of inflammation or instead is etiologic in increasing the risk of endpoints. One way to elucidate the relationship is to evaluate persons who have gene polymorphisms that lead to elevated CRP levels.

Danish investigators identified genotypes associated with elevated CRP; a high-sensitivity CRP level of > 3.0 was defined as high. Several populations were available for comparison: the Copenhagen City Heart Study (n = 10, 276); the Copenhagen General Population Study (n = 37,690); and the Copenhagen Ischemic Heart Disease Study (n = 2238).

Overall, an elevated CRP was associated with an increased risk of ischemic heart disease (2.2 relative risk). However, when the population of individuals with genetic polymorphisms leading to elevated CRP was evaluated, there was no increased CV risk identified. If elevated CRP levels were causal in CVD endpoints, one would expect that persons with genetically influenced elevations would show a similar risk relationship as study groups with known CVD. The concluding statement of the authors summarizes their findings: "…the risk of ischemic vascular disease associated with higher plasma CRP levels observed in epidemiologic studies may not be causal, but rather that increased CRP levels are simply a marker for atherosclerosis and ischemic vascular disease." ■

Benefits of Extended Duration Detoxification

Source: Woody GE, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth. *JAMA* 2008;300:2003-2011.

MISUSE OF PHARMACEUTICAL OPIOIDS is increasing. Data from 2004 indicate that as many as 10% of high school seniors acknowledge prescription opioid use in the prior year. Although the majority of opioid misuse is sporadic, a substantial minority of young adults suffer opioid addiction, for which short-term (14 days) buprenorphine combined with naloxone (s-B/N) has shown some detoxification benefit. Whether a more extended e-B/N (e-B/N) program could reduce opioid addiction relapse was the object of this study.

Woody et al randomized opioid-addicted adults (n = 153) to either s-B/N (14 days) or e-B/N (12 weeks). The primary outcomes measure was the number of patients with opioid-positive urine drug testing (UDT) at week 12.

UDT was opioid-positive in 51% of s-B/N subjects, compared with 43% of the e-B/N group. Post-treatment outcomes at months 6, 9, and 12 showed no statistically significant difference in use

of opioids, alcohol, or marijuana between the groups; on the other hand, cocaine use was approximately half as common in the e-B/N group. Extending the duration of B/N treatment merits further study, based upon the favorable results of this trial. ■

CPAP for OSA in Metabolic Syndrome

Source: Dorkova Z, et al. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest* 2008;134: 686-692.

The association of obstructive sleep apnea (OSA) with adverse cardiovascular (CV) outcomes is strong. Encouraging data from persons with OSA who have been treated with continuous positive airway pressure (CPAP) have demonstrated that effective CPAP treatment reduces blood pressure. Whether CPAP might have favorable effects on other CV risk factors such as glucose, lipids, and markers of inflammation is less clear. Individuals with metabolic syndrome, who are at increased risk for CV events, provide an appropriate population to study the impact of CPAP treatment for OSA upon CV risk factors.

Dorkova et al studied 32 metabolic syndrome patients with OSA. At baseline and after 8 weeks of CPAP for OSA, risk factors associated with CVD were measured and compared: BP, cholesterol, triglycerides, HDL, fibrinogen, CRP, insulin resistance, and others. Subjects who used their CPAP for at least 4 hours nightly were considered compliant.

Compliant CPAP users enjoyed reduced BP, cholesterol, and insulin resistance. Non-compliant CPAP subjects (i.e., < 4 hrs/night) did not demonstrate these favorable changes. CPAP has been shown, in the high-risk group of patients with metabolic syndrome, to improve the CV risk factor profile. ■

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Uric Acid and CV Risk: Not Ready Yet

Source: Feig DI, et al. Uric acid and cardiovascular risk. *N Engl J Med* 2008; 359:1811-1821.

The relationship between uric acid (URA) and cardiovascular (CV) risk has been the subject of controversy for decades. Even if one were to fully accept that the various associations between URA and unfavorable CV outcomes have a causal relationship, the hurdle of prospectively proving that reduction of URA will improve outcomes has yet to be addressed.

