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INSIDE

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IV Thrombolysis 3-4.5 Hours After Stroke: Time for a Change?

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

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

Synopsis: *Intravenous thrombolysis is safe and effective for the treatment of ischemic stroke in the time window of 3-4.5 hours after the onset of symptoms.*

Sources: Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-1329; Wahlgren N, et al. Thrombolysis with alteplase 3-4.5 h after acute ischemic stroke (SITS-ISTR): an observational study. *Lancet* 2008 Sept 12 [E pub ahead of print]

INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (tPA) for acute ischemic stroke benefits a tiny minority of patients due to its strict limitation to a 3-hour period following symptom onset. Until now, attempts to extend this narrow time window have failed. Clinical trials enrolling patients between 3 and 6 hours have produced negative results, and protocol violations (notably, "late" treatment) contribute to increases in hemorrhagic complications. Even under three hours, there is more benefit (nearly double) for tPA in the 0-90 minute than in the 90-180 minute time interval. As each moment elapses following stroke, our ability to help patients diminishes.

Despite these data, there has been a growing body of evidence that 3 hours may not be as strict a line in the sand as previously thought. In pooled analysis of the NIH tPA trial, the European ECASS trials, and two ATLANTIS trials, Hacke et al[1] showed that the odds ratio for benefit from tPA was 1.4 in the 180-270 minute time period. Although this was not as profound as for 0-90 minutes (OR 2.8) or for 90-180 minutes (OR 1.6), it was superior to the group treated between 270 and 360 minutes. Patients treated beyond 4.5 hours showed no benefit, but had increased hemorrhage and mortality rates.

Wahlgren and coworkers reported findings from the SITS-ISTR registry that examined 664 patients in the 3-4.5 hour range, and showed that these patients were equivalent to 0-3 hour patients,

spanning multiple endpoints including clinical outcome, mortality and hemorrhage rates. Of note, the patients treated in the SITS-ISTR "late" group were 3 years younger and had milder strokes (1 point lower on NIH-SS) than those treated early. Also, half of the patients treated late were actually treated only 15 minutes after the 3-hour window. Even more striking was that the 3-3.5 hour time window comprised 72% of SITS-ISTR patients, compared with 20% in the 3.5-4 hour period and only 8% in the final 30 minutes (4-4.5 hours).

Now Hacke et al, reporting for the ECASS III trial, provides randomized data to support the use of tPA in the 3-4.5 hour time period. ECASS included 821 patients assigned to tPA compared to placebo. A favorable outcome (defined as a score of 0-1 on the Rankin scale) was found in 52% of tPA-treated patients compared with 45% for placebo, for a statistically significant odds ratio of 1.34 (CI 1.02 to 1.76). Interestingly, this odds ratio nearly exactly matches that found in the previous pooled analysis for patients in this time period — a modest, but nevertheless, meaningful difference. The incidence of total hemorrhages in the tPA arm was 27%, compared with 17.6% for placebo; however, importantly, symptomatic hemorrhage rates in tPA-treated patients were only 2.4%. Although this was 10-fold higher than symptomatic hemorrhages in placebo-treated patients (0.2%), it was lower than the 6% symptomatic hemorrhage rate found in the NINDS study. Mortality did not significantly differ between tPA and placebo patients.

Patients with severe stroke (NIH Stroke Scale > 25) were excluded from this study, differentiating this study from the NINDS cohort and producing an overall milder stroke population. Mean NIH Stroke Scale in ECASS III was approximately 11, compared with 14 in NINDS. Overall rates of favorable outcomes were more than 10% higher in ECASS III tPA patients compared with NINDS, and this difference was nearly 20% in the placebo group.

■ COMMENTARY

As both the ECASS III study and its accompanying editorial emphasize,[2] these data are not an invitation to relax our efforts to trim door-to-needle times to the shortest possible time frame, or to forget that "time is brain" and every minute counts. To paraphrase the ECASS authors and the great Yogi Berra, "having more time does not mean we have more time." The true excitement of ECASS III is that we can hopefully extend the benefit of IV tPA for acute ischemic stroke to a larger cohort of patients.

It is likely that not every patient in the 3-4.5 hour time window will be an ideal candidate for IV tPA. Patient age will be a factor. Although IV tPA has been deemed safe for patients who are 80+ in observational studies, ECASS III did not include patients older than age 80 and the oldest patient enrolled in SITS-ISTR was 73. Stroke severity also will be important. Milder strokes might not justify the risk, while large strokes (such as complete middle cerebral artery syndromes), which were excluded from ECASS III, will still most optimally be treated with endovascular therapies such as mechanical clot extraction. Advanced imaging with MRI diffusion-perfusion or CT perfusion also might be helpful in defining patients who have an ischemic penumbra. Diabetes may be an additional limitation. Hyperglycemia has been shown to cause more complications among patients treated with tPA. ECASS III excluded patients with a prior history of diabetes and stroke, and thus had a lower incidence of diabetes than did NINDS.

