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A Lung Cancer 'Story Problem'

ABSTRACT & COMMENTARY

Synopsis: *Screening for lung cancer with helical CT has high costs and uncertain benefits.*

Source: Mahadevia PJ, et al. *JAMA*. 2003;298:313-322.

In 2003 the American Cancer Society estimates that there will be 171,900 new cases of and 157,200 deaths from lung and bronchial cancer in the United States.[1] While this represents about 13% of all cancer diagnoses, it accounts for about 28% of all cancer deaths. There is no cancer that kills as many men and women as lung cancer. Early detection, presumably before it has metastasized, remains the Holy Grail of lung cancer treatment. Mahadevia and colleagues performed a decision and cost-effectiveness analysis of screening for lung cancer with helical computed tomography (CT), using data from the Surveillance, Epidemiology, and End Results (SEER) national cancer database.

To do this kind of analysis, they accounted for all possible outcomes and assigned probabilities to them. If there were no published data for a particular outcome, they made an educated guess. Finally, they made certain assumptions: a hypothetical study population of 100,000, aged 60 years old, 55% male, heavy smokers (> 20 pack-years), eligible for lung resection. This group was divided into 3, based on smoking status: current, quitting at the start of screening, and quitting 5 years before screening. These 3 groups were divided into screened and nonscreened. The scenarios were run with annual screening until age 80 years and follow-up to age 100 years.

The SEER database contains probabilities of what happens to smokers: alive without apparent cancer, developing and dying of lung cancer, and dying of other causes. They adjusted these probabilities based on the 3 smoking-status groups. All patients developing signs or symptoms of lung cancer underwent invasive testing. Those diagnosed with lung cancer were assigned to localized-stage non-small-cell lung cancer (NSCLC), advanced-stage NSCLC, or small-cell lung cancer (SCLC). Depending on the diagnosis, the patients could receive surgery, radiation therapy, and/or chemotherapy. Helical CT sometimes identifies indeterminate nodules that need

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INSIDE

to be followed or biopsied. Using previously published studies of lung cancer screening by helical CT, Mahadevia and colleagues obtained probabilities for these events. One interesting aspect of helical CT screening is that the cancers it picks up are usually peripheral. It tends to miss cancers hidden in endobronchial locations. These cancers are histologically different from peripheral cancers (squamous cell carcinoma vs adenocarcinoma, respectively). As might be expected, the cancers detected by helical CT are more likely to be not as advanced in clinical stage. These differences were factored in. All costs (facility and professional fees, additional monitoring, surgery, diagnostic tests, etc) were calibrated to 2001 US dollars. Quality-of-life measurements (including anxiety from testing indeterminate nodules, surgery, radiation, chemotherapy, etc) were calculated.

There were 4168 lung cancer deaths per 100,000 unscreened patients and 3615 per 100,000 screened patients (553 fewer deaths, 13% relative mortality reduction). The screened group underwent 1186 invasive tests for benign lesions. The average incremental cost for screening was $116,300 per quality-adjusted life-year (QALY). The incremental cost-effectiveness increased as the risk of cancer decreased; the cost for former smokers was $2,322,700 per QALY.

COMMENT BY ALLAN J. WILKE, MD

Earlier attempts to screen for lung cancer with periodic chest x-rays and sputum cytology failed to reduce mortality.[2] We will have to wait several more years before the results of the National Cancer Institute's National Lung Screening Trial (NLST), a study comparing spiral CT and chest x-ray, will be available.[3] Enrollment began in September 2000, and patients will be followed until 2009. Until then, this is the best information we are likely to get. Like any simulation (Pentagon war games or *The Sims*®), the results are only as good as the assumptions. The most basic assumption is that early detection will reduce mortality by "catching" cancer before it has metastasized. We can only hope that NLST will demonstrate that. If it does, then we will have to ask ourselves if we, as a society, are ready to allocate already scarce health care resources to widespread screening. It is ironic that screening was most cost-effective for the group most likely not to benefit from it: heavy smokers who haven't quit.