URA elevation has been identified as a harbinger of hypertension, as well as obesity, diabetes, and kidney disease, but that may only be part of the story. For instance, that renal disease develops disproportionately in gouty patients is certainly true, but so does hypertension, which is more often the cause of renal disease than uric acid stones or urate nephropathy. The Framingham Heart Study suggests that the relationship of URA and CV risk is not independent of hypertension, hence, it does not qualify as an independent risk factor.

URA may play an etiologic role in development of metabolic syndrome. Even though insulin resistance is regarded by some as a *sine qua non* of metabolic syndrome, URA often precedes the insulin resistance; indeed, animal studies suggest that decreasing URA forestalls metabolic syndrome.

URA is also associated with vascular disease in the carotids and peripheral circulation. Some even attribute favorable CV effects seen in the LIFE study (utilizing losartan) to its favorable effects on lowering uric acid (losartan is the only antihypertensive agent known to lower uric acid).

The pathophysiologic underpinnings linking URA to CV misadventure have some plausibility. All-in-all, the relationship between URA and CV risk is tantalizingly close to compelling. However, even though we have expanded the old aphorism that "close only counts in horse shoes and hand grenades" to include archery, darts, lawn bowling, etc., close still doesn't count in science. ■

Documentation of Coronary Ischemia Prior to PCI

Source: Lin GA, et al. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008;300:1765-1773.

For the sake of discussion, let's momentarily agree that percutaneous coronary intervention (PCI) is an appropriate step for persons suffering symptomatic coronary artery disease. The reason to establish this premise is that whether PCI actually offers any meaningful advantage over simple medical management is a matter of great debate. Indeed, the majority of PCIs in the United States are performed for patients with stable coronary disease, despite lack of evidence that outcomes with PCI in this setting are superior to intensive risk factor modification combined with medical therapy. Guidelines for PCI in stable CAD patients suggest that documentation of ischemia (most commonly by treadmill testing) should be obtained prior to PCI.

This study looked at Medicare beneficiaries undergoing elective PCI to see how often PCI had been preceded by stress testing. Of 23,887 Medicare recipients who underwent PCI in 2004, slightly less than half had any record of stress testing within the 90 days immediately preceding their PCI. The authors comment that in the absence of corroboration of ischemia, PCI may have been performed in patients who may not have benefited. ■

PHARMACOLOGY WATCH

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

JUPITER: C-reactive Protein a Marker for CV Events?

In this issue: The JUPITER trial causes a stir; ACP practice guideline for antidepressant use; testosterone for low libido; continued shortage of Hib vaccine; FDA Actions.

The JUPITER trial causes a stir

Elevated high-sensitivity C-reactive protein (CRP) may help identify otherwise healthy patients with normal cholesterol levels who will benefit from statin therapy, according to the JUPITER trial published in November. Researchers randomized nearly 18,000 healthy men and women with normal cholesterol levels (LDL < 130 mg/dL) with CRP levels of 2.0 mg/L or greater to rosuvastatin (Crestor) 20 mg daily or placebo. The combined primary endpoint was myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular cause. The trial was stopped early at 1.9 years when the rate of the primary endpoint was found to be 0.77 per 100 person-years in the treatment group vs 1.36 per 100 person-years in the placebo (HR 0.56; 95% CI, 0.46-0.69; $P < 0.00001$). Overall, the rate of events was low in both groups: 142 of 8901 in the treatment group vs 251 of 8901 in the placebo group. The individual endpoints of myocardial infarction, stroke, and revascularization or unstable angina were all reduced by approximately 50% in the rosuvastatin group, LDL cholesterol levels were decreased by 50%, and CRP levels were decreased 37%. There was not a significant increase in myopathy or cancer in the treatment group, but there was a higher incidence of physician-reported diabetes. The authors conclude that in apparently healthy persons without hyperlipidemia but with elevated CRPs, rosuvastatin significantly reduced the incidence of major cardiovascular events (*N Engl J Med* 2008;359:2195-2207).