It can be expected that the American Stroke Association and other governing bodies (such as the FDA) will modify recommendations for the treatment of stroke based on these data and that the labeling for IV tPA will change in the coming months. It is not completely clear at this time what exact conclusions will be drawn. In the interim, it is quite certain that the 3-hour time window should no longer be an inviolable rule. Should Cinderella have a stroke at 9 p.m., the stagecoach should not be expected to turn into a pumpkin at 12:01 a.m. ■

Reference

1. Hacke W, Donnan G, Fieschi C, et al. *Lancet* 2004;363:768-774.
2. Lyden P. *N Engl J Med* 2008;359:1393-1395.

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Botulinum Toxin Type A in Painful Focal Neuropathy

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD

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

Synopsis: *There is promising evidence that botulinum toxin type A provides analgesia in patients with painful focal neuropathy independent of its neuromuscular blocking action.*

Sources: Ranoux D, Attal N, Morain F, et al. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Ann Neurol* 2008;64:274-283; Murinson BB. Botulinum toxin type A treatment of painful focal neuropathies: new evidence for efference of afferents. *Ann Neurol* 2008;64:236-238.

BOTULINUM TOXIN TYPE A (BTX-A) HAS BEEN USED for dystonia, spasticity, and glandular hyperactivity. Ranoux and colleagues investigated the analgesic effects of one-time intradermal injections of BTX-A in patients with focal neuropathic pain associated with allodynia, using a randomized, double-blind, placebo-controlled, parallel group design.

In the BTX-A group (n=12), the mean number of injection sites was 20 ± 8.3, with doses ranging from 20 to 190 units. In the placebo group (n=10), the number of injection sites was 19.8 ± 5.2, with total volumes of injection similar to the BTX-A group (3.9 ± 1.1 for placebo and 4.4 ± 1.6 for BTX-A).

BTX-A improved average pain intensity 2 weeks after the injections. The effect increased for up to 4 weeks and was sustained for up to 14 weeks. The area and intensity of allodynia to brush and cold pain thresholds were reduced, without an effect on thresholds to non-painful thermal and mechanical stimuli, or on heat and mechanical pain thresholds. Although burning, paroxysmal pain, and allodynia were improved by BTX-A, deep pain, paresthesia, and dysesthesia were unaffected. BTX-A also improved general activity and anxiety. However, depression was unchanged.

The analgesic effects of BTX-A did not correlate with sex, age, pain duration or intensity, or neuropathic symptoms. But, it was inversely related with the magnitude of thermal deficits, burning pain, and brush-evoked pain. Besides pain due to injections, there was no other local or systemic side effect. The pain was greater when the injections were to the hand or elbow.

Preclinical data showed that BTX-A blocks protein kinase C potentiation of transient receptor potential vanilloid 1, a capsaicin and heat-sensitive ion channel expressed in nociceptors. So, it is possible that BTX-A acts on sensitized nociceptive fibers to produce analgesic effects. However, there are discrepancies in the results of studies concerning BTX effects on pain due to different preparations of BTX, different experimental stimuli, and different binding capacity of BTX to the receptors in acute and chronic conditions (probably greater in chronic conditions). A possible central effect of BTX-A cannot be ruled out.

The authors concluded that BTX-A may induce direct analgesic effects on nociceptive fibers in patients with chronic focal neuropathic pain independent of its effects on muscle tone.

In an accompanying editorial, Murinson commented that this study is an important landmark in the treatment of neuropathic pain. However, the application to a broader patient population is limited because neuropathic pain in the patients in this study was only due to postherpetic neuralgia or focal nerve injury.

Although it is known that BTX-A blocks cholinergic transmission at the neuromuscular junction, many studies show that BTX-A effects are not limited to cholinergic neurons and that its effects on pain control are likely independent of neuromuscular blocking property. For instance, BTX-A can block calcitonin gene-related peptide (CGRP) release from rat trigeminal neurons. In addition, cultured dorsal root ganglion neurons are highly sensitive to BTX-A effects on potassium-evoked substance P release. For basic signaling of painful sensations, it is clear that exocytic signaling in the periphery is not required. However, there is evidence supporting a role for exocytosis in painful inflammatory conditions. Moreover, there has been some controversy about whether primary pain afferents contain the machinery necessary to support the exocytic signaling in the periphery and whether primary pain afferents synthesize and package compounds, that if released, would produce pain or augment pain signaling.

Murinson suggested that each of the pain models needs to be considered separately and weighed for relevance to human forms of neuropathic pain. She recommended a multicenter trial to confirm the effects of BTX-A on neuropathic pain. Finally, she noted that its efficacy, long-lasting effects, and freedom from cognitive side effects are the advantages of treatment with BTX-A.

■ COMMENTARY

While the effects of BTX-A on neuromuscular junction and glandular secretion are well known, its effects

on sensory systems are debated in the literature. Although exocytic signaling (releasing of neuropeptides such as substance P, glutamate, and CGRP) in the periphery is not required in basic pain signaling, it plays a role in the pain induced by an inflammatory process. Interestingly, in vitro studies have shown that BTX-A can block release of substance P, glutamate, and CGRP, which can explain the analgesic effects of BTX-A. In keeping with in vitro studies, the study by Ranoux and colleagues has shown that intradermal BTX-A injections can reduce focal neuropathic pain. However, because this study is small and the etiologies of pain are limited to postherpetic neuralgia and post-traumatic/post-operative pain, further studies in a broader range of painful conditions are required for better understanding of BTX-A effects on pain control. Given the focal effect of BTX-A, its duration of action, and relatively low systemic side effects, BTX-A is a promising treatment option for focal neuropathic pain. ■

What Distinguishes Neuromyelitis Optica from Multiple Sclerosis?

