

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Influenza Prevention 2002-2003

The influenza vaccine for the 2002-2003 season will include last year's A strains and a new B strain, B/Hong-Kong/330/01-like. Three manufacturers will supply the vaccine. The Public Health Service has issued a statement encouraging vaccine use, particularly in healthy children 6 to 23 months, because this age group has been shown to be at increased risk for complications associated with influenza infection.

Antibodies reach protective levels about two weeks after injection and generally persist six months or longer, but serum antibodies in some elderly people fall below protective levels in four months or less. Based on these considerations, the optimal time to receive the influenza vaccine is October or November.

In the event of shortages, groups with high priority are adults 65 years of age or older, children 6 to 23 months, pregnant women who will be in their second or third trimester during the influenza season, residents of nursing homes, patients with chronic diseases, healthcare workers, caregivers of high-risk patients, and children less than nine years of age [*Medical Letter* 2002;44:75].

Guidelines on Breast-Cancer Chemoprevention

The U.S. Preventive Services Task Force has published clinical guidelines for chemoprevention of breast cancer with tamoxifen and raloxifene. The task force concluded that, for women who are at a low to average risk of developing breast cancer, the potential harms of chemoprevention may outweigh the potential benefits. For women at high risk of developing breast cancer, the task force does not recommend use of these drugs, but rather that physicians discuss their use with their patients [www.preventiveservices.ahrqu.gov].

The guidelines are based on a systematic review done at an evidence-based practice center in North Carolina. A survey of the medical literature uncovered only four trials that met the inclusion criteria. Three of the selected trials evaluated tamoxifen effects on breast-cancer risk and the fourth primarily studied raloxifene in women with osteoporosis. The reviewers concluded that the evidence was "fair" that tamoxifen can reduce the risk of invasive estrogen-receptor positive breast cancer in women at high risk. The evidence for raloxifene, which is not approved by the FDA for chemoprevention, was consistent with that for tamoxifen. Benefits