Your patients are being bombarded with direct-to-consumer advertising about this technology. If you enter "lung cancer screening" into your favorite Internet search engine, you will get many links that will take you to commercial sites that offer helical CT services—for a fee or upon referral from your primary care physician. Based on this study, I won't be ordering screening helical scans any time soon. On the other hand, I'm as big a fan of the free enterprise system as the next guy. On that basis, my advice to patients who request lung cancer screening by helical CT is "if you gotta know, and you've got the dough, then you pay the tow!" Since cigarette smoking causes almost all lung cancer, I will also advise them to save their money and quit their habit. ■

References

1. Cancer Facts and Figures 2003. American Cancer Society. p. 4.
2. Fontana RS. *Cancer*. 2000;89(Suppl 11):2352-2355.
3. National Cancer Institute. http://www.cancer.gov/NLST. Accessed February 11, 2003.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $20. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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NSAIDs and GI Bleeding

ABSTRACT & COMMENTARY

Synopsis: *Current guidelines for NSAID use in patients at high risk for ulcer disease recommend use of NSAIDs selective for cyclo-oxygenase-2 inhibition or nonselective NSAIDs plus a proton pump inhibitor. This study compared diclofenac plus omeprazole with celecoxib in patients with previous GI hemorrhage. Neither regimen successfully prevented rebleeding, and both exhibited significant toxicities.*

Source: Francis KL, et al. *N Engl J Med*. 2002;347(26): 2104-2110.

THIS HONG KONG STUDY ADDRESSED A TOPIC OF GREAT clinical relevance: the avoidance of ulcer re-activation and bleeding in patients requiring nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis treatment. In this trial, 287 patients were studied over 6 months: 144 receiving celecoxib 200 mg twice daily and 143 receiving diclofenac 75 mg twice daily plus 20 mg of omeprazole. Previous studies have suggested that COX-2 selective NSAID use leads to reduced GI events, and American College of Rheumatology guidelines strongly recommend the use of this drug class in patients at risk for ulcer disease. Along with high-dose H2-receptor antagonists and misoprostol, proton pump inhibitors (PPIs) have also been shown to lessen GI complications.

This is the first trial to directly compare these 2 approaches in patients with prior documented ulcer hemorrhage. All patients studied were *Helicobacter pylori*-negative, and all had previous endoscopically documented gastric or duodenal ulcer healing. The primary study end point was endoscopically documented ulcer bleeding (following presentation with hematemesis and/or melena). Anti-arthritic efficacy did not differ between the 2 regimens. Seven patients bled with celecoxib therapy, and 9 bled who received omeprazole and diclofenac. Renal adverse events were common including hypertension, peripheral edema, and renal failure (24.3% with celecoxib and 30.8% with diclofenac and omeprazole). These toxicities were especially prominent in patients with baseline renal impairment.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

This study substantiates the intuitive notion that ulcer complications are far better markers of NSAID injury than the surrogate end points so often used in endoscopic studies of normal subjects or patients. In an editorial in the issue of the *New England Journal of Medicine*, Dr. David Graham complained that this study combined patients who had *H pylori* eradicated with those who had never been infected despite the absence of data that these groups would be comparable.[1] Nevertheless, both he and I would agree that this is the best study yet to elucidate data regarding NSAIDs and ulcer complications.

It is discouraging that neither PPI prophylaxis nor use of COX-2 NSAID therapy can avert ulcer recurrence and bleeding in this setting. The next generation of studies should probably combine COX-2 NSAID therapy with antisecretory drugs and/or misoprostol. An alternative might be more aggressive PPI therapy (eg, a second-generation PPI and/or b.i.d. therapy and possibly with addition of low-dose H2RA therapy at bedtime). Dr. Graham believes that all *H pylori* should be eliminated in patients requiring long-term NSAID therapy, but I personally still do not find the data fully supportive of this approach. ■

Reference

1. Graham D. *N Engl J Med*. 2002;347(26):2162-2164.

A New and More Successful Means of Treating Multiple Sclerosis

ABSTRACT & COMMENTARY

Synopsis: *Treatment with natalizumab, an antibody to α_4 integrin, led to fewer inflammatory brain lesions and fewer relapses in patients with relapsing multiple sclerosis.*

Source: Miller DH, et al. *N Engl J Med.* 2003;348:15-23.

IN PATIENTS WITH MULTIPLE SCLEROSIS, INFLAMMATORY lesions appear to arise from an autoimmune response involving lymphocytes and monocytes. The glycoprotein α_4 integrin is expressed on the surface of these cells and plays a critical part in their adhesion to the vascular endothelium and migration into the parenchyma. Natalizumab is an antibody against α_4 integrin that reduced the development of brain lesions in experimental models in a preliminary study of patients with multiple sclerosis.