ABSTRACT & COMMENTARY

By Susan A. Gauthier, DO, MPH
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Dr. Gauthier reports no financial relationships relevant to this field of study.

Synopsis: *Neuromyelitis optica (NMO) may be a unique central nervous system demyelinating disease with distinct clinical and MRI manifestations, as well as different immune and pathological characteristics as compared to multiple sclerosis (MS).*

Sources: Argyriou AA, Makris N. Neuromyelitis optica: a distinct demyelinating disease of the central nervous system. *Acta Neurol Scand* 2008;118:209-217; Li Y, Xie P, Lv F, et al. Brain magnetic resonance imaging abnormalities in neuromyelitis optica. *Acta Neurol Scand* 2008;118:218-225.

NEUROMYELITIS OPTICA (NMO) IS AN AUTOIMMUNE inflammatory disease of the central nervous system, usually included within the spectrum of multiple sclerosis, however, more recently, NMO has been proposed to be a distinct clinical entity. NMO characteristically results in demyelination of the optic nerves and spinal cord, resulting in relapsing episodes of unilateral or bilateral visual loss and/or severe paraparesis; this differs from the milder episodes in MS. Similar to MS, the majority of patients have a relapsing course (80-90%), with a female predominance; however, patients with NMO rarely enter a secondary progressive stage and disability accumulates as a result of severe and frequent relapses.

Pathological damage in NMO ranges from demyelination to necrosis within the optic nerves and spinal cord, with the humoral immune system having a predominant role as compared to MS. Similar to the type II pathological subset of MS, NMO lesions show prominent immunoglobulin and complement deposits. Further implicating the role of B cells in NMO, as opposed to the predominant T-cell mediated damage found in MS, was the discovery of an antibody to aquaporin 4, also referred to as NMO-IgG. Aquaporin 4 is the predominant water channel in the brain and is located in the foot processes of the astrocytes surrounding the blood-brain barrier. A predominant perivascular distribution of immune complex deposition is found in NMO corresponding to the normal expression of aquaporin 4 in the foot processes of astrocytes. The sensitivity of NMO-IgG seropositivity alone for the diagnosis of NMO is only 73%, although the specificity is 91%. However, the recently revised criteria for NMO provides a 99% sensitive and 90% specific diagnostic combination that includes two absolute criteria (optic neuritis and acute myelitis) and at least two of three supportive criteria (a longitudinally extensive cord lesion, brain MRI not meeting criteria for MS at disease onset, or NMO-IgG seropositivity).

Intravenous methylprednisolone is used for acute relapses in NMO in doses similar to MS. In NMO relapses refractory to corticosteroid treatment, rescue therapy with plasma exchange has been found to be beneficial. In general, MS immunomodulatory agents are ineffective in preventing relapses in NMO and the use of an oral immunosuppressant such as azathioprine (2-3 mg/kg/daily) in combination with oral prednisone is the most common prophylactic treatment approach. In a recent study of rituximab, which targets CD20-positive B-cells, stabilization was found in 7 of 8 patients; the small sample size of the study limits any clear conclusions, but is a promising observation.

Classically, NMO was felt to only affect the optic nerves and spinal cord and to spare the brain, yet many recent studies have shown that brain abnormalities are not uncommonly found in patients with NMO. In a series published by the Mayo Clinic, 60% of NMO patients had evidence of brain lesions; the majority were non-specific white matter lesions and occasionally were lesions resembling MS.[1] A subsequent publication focused on lesions corresponding to sites of high

aquaporin 4 expression.[2] Although these were the minority of lesions found in NMO patients, the locations occurred most commonly around the third and forth ventricles, as well as the aqueduct of Sylvius; this corresponded to the periventricular and hypothalamic localization of aquaporin 4. These lesions were felt to be characteristic MRI lesions of NMO. Recently, Li et al described brain lesions in a series of Chinese patients with NMO for which 28 of 33 (84.6%) had brain parenchymal abnormalities. Well defined brain lesions were found in 22 patients (66.7%), with the majority having more than one lesion. Most lesions were scattered and described as small or punctuated (<3 mm), although unique patterns were described; these included symmetrical hyperintense T2 signal changes in the bihemispheric deep white matter regions and belt-like hyperintensities along the margin of the lateral ventricles. Brainstem involvement was higher, specifically in the medulla, in this series of patients (42.4%) as compared to other published clinicopathological studies. Only one patient had involvement of the hypothalamus. The Li et al study concluded that the prevalence of brain lesions in Chinese NMO patients was higher than previously reported in other populations with NMO and that the pattern of involvement differs in the Chinese population.

■ COMMENTARY

Distinct clinical differences between NMO and MS have been well recognized; although without evidence of pathophysiological differences, patients were generally treated with MS therapies. With the discovery of NMO-IgG, the treatment approach to this disease has changed; specifically, there is a focus on general immunosuppression and, recently, on anti-B-cell therapies. As the diagnostic use of the NMO-IgG test expands, a better understanding of the clinical spectrum of NMO will follow, as well as the opportunity to determine the actual rate of brain involvement. The study by Li et al found, as others have, that the majority of brain lesions in NMO are non-specific small white matter abnormalities; however, they identified unique features in their patient population. The Chinese population lacked the characteristic NMO lesions described in the Mayo series; however, the small sample sizes in both studies limit any definite conclusions. ■

References

1. Pittock SJ, Lennon VA, Krecke K, et al. *Arch Neurol* 2006;63:390-396
2. Pittock SJ, Weinshenker BG, Lucchinetti CF, et al. *Arch Neurol* 2006;63:964-968.