In an accompanying editorial, Mark Hlatky, MD, Stanford University School of Medicine, points out that although the relative risk reductions in the JUPITER trial were clearly significant, the absolute difference in risk was less impressive with 120 participants treated for 1.9 years to prevent one event. It is also difficult to know the role of CRP in risk stratification since patients with normal CRP levels were not treated and it is possible that lowering cholesterol with statins may benefit even those with low CRP levels. CRP may have a role in deciding whether to treat patients with intermediate risk, but it may be too early to use it to recommend treatment for those at low risk. Hlatky writes that "guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and long-term safety and cost" (*N Engl J Med* 2008;359:2280-2282). It is safe to say that JUPITER has been the subject of many lively discussions in hospital lunchrooms

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across the country. Whether the benefit of rosuvastatin can be generalized to all statins, whether CRP should be a standard part of yearly blood panels for adults patients, and whether everyone with an elevated CRP should be offered treatment with a statin are all questions that are being hotly debated and will need further evaluation.

ACP treatment guideline for antidepressants

The American College of Physicians has issued a practice guideline for the use of antidepressants to treat depressive disorders. The guideline encompasses the use of newer "second-generation antidepressants," including the SSRIs: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox). Also included were the SNRIs venlafaxine (Effexor), and duloxetine (Cymbalta), as well as other drugs such as mirtazapine (Remeron), bupropion (Wellbutrin), nefazodone, and trazadone. After reviewing 203 clinical trials, the guideline group concluded that there were no significant differences between the drugs with regard to efficacy. The guideline group recommends that second-generation antidepressants should be selected on the basis of adverse effect profiles, cost, and patient preference. They further recommend that clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1-2 weeks of initiation of therapy and that treatment should be modified if the patient does not have an adequate response to pharmacotherapy within 6-8 weeks. Finally, they recommend that clinicians continue treatment for 4-9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients with history of depression, a longer duration of therapy may be beneficial (*Ann Intern Med* 2008;149:725-733).

Testosterone for low libido: Questions remain

Low sexual desire is commonly reported by postmenopausal women. A new study suggests that testosterone replacement may be of benefit. Researchers randomized 814 postmenopausal women with hypoactive sexual desire or disorder to testosterone patches delivering 150 or 300 mg of testosterone per day or placebo. The primary endpoint was change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes. Safety outcomes were followed out to one year. At 24 weeks the primary endpoint was significantly greater in the group receiving 300 mg of testosterone per day than placebo (increase in sexually satisfied episodes of 2.1 vs 0.7, $P < 0.001$) but not in the group receiving 150 mg per day. Both doses of testosterone were associated with significant increases in desire and decreases in distress. The rate of androgenic side effects including unwanted hair growth was higher in the group receiving 300 mg per day. Breast cancer was diagnosed in 4 women who received testosterone vs none in the placebo group. The authors conclude that a testosterone patch delivering 300 mg per day results in modest but meaningful improvement in sexual function although the long-term effects of testosterone including effects on the breasts remain uncertain (*N Engl J Med* 2008;359:2005-2017). This study confirms previous reports that testosterone has a positive effect on sexuality in women. The rate of breast cancer, although not reaching statistical significance in this study, raises concern.

Continued shortage for Hib vaccine

The continued shortage of the *Haemophilus influenza* type b (Hib) vaccine has not led to an increase in *Haemophilus* infections according to the *MMWR*. It has been a year since the CDC recommended deferring the fourth dose of the Hib vaccine in healthy children (at 12-15 months of age) because of a shortage due to contamination concerns in the manufacturing process. Merck & Co. now reports that mid-2009 is a realistic date for normal production. The CDC has undertaken national surveillance for Hib infections including 748 cases in children < 5 years old. Of these, only 6% were clearly identified as serotype b (the most invasive strain of *Haemophilus*), although serotyping information was missing in nearly 40% of cases. The CDC is concerned because antibody levels fall 12 months after vaccination in children. In the U.K., where the fourth booster was not initially recommended, Hib infections rebounded after 12-15 months. CDC is recommending vigilance on the part of pediatricians and also is emphasizing that state and hospital labs should perform serotyping on all *Haemophilus* infections.

FDA Actions

The FDA has approved fesoterodine fumarate for the treatment of overactive bladder. The drug relaxes smooth muscle of the bladder reducing urinary frequency, urge to urinate, and sudden urinary incontinence. Fesoterodine fumarate will be available in 4 mg and 8 mg strengths for use once daily. The drug is manufactured by Schwartz Pharma and will be marketed as Toviaz . ■