In a randomized, double-blind trial, Miller and colleagues randomly assigned a total of 213 patients with relapsing-remitting or relapsing secondary progressive multiple sclerosis to receive 3 mg of intra-

venous natalizumab per kilogram of body weight (68 patients), 6 mg per kilogram (74 patients), or placebo (71 patients) every 28 days for 6 months. The primary end point was the number of new brain lesions on monthly gadolinium-enhanced magnetic resonance imaging during the 6-month treatment period. Clinical outcomes included relapses and self-reported well-being.

There were marked reductions in the mean number of new lesions in both treatment groups—9.6% in the placebo group, as compared to 0.7% in the group given 3 mg of natalizumab per kilogram ($P = 0.001$) and 1.1% in the group given 6 mg per kilogram ($P < 0.001$). Twenty-seven patients in the placebo group had relapses as compared to 13 in the group given 3 mg per kilogram ($P = 0.02$) and 14 in the group given 6 mg per kilogram ($P = 0.02$). The placebo group reported a slight worsening in well-being, whereas the groups receiving natalizumab reported improvement.

COMMENT BY RALPH R. HALL, MD, FACP

Safety and tolerability is an important aspect of new trials such as this. In this study, similar numbers of patients in each group had adverse events during treatment. Eleven serious events occurred in 7 patients in the placebo group, 5 serious events in 5 patients in patients receiving the 3-mg dose and 4 events occurred in 3 patients in the group receiving 6 mg. Four of these events were considered to be immune-mediated and related to the study drug. One subject receiving natalizumab had an anaphylactoid reaction, which was rapidly reversed with antihistamines and corticosteroids.

It is of note that the reductions in the formation of lesions was approximately 90% in both the 3- and 6-mg doses of natalizumab and was thus greater than the reduction of 50-80% reported with beta-interferons and of approximately 30% with glatiramer acetate. Further, the patients receiving natalizumab had improved feeling of well-being and did not experience the flu-like symptoms and painful injection sites that are experienced with the interferons.

Binding antibodies against the natalizumab developed in 11% of the patients. It is not known whether this will affect more continuous treatment.

In the same issue of this edition of the *New England Journal of Medicine*, Ghosh and colleagues report the use of natalizumab for the treatment of active Crohn's disease. Natalilzumab increased the rates of clinical remissions and improved the quality of life.[1] This study found that natalizumab significantly lowered the levels of C-reactive protein, an acute phase reactant whose measurement is used to quantify generalized inflammation. (Both the multiple sclerosis and the Crohn's disease studies were funded by Elan Pharmaceuticals and Biogen.)

These reports are encouraging, but, as usual, longer studies are in order. There are still the concerns of whether the autoimmune response in multiple sclerosis is the primary cause of the disease or an epiphenomenon of another disease process. Our treatments directed at the autoimmune process, therefore, may not be as effective as targeting the initiating event. ■

Reference

1. Ghosh S, et al. *N Engl J Med*. 2003;348:24-32.

Do Statin Drugs Prevent Dementia? Data from the PROSPER Study

ABSTRACT & COMMENTARY

Synopsis: *Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals. The PROSPER study therefore extends to elderly individuals the treatment strategy currently used in middle aged people.*

Source: Shepherd J, et al. *Lancet*. 2002;360:1623-1630.

Among patients with coronary artery disease, HMG CoA reductase inhibitors (statins) are a mainstay of therapy. These drugs have also become widely prescribed with a low threshold to patients with elevated cholesterol and even minimal cardiac risk factors. The role of statins in patients with stroke and other forms of neurological disease is less well defined. Because statins inhibit the activity of beta and gamma secretases, enzymes involved with the cleavage of amyloid precursor protein, they are now thought to be potentially efficacious in preventing the formation of amyloid plaques and the onset of clinical Alzheimer's disease (AD). Cholesterol lowering may further protect against dementia by limiting the damaging effects of apolipoprotein E, specifically in those patients with the APO e4 allele, a known risk factor for AD. Statins may furthermore be beneficial in the prevention of "vascular" or "multi-infarct" dementia by preventing small vessel strokes or by endothelial remodeling on a microvascular level.