Results of the PRoFESS Trial: Use Any Antiplatelet Agent and Get Back to the Basics

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

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Dr. Jamieson reports that she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil; and is on the speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Aspirin plus extended-release dipyridamole and clopidogrel are both appropriate options to decrease disability from recurrent stroke; however, telmisartan does not lower risk of suffering a second stroke.*

Sources: Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238-1251; Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008;359:1225-1237; Kent DM, Thaler DE. Stroke prevention — insights from incoherence. *N Engl J Med* 2008;359:1287-1289; Diener HC, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischemic stroke in the PRoFESS trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008;7:875-884; Hankey GJ, Eikelboom JW. What do the results of the PRoFESS trial teach us? *Lancet Neurol* 2008;7:860-862.

ANTIPLATELET THERAPY IS APPROPRIATE FOR RECURRENT stroke risk reduction in patients with non-cardioembolic ischemic stroke; current options include aspirin and two branded products (clopidogrel and the combination of aspirin plus extended-release dipyridamole [ASA-ERDP]). The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial is a double-blind, 2-by-2 factorial trial, in which patients with a recent ischemic stroke were randomized to receive 25 mg of aspirin plus 200 mg of ASA-ERDP twice daily or 75 mg of clopidogrel daily. The primary outcome was first recurrence of stroke; the secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. A total of 20,332 patients were followed for a mean of 2.5 years. Premature discontinuation of the study drug was significantly more frequent among patients

receiving ASA-ERDP (29.1%) than among those receiving clopidogrel (22.6%). Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11). Major hemorrhagic events, including intracranial hemorrhage, were more common in ASA-ERDP recipients (4.1%) than in clopidogrel recipients (3.6%) (hazard ratio, 1.15; 95% CI, 1.00 to 1.32). The net risk of recurrent stroke or major hemorrhagic event was similar in the ASA-ERDP (11.7%) and clopidogrel (11.4%) groups (hazard ratio, 1.03; 95% CI, 0.95 to 1.11). There was no difference in the incidence of composite vascular events between patients on ASA-ERDP or clopidogrel.

Inhibition of the renin-angiotensin system reduces the rate of secondary vascular events, but the cerebrovascular benefit of an angiotensin II receptor blocker (ARB) initiated early after an ischemic stroke is uncertain. The patients of PRoFESS also were randomized to the ARB telmisartan (80 mg daily) or placebo. A total of 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group had a subsequent stroke (hazard ratio in the telmisartan group, 0.95; 95% CI, 0.86 to 1.04; p=0.23). The mean blood pressure was 3.8/2.0 mm Hg lower in the telmisartan group than in the placebo group. Therapy with telmisartan did not significantly lower the rate of recurrent stroke, composite vascular events, or diabetes.

The putative neuroprotective effects of antiplatelet compounds and telmisartan also were investigated in the PRoFESS trial. The predefined endpoints for the substudy evaluating disability and cognitive function after recurrent stroke were the modified Rankin scale and Barthel index at 3 months, and cognitive function, assessed with the mini-mental state examination score at 4 weeks after randomization and at the penultimate visit. There were no significant differences in the proportion of patients with cognitive impairment or dementia among the treatment groups. This substudy concluded that disability due to recurrent stroke and cognitive decline were not different between the two antiplatelet regimens and were not affected by the preventive use of telmisartan.

■ COMMENTARY

The results of the PRoFESS study were surprising based on expectations from older clinical trials. Prior to this head-to-head comparison, the indirect comparison of the results of other clinical trials such as the Second European Stroke Prevention Study (ESPS-2), Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), and Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH) indicated the superiority of ASA-ERDP over clopidogrel in the prevention of recurrent ischemic stroke. Trials of clopidogrel plus aspirin showed a greater risk of life-threatening bleeding as compared with monotherapy; however, earlier trials of ASA-ERDP showed no increased risk of life-threatening bleeding as compared with aspirin alone. The major concern with treatment with ASA-ERDP was the transient headache in up to one-third of patients at initiation of treatment.

PRoFESS did not indicate the expected clinical superiority of ASA-ERDP, and the discontinuation rate of the medication due to headache was lower than expected. The conclusion of the trial was that net risk of recurrent stroke or major hemorrhagic event was similar with the two antiplatelet agents and that there was no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke. The increased risk of intracranial bleeding among patients treated with ASA-ERDP emphasizes the risk of treatment with dual antiplatelet treatment, including aspirin plus clopidogrel, despite lack of such evidence for ASA-ERDP prior to PRoFESS.

The results of PRoFESS indicate that we have a choice of antiplatelet agents of overlapping efficacy; other factors in the choice include cost and tolerability. In the next few years we may have even more choices if prasugrel, a new thienopyridine with greater antiplatelet potency but more hemorrhagic risk, becomes available for recurrent ischemic stroke risk reduction.

The editorial by Kent and Thaler accompanying the *New England Journal of Medicine* publication used a zen approach to interpret the results, concluding "For stroke prevention, use an antiplatelet drug. Treat hypertension." Treatment with any antiplatelet agent decreases the recurrent stroke rate by 9%, three years after the prior non-cardioembolic stroke. Antiplatelet treatment must be accompanied by aggressive life style adjustment and management of medical risk factors, especially hypertension. In addition, by the time recurrent ischemic stroke risk reduction is considered, the patient may already have permanent neurological disability. We need better implementation of the life-styles and medical treatments that we know will prevent the first ischemic stroke. Then we can effectively prevent ischemic stroke recurrence. ■

Statins and Myasthenia

ABSTRACT & COMMENTARY

By Michael Rubin, MD, FRCP(C)

Professor of Clinical Neurology, Weill-Cornell Medical College

Dr. Rubin reports the he is involved in grant/research support for Pfizer and is on the speaker's bureau of Athena Diagnostics.

Synopsis: *Statins may cause worsening symptoms in patients with myasthenia gravis.*

Sources: Oh SJ, Dhall R, Young A, et al. Statins may aggravate myasthenia gravis. *Muscle Nerve* 2008;38;1101-1107; De Sousa E, Howard J. More evidence for the association between statins and myasthenia gravis. *Muscle Nerve* 2008;38:1085-1086.

DO STATINS INDUCE THE DEVELOPMENT OF MYASTHENIA gravis, worsen pre-existing myasthenia, or do none of the above? To address this question, clinic charts of all myasthenic patients seen in the Neuromuscular Clinic at the University of Alabama (Birmingham) from January 2005 to June 2007 were reviewed. Any patient whose chart did not mention statin use was contacted by phone, questioned, and seen in follow-up for confirmation of history. Myasthenia gravis diagnosis was based on symptoms of fluctuating weakness, in the presence of either positive antibody titers (acetylcholine receptor antibodies or muscle-specific protein tyrosine kinase antibodies), decremental response on repetitive nerve stimulation study, or increased jitter on single-fiber electromyography. Myalgia complaints were elicited from the patient but myasthenic worsening was determined objectively on follow-up examination. Statin use was implicated as the cause of myalgia or myasthenia worsening if symptoms occurred within 4 months of statin administration, no other cause could be established, and symptoms improved with or without statin withdrawal.

Among 185 myasthenic patients seen during the study period, information on statin usage was available for 170, evenly divided between men and women. Mean age of myasthenia onset was 48.7 years, mean age of the study group was 58.7 years, and mean duration of myasthenia was 9.1 years. Ocular myasthenia was present in 15%. Statins were used by 54 patients (31%), and, compared to the non-statin group, all were older than age 40 and males were predominant. Among the statin group, 13% (n = 7) experienced myalgias, and 11% (n = 6) worsening of their myasthenia. None developed myopathy or myoglobinuria. Statin withdrawal resulted in resolution of myalgia within 2 months in all 7 affected, but 4 of 6 patients with myasthenia exacerbation required medical treatment for symptom improvement: Azathioprine and steroids for 1 patient; intravenous immunoglobulin (IVIG) for 2 patients; and tracheostomy, gastrostomy, plasmapheresis, and IVIG for the fourth patient. Worsening consisted of oculobulbar symptoms in 5 patients and limb weakness in 1 patient, requiring hospitalization in 2 patients. Symptoms began within 1-16 weeks of statin administration, both generalized and ocular myasthenia patients were susceptible, and all statin brands were invoked. The authors concluded that statins are safe but may worsen myasthenia symptoms.

■ COMMENTARY

Design of this study did not permit the determination of whether statins precipitate new onset of myasthenia, but exacerbation of pre-existing myasthenia may be a concern. Possible mechanisms for this remain unclear. Inhibition of B-lymphocyte activation[1] and inhibition of MHC class II antigen presentation, by impairing Ras superfamily ATPases,[2] indicate that statins have an immunomodulatory effect on B cells in humans. In mice, they appear to have T cell effects as well.[3] Mitochondrial dysfunction from endogenous depletion of coenzyme Q10 is another possible mechanism.[4] Surprisingly, in pilot studies, statins may be of therapeutic value in treating autoimmune disease, such as multiple sclerosis.[5] Fortunately, non-hydroxy coenzyme A reductase inhibitors

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.

may be used in place of statins if statin myopathy or myasthenia exacerbation occurs.[6] ■

References

1. Rudich SM, Mongini PK, Perez RV, et al. *Transplant Proc* 1998;30:992-995.
2. Ghittoni R, Napolitani G, Benati D, et al. *Eur J Immunol* 2006;36:2885-2893.
3. Koido S, Hara E, Homma S, et al. *J Immunol* 2007;178:3613-622.
4. Cartwright MS, Jeffery DR, Nuss GR, et *Neurology* 2004;63:2188.
5. Neuhaus O, Hartung NP. *Expert Rev Neurother* 2007;7:547-556.
6. Florentin M, Liberopoulos EN, Elisaf MS. *Int J Clin Prac* 2008;62:88-96.