In the pravastatin in elderly individuals at risk of vas-

cular disease (PROSPER) study, 5804 individuals aged 70-82 were randomized to pravastatin 40 mg/d or placebo. Subjects either had a history of vascular disease or had vascular risk factors. The primary outcome measure was a composite end point of coronary death, nonfatal myocardial infarction, or stroke, measured after 3 years of therapy. Pravastatin reduced LDL cholesterol by 34%, from a mean of 146 mg/dL to approximately 100 mg/dL. Statin therapy reduced the risk of a primary end point by 15%. In subgroup analysis, coronary events were reduced by 19%, while no discernable effect was found for stroke. Transient ischemic attack was reduced by 25% but was of borderline significance. The overall incidence of stroke outcomes was low, occurring in 116 treated patients and 119 in the placebo group.

Cognitive outcomes were studied by multiple measures, including digit span, picture-word recall, Stroop test, and mini-mental status examination. Functional outcomes were also explored, including the Barthel index and the instrumental activities of daily living score. Statin therapy had no significant effect on any of these outcomes.

COMMENT BY ALAN Z. SEGAL, MD

The results of the PROSPER study are taken in the context of those of the larger British Heart Protection Study (HPS), which was also reported in *Lancet* this year.[1] Unlike PROSPER, the HPS study did show a decrease in stroke risk. HPS followed patients for a longer period of time (5 years) and had more cerebrovascular outcomes, 444 treated vs 585 placebo (P = 0.002). These differences, however, did not impact cognitive decline. As in PROSPER, statin therapy (in the case of HPS-simvastatin) did not prevent dementia. Although pravastatin and simvastatin are quite similar, it is intriguing that the latter is a possibly more efficacious cerebrovascular drug since it is more lipophilic and may have greater CNS penetration.

These data provide further support to the concept that statin therapy should be prescribed to prevent coronary events in patients with known disease or with risk factors, regardless of age. Both PROSPER and HPS indicate that older age patients (older than 70) derive similar cardiac benefits to younger patients.

These data are less clear about the prevention of stroke and dementia. Part of this problem lies in the heterogeneity of the dementing disorders. Do statins prevent vascular dementia through the prevention of small vessel strokes and microvascular disease? Or do they prevent AD through effects on amyloid? Do other forms of dementia such as Diffuse Lewy Body Disease factor into this equation in any important way?

In addition to their high cost, statins are not free of side effects. Particularly when taking atorvastatin, patients develop often-disabling myalgias, even with normal measurements of CPK. Perhaps as more elderly individuals are treated with statins we may be able to glean information from observational studies. There does not seem justification to begin widespread prophylactic use at this time. ■

Dr. Segal is Assistant Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, New York Presbyterian Hospital, New York, NY.

Reference

1. *Lancet*. 2002;360:7-22.

Pharmacology Update

Cyclosporine Ophthalmic Emulsion 0.05% (Restasis—Allergan)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

THE FDA HAS APPROVED CYCLOSPORINE OPHTHALMIC emulsion for the treatment of dry eyes due to keratoconjuctivitis sicca (KCS) and associated reduced tear production. Cyclosporine is an immunomodulating agent that increases tear production in patients with KCS. It will be marketed by Allergan as Restasis.

Indications

Cyclosporine ophthalmic is indicated for patients with suppressed tear production due to ocular inflammation associated with KCS.[1]

Dosage

The recommended dose is 1 drop in each eye twice daily (12 hours apart). It may be used concomitantly with artificial tears but should be instilled 15 minutes apart.[1] Cyclosporine emulsion is supplied as preservative-free, single-use vials each containing 0.4 mL of emulsion. The drug should not be administered with a contact lens in place. The lens should be removed and reinserted after 15 minutes.

Potential Advantages

Cyclosporine emulsion provides certain objective and subjective improvement in patients with moderate-to-

severe dry eye disease.[1,2] Improvement in the integrity of the ocular surface and on baseline tearing has also been reported. The patients also reported less blurred vision and decrease in the use of artificial tears.