CME Questions

12. According to this study, what is the proposed action of BTX-A in focal painful neuropathy?

a. Anti-inflammatory effects
b. Muscle relaxation with subsequent pain reduction
c. Local peripheral effect on nociceptive fibers
d. Direct effect on myelin function

13. Which of the following is appropriate for reduction of risk of recurrent stroke?

a. ASA-ERDP
b. Clopidogrel
c. Aspirin
d. Maintenance of blood pressure < 120/80
e. All of the above

14. Which of the following statements apply to both NMO and MS?

a. Caused by humoral-mediated mechanisms
b. Oral immunosuppressant therapy is first-line treatment
c. Acute exacerbations are treated with IV methylprednisolone
d. Episodes of complete transverse myelitis
e. Secondary progression occurs after years of relapses

15. Which of the following statements is *incorrect?*

a. Statins may cause myalgia
b. Statins may exacerbate myasthenia
c. Statin withdrawal alone will be enough to resolve statin-induced myalgias or myasthenia worsening
d. Statins inhibit MHC class II antigen presentation
e. Depletion of coenzyme Q10 is a possible mechanism for statin-induced myalgias or myasthenia worsening

Answers: 12. c; 13. e; 14. c; 15. c

In Future Issues:

New Treatments for Alzheimer's Disease

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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*.

Safety of Inhaled Anticholinergics for COPD Scrutinized

In the Issue: Ongoing safety review of tiotropium; raloxifene reduces the risk of endometrial cancer; one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir; new Clinical Practice Guideline from the American College of Physicians regarding pharmacologic treatment for low bone density and osteoporosis; FDA Actions.

THE SAFETY OF INHALED ANTICHOLINERGICS FOR the treatment of chronic obstructive pulmonary disease (COPD) has come under scrutiny in recent months. In July, the FDA issued an "Early Communication" about an ongoing safety review of tiotropium (Spiriva®) the most widely used agent for the treatment of COPD. The review is focused on a possible increased risk of stroke and is based on a pooled analysis of 29 trials which showed the risk of stroke at 8 patients per 1000 treated with tiotropium versus 6 patients per 1000 treated with placebo.

Now two new studies suggest that inhaled anticholinergics (ipratropium [Atrovent®] and tiotropium) increase the risk for all-cause mortality and cardiovascular disease in patients with COPD. In a large meta-analysis (*JAMA* 2008;300: 1439-1450), researchers reviewed 17 trials involving nearly 15,000 patients with COPD who were randomized to an inhaled anticholinergic or control. The primary outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. The primary outcome occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR 1.58, 95% CI, 1.21-2.06; $P < 0.001$). Inhaled anticholinergics significantly increased risk of MI, cardiovascular death, and all-cause mortality (RR 1.26). When the analysis was restricted to long-term trials, the risk was even greater for cardiovascular death, MI, or stroke (RR 1.73). The number needed to harm for MI was 174 per year, while the number needed to harm for cardiovascular death was 40 per year. The authors concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

In a second nested, case-control study (*Ann Intern Med* 2008;149:380-390), the National Veterans Affairs databases were used to review all-cause mortality, respiratory and cardiovascular deaths, and exposure to COPD medications including inhaled corticosteroids, ipratropium, long-acting beta agonists, and theophylline in the 6 months preceding death. The adjusted odds ratios for all-cause mortality were 0.80 for inhaled chronic steroids, 1.11 for ipratropium, 0.92 for long-acting beta agonists, and 1.05 for theophylline. Ipratropium was associated with increased cardiovascular deaths (OR 1.34), whereas inhaled corticosteroids were associated

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

with reduced risk for cardiovascular death (OR 0.80). The authors conclude that there is a possible association between ipratropium and elevated risk for all-cause and cardiovascular death and that further studies are needed. They also suggest that the risk of ipratropium may be somewhat mitigated by concomitant use of inhaled corticosteroids, but caution should be exercised if ipratropium is used alone in patients with recently diagnosed COPD.

Raloxifene reduces endometrial cancer risk

It is well known that raloxifene reduces the risk of breast cancer; now there is evidence that the drug reduces the risk of endometrial cancer as well. Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM) that is indicated for treatment and prevention of osteoporosis and for breast cancer prevention. Researchers from the University of Pennsylvania compared endometrial cancer rates in women on raloxifene, tamoxifen, and non-users of SERMs in a case-control study of 547 women with endometrial cancer and 1410 controls. After adjustment for other risk factors the odds of endometrial cancer among raloxifene users was 50% that of non-users (OR = 0.50; 95% CI, 0.29-0.85), whereas tamoxifen users had 3 times the odds of developing endometrial cancer compared to raloxifene users (OR = 3.0; 95% CI, 1.3-6.9). Among raloxifene users who developed endometrial cancer, the tumors had a more favorable histologic profile and were predominantly stage I and low grade. The authors conclude that raloxifene users have significantly lower risk of developing endometrial cancer compared with tamoxifen users and SERM non-users, perhaps even suggesting a role for raloxifene and prevention of endometrial cancer (*J Clin Oncol* 2008; 26:4151-4159).

One-day famciclovir = three-day valacyclovir

For patients with recurrent genital herpes outbreaks, one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir, according to a new study. In a double-blind parallel group study, 1179 adults with a history of recurrent genital herpes were randomized to receive either famciclovir 1000 mg twice daily for one day vs valacyclovir 500 mg twice daily for 3 days. Patients initiated treatment within 6 hours after a recurrence. Approximately one-third of patients in each group aborted genital herpes outbreaks altogether, but for those who went on to develop lesions, median time to healing was 4.25 days for famciclovir vs 4.08 days for valacyclovir. Time to healing was the same in both groups and the incidence of adverse affects was 23.2% for famciclovir vs 22.3% for valacyclovir. The study demonstrates that a single day of famciclovir (1000 mg twice daily) is equivalent to 3 days of valacyclovir (*Clin Infect Dis* 2008;47:651-658). Other regimens for treatment of recurrent HSV episodes include acyclovir 800 mg 3 times daily for two days or 400 mg three times daily for 3-5 days, famciclovir 125 mg twice a day for 3-5 days, or valacyclovir 500 mg twice daily for 3 days. Both acyclovir and famciclovir are available generically, but acyclovir is considerably less expensive; however, the convenience of a one-day treatment with famciclovir may be worth the extra cost for many patients.

New practice guideline for osteoporosis

The American College of Physicians has issued a Clinical Practice Guideline regarding the pharmacologic treatment of patients with low bone density or osteoporosis (*Ann Intern Med* 2008; 149:404-415). The expert committee recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures. They also recommend that pharmacologic treatment should be considered for men and women who are at risk of developing osteoporosis and that the choice of pharmacologic treatment should be based on assessment of risk and benefits in individual patients. The guideline reviews different treatment modalities including bisphosphonates, calcitonin, estrogen, teriparatide, SERMs, testosterone, and calcium plus vitamin D. Left unanswered are the questions of duration of treatment with bisphosphonates and the optimal dose of calcium and vitamin D.

FDA actions

The FDA has issued warning letters to Ranbaxy Laboratories Ltd. of India in an Import Alert for the company's generic drugs produced in two Indian plants. The warning letters identify concerns about deviations from U.S. current Good Manufacturing Practice requirements at Ranbaxy's manufacturing facilities and the Import Alert allows officials to detain at the rest border any active pharmaceutical ingredients manufactured at Ranbaxy facilities. Ranbaxy manufacturers more than 30 generic drugs including commonly used antibiotics, antihypertensives, and antivirals. ■

Clinical Briefs in
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Cognitive Impairment Progression Blunted by Exercise

Source: Lautenschlager NT, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA* 2008; 300:1027-1037.

CLINICAL TRIALS OF PHARMACOTHERAPY to prevent progression of cognitive decline in those with mild cognitive impairment (MCI) have been disappointing; neither cholinesterase inhibitors (donepezil, rivastigmine, galantamine), vitamin E, nor COX-2 inhibitors has demonstrated any clinically meaningful benefit in placebo-controlled MCI trials.

Observational data are consistent that regular physical activity, even if started late in life, is associated with reduced risk of dementia. Whether exercise might prevent progression in persons with MCI was the subject of this first randomized trial to address the issue.

Subjects (n = 170) with MCI between the ages of 50-77 (mean age, 68.6 years) were randomized to receive either 50-min sessions of moderate-intensity exercise (e.g., brisk walking, ballroom dancing, and swimming) three times weekly vs control (general education about health, including physical activity, diet, alcohol, and stress management). All educational materials were also provided to the intervention group. All participants (control and intervention) wore a pedometer and provided diaries of daily total number of steps. Physical activity and cognitive function were assessed at 6, 12, and 18 months after randomization.

At each assessment point, cognitive scores for the intervention group were better than the control group. The intervention group averaged approximately 6000 more steps/week than the control group. Exercise, averaging as little as 21 min/day, reduces cognitive decline in persons with MCI. ■

Incidentalomas in the Knee

Source: Englund M, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108-1115.

ONE OF THE PRIMARY THINGS THAT has stood in the way of definitive diagnosis of acute low back pain is the extraordinarily high rate of false-positive findings seen on plain films, CT, or MRI. Indeed some studies suggest that as many as half of healthy, asymptomatic individuals studied by MRI of the lumbar spine have findings consistent with disk pathology.

Little is known about the frequency of incidental findings seen upon MRI of the knee, since studies generally investigate symptomatic individuals; subsequent radiographic findings, if they correlate with symptomatology, have been taken to support a causal relationship.

Englund et al performed an MRI of the right knee in 991 randomly selected adult subjects ages 50-90 in Massachusetts. Excluded subjects included those with rheumatoid arthritis, knee replacement, terminal illness, or non-ambulatory status.

The incidence of meniscal tears seen ranged from 19% in the youngest women (ages 50-59) to 56% in senior men (ages 70-90). Among the group with radiographic changes of osteoarthritis, the frequency of meniscal tears in symptomatic and asymptomatic individuals was similar (63% vs 60%, respectively). Overall, the majority of persons (60%) with meniscus tears confirmed by MRI had no symptoms referable to the knee.

It appears that as with back MRI, incidental findings of pathology are frequent, and call into question an ironclad attribution of knee symptoms to positive findings on MRI. ■

Hormone Replacement and Skin Health in Menopausal Women

Source: Phillips TJ, et al. Does hormone therapy improve age-related skin changes in postmenopausal women? *J Am Acad Dermatol* 2008;59:397-404.