Potential Disadvantages

The most common side effect is burning eyes (14.7% vs 6.5% for vehicle). No increases in tear production were seen in patients on topical anti-inflammatory drugs or using punctal plugs.[1] Cyclosporine appeared to affect baseline tearing but not reflexive tearing.[2]

Comments

Cyclosporine appears to have modest beneficial effects on moderate-to-severe dry eyes in patients with KCS. The mechanism of action is not well understood but may involve suppression of the inflammatory process. After 6 months of treatment, cyclosporine emulsion was reported to result in an increase of goblet cells in the conjunctiva and reduction in the number of activated T lymphocytes within the ocular surface in patients with non-Sjögren syndrome-associated and Sjögren syndrome-associated KCS.[3,4] Efficacy was demonstrated in 4 multicenter, randomized studies in about 1200 patients with moderate-to-severe KCS. Two multicenter, randomized studies (293 treated with cyclosporine 0.05% and 292 treated with vehicle) were published. Statistically significant improvement was seen in 2 objective measures (corneal staining and Schirmer values) and 2 subjective measures (blurred vision and use of lubricating drops).[2] The beneficial effects appeared to be relatively modest at 6 months. A mean difference of 0.5 units from baseline in the Schirmer score (5-point scale) was observed. Significant tear production (Schirmer wetting of 10 mm) was seen in 15% of cyclosporine-treated patients compared to 5% for the vehicle.[1] A mean difference of about 0.5 units was observed in the blurred vision score (4-point scale). There was mean reduction of a 0.5 unit per day use of artificial tears compared to vehicle. Based on physicians' subjective assessment of global response, 35.5% of treated patients were considered to have at least a moderate response compared to 31.9% in the vehicle group. The castor oil in the vehicle may contribute to improvement of symptoms by reducing the evaporation of the natural tears.[2] Patients with end-stage lachrymal gland disease or destruction of conjunctival goblet cells or scarring were excluded. Cyclosporine ophthalmic emulsion appears to be well tolerated. There are no detectable cyclosporine levels detected in the blood after 12 months of treatment.[1]

The product is expected to be launched in the second quarter of 2003.

Clinical Implications

The pathophysiology of KCS is believed to be an immune-based inflammatory condition characterized by decreased tear production by lacrimal gland and increase evaporation of tears from the ocular surface.[3,5] Symptoms include burning, irritation, blurred vision, contact lens intolerance, and the inability to produce emotional tears. These patients are also at increased risk of infections and ocular surface damage. The incidence increases with age, in postmenopausal women, and patients with diseases such as Sjögren's syndrome, rheumatoid arthritis, lupus, and diabetes. Current treatment is artificial tears and punctal occlusion procedures. Cyclosporine ophthalmic emulsion is the first therapeutic treatment approved by the FDA. While improvements appeared to be modest, it does, however, offer a new treatment option for patients suffering from moderate-to-severe KCS. ■

References

1. Restasis Product Information. Allergan, Inc. 2002.
2. Sall K, et al. *Opthalmology*. 2000;107:631-639.
3. Kunert KS, et al. *Arch Ophthalmol*. 2002;120:330-337.
4. Kunert KS, et al. *Arch Ophthalmol*. 2000;118: 1489-1496.
5. Lemp M. *Rheumatolol*. 2000;61(Suppl):11-14.

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8. In the cost-effectiveness analysis of lung cancer screening with helical CT:

a. helical CT detected lung cancers at an earlier stage.
b. there were more lung cancer deaths in the unscreened group.
c. helical CT detected more peripheral cancers than endobronchial cancers.
d. the screened group underwent 1186 procedures for benign

lesions.

e. All of the above

9. Which one of the following is incorrect?

a. The use of natalizumab is associated with and improved feeling of well being.

b. Natalizumab lowered the levels of C-reactive protein in patients with Crohn's disease.

c. The use of interferon in the treatment of multiple sclerosis is associated with fewer side effects than treatment with natalizumab.

d. Whether the development of antibodies against natalizumab will effect long-term treatment with this antibody is unknown.

10. In the recent Hong Kong study of arthritic patients receiving COX-2 NSAID therapy with celecoxib 200 mg b.i.d. or diclofenac 75 mg b.i.d. plus omeprazole 20 mg daily, which of the following statements applies?

a. Ulcer recurrence and bleeding can be successfully averted using either COX-2 NSAIDs or combining nonselective NSAID therapy with a PPI.

b. Renal toxicity is rare with NSAID therapy in high-risk patients.

c. *H pylori* infection probably has no effect on the likelihood of ulcer complication in NSAID users.

d. Efficacy of nonselective NSAID therapy for arthritis is clearly superior to treatment using a COX-2 inhibitor

e. None of the above

Answers: 8 (c); 9 (c); 10 (c)

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By Louis Kuritzky, MD

Ice Cream-Evoked Headaches Study: A Randomized Trial of Accelerated vs Cautious Ice Cream Eating Regimen

ICE CREAM HEADACHE (ICH) IS A COMmonplace phenomenon induced by ingestion of cold substances, of which ice cream is but one of many potential precipitants. The limited literature on this topic had suggested that ICH only occurs in hot weather, as if the contrast between hot ambience and cold palatal or pharyngeal stimulation might foster ICH. Kaczorowski and Kaczorowski, "in order to fill this important knowledge gap . . . " as they so state in their publication, carried out a winter-time randomized trial (n = 145) amongst high-school students to determine whether, indeed, ICH is an experience only attained in hot weather. Additionally, subjects were divided into 2 different ingestion modes, one "accelerated" (eating 3 ounces of ice cream within 5 seconds) the other "cautious" (3 ounces within 30 seconds). There were no refusals, dropouts, or subjects lost to follow-up.

Overall previous experience with ICH was 79% amongst participants. In this trial, cautious eaters reported less than half the incidence of ICH than accelerated eaters (13% vs 27%). ICH is readily precipitated in cold weather, as demonstrated in this trial. Kaczorowski and Kaczorowski graciously acknowledge that the funding of the study was supported "by an unrestricted grant from mum and dad." ■

Kaczorowski M, Kaczorowski J. BMJ. 2002;325:1445-1446.

Treatment of Antidepressant-Associated Sexual Dysfunction with Sildenafil

SEXUAL DYSFUNCTION (SXD), WEIGHT gain, and sleep disturbance comprise as much as 75% of the adverse events that ultimately lead to antidepressant medication discontinuation. Of course, premature medication discontinuation is associated with a substantial risk of depression relapse, with its attendant morbidity and mortality.

Between 30-70% of persons who take SSRIs experience sexual dysfunction and will subsequently prematurely discontinue medication. The favorable retrospectively observed results of providing sildenafil to persons suffering SSRI-induced SXD prompted this prospective, randomized, placebo-controlled trial (n = 90).

Inclusion criteria required at least 6 weeks stable dosing of SSRI, and at least 4 weeks duration of SXD. Subjects were randomized to sildenafil 50-100 mg or placebo, and instructed to attempt intercourse at least twice weekly.

Sildenafil recipients showed significant improvements in erectile function, orgasm, intercourse satisfaction, and overall satisfaction compared with placebo. No serious adverse events attributable to sildenafil were seen. Overall, sildenafil allowed over 55% of recipients to experience 'much/very much improved' sexual function, as compared to 4-6% in the placebo group. ■

Nurnberg HG, et al. JAMA. 2003;289: 56-64.

Prophylactic Treatment of Migraine with an Angiotensin II Receptor Blocker

DESPITE THE VERY FAVORABLE effect of triptans upon migraine morbidity, a substantial population of persons either does not respond to, or chooses not to use, these agents. Expert advice has suggested that prophylaxis be considered predicated upon headache frequency, typically 2-4 headaches per month providing sufficient burden to merit a preventive pharmacotherapeutic agent. Recently lisinopril has been found to be an effective agent for migraine prophylaxis. Similarities in neurohumoral modulation of ACE inhibitors, when compared with angiotensin I receptor blockers (ARBs), would suggest that the latter might also be of benefit. Indeed, clinical trials in hypertension patients have consistently found a lower frequency of headache amongst ARB-treated patients than with placebo.

This randomized, double-blind placebo-controlled crossover study (n = 60) compared candesartan (CAN) 16 mg/d with placebo, in 2 12-week periods of observation (after a 4-week placebo run-in to verify attack frequency). Study subjects were normotensive throughout the trial, but did experience a 11/7 decline in BP. CAN was found to produce a statistically significant reduction in number of days with headache (13.6 vs 18.5), headache severity index, and level of disability. ARBs may be a new tool for prevention of migraine, especially because of their very favorable tolerability profile. ■

Tronvik E, et al. JAMA. 2003;289: 65-69.

In Future Issues: **ECG Review: Chest Pain in a 21-Year-Old**