AS LITTLE AS A DECADE AGO, MENOpausal status alone was the ticket of admission to advocate hormone replacement therapy (HRT). The "story line" went that HRT prevented cognitive decline, improved symptoms, enhanced cardiovascular health, and preserved cutaneous health, i.e., reduced age-related wrinkles, dryness, and laxity. Unfortunately, HRT has failed to live up to numerous of its hopeful claims.

To study the effects of HRT on menopausal women's skin, 485 subjects were randomly assigned to placebo or two different HRT doses in double-blind fashion. Dermatologists evaluated skin wrinkling, laxity, and texture (as did the patients) over a 48-week interval. The mean age of the women was 54 years.

At study end, there were no statistically significant differences in any primary endpoint of the trial. When the data were analyzed for impact of baseline levels of estradiol, race, or age, no meaningful differences were found. During the trial, all study groups enjoyed some skin improvements attributable to daily application of moisturizing cream and sunscreen, but HRT added nothing to this. Claims that HRT provides reduced risk of age-related skin changes are not supported by this trial. ■

Reconfirmation of the Death of Homocysteine

Source: Ebbing M, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial. *JAMA* 2008;300:795-804.

HOMOCYSTEINE (HCYS) HAS ALL THE trappings of a first-rate cardiovascular risk factor: as strong an association with CVD endpoints as cholesterol, ease of identification, and simplicity of modulation. Trouble is, trials to date have been unable to show that reductions of homocysteine provide meaningful benefits to patients. Indeed, one recent commentary following a large double-blind intervention-

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al trial of HCYS for cardiovascular endpoints began with "The homocysteine hypothesis is dead … ."

Apparently as undaunted as Mark Twain ("The reports of my death are greatly exaggerated …"), Ebbing et al tested HCYS reduction through B vitamins after coronary angiography. The primary endpoint of the study was all-cause mortality, non-fatal stroke and MI, and hospitalization for unstable angina (composite).

The trial (n = 3096) was designed to follow patients for 4 years, but was stopped at 38 months due to information from another trial that had reported a possible negative effect of B vitamin intervention. B vitamins did reduce HCYS by approximately 30%, but failed to have any impact (positive or negative) upon endpoints. The HCYS hypothesis is still dead. ■

Pramlintide as a Weight-Loss Adjunct

Source: Smith SR, et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008;3:1816-1823.

SOMETHING THAT NEITHER MOTHER NOR medical school taught us was that more than one hormone is secreted from the beta cells of the pancreas in response to rising glucose. In conjunction with insulin, the hormone amylin is released. Pramlintide is a synthetic form of amylin. The physiologic effects of amylin include slowed gastric emptying (thereby slowing the rate of glucose delivery to the intestine), suppression of glucagon, and centrally mediated satiety. For addressing obesity, there is great conceptual appeal to an agent that improves satiety.

Smith et al performed a double-blind, placebo-controlled trial of various doses of subcutaneous pramlintide (bid to tid) in obese, nondiabetic subjects, who were also receiving intensive lifestyle (diet/exercise) intervention. The initial 4-month double-blind phase was followed by a 4-month single-blind extension (for those who completed the initial phase without protocol violation).

Weight loss was dose-proportional: At 360 µg twice daily the placebo-corrected weight loss was 3.3 kg at month 4 and 7.2 kg at month 12. No safety concerns were seen. Nausea, which is also the most common adverse event seen in diabetic subjects, was mostly mild to moderate, and improved over time. Nausea is not the mechanism of action, since weight reduction was similar in those who did and did not experience nausea. These initial data are encouraging that pramlintide may find a role in enhancing weight loss when used in conjunction with lifestyle intervention. ■

Undiagnosed Diabetes in Obese Americans

Source: Wee CC, et al. Obesity and undiagnosed diabetes in the U.S. *Diabetes Care* 2008;31:1813-1815.

NO CLINICIAN IS SURPRISED TO SEE that diabetes often goes undiagnosed. Patients can persist with modest symptoms, or even asymptomatically, for protracted periods during the early stages of type 2 diabetes. The fact that literally half of type 2 diabetics have one or more of the traditional complications of diabetes (neuropathy, nephropathy, retinopathy, dermopathy) at the time of clinical diagnosis attests to the fact that diagnosis lags substantially behind disease onset.

Most type 2 diabetics are obese, and obesity provides an environment that promotes insulin resistance, a cardinal dysfunction in early diabetes and pre-diabetes. Hence, scrutiny of obese subjects provides a window of observation into a population felt to be at greater risk for developing diabetes. On the one hand, the clinician might think that the presence of obesity would prompt greater vigilance for diabetes; on the other hand, there is evidence that compared to the non-obese, obese individuals experience delays in receiving preventive care.

From the 1999-2004 NHANES data, it was determined that 9.8% of the population had diabetes (defined as FBG > 126 mg/dL). Slightly more than one-fourth (28.1%) of persons with FBG > 126 mg/dL had not been diagnosed with diabetes. When parsed into BMI categories, normal weight individuals were actually less likely to have undiagnosed diabetes than overweight or obese persons (22.2% vs 32.5% vs 27.4%, respectively). Because more than one-half of undiagnosed diabetes is seen in overweight and obese individuals, enhanced vigilance is appropriate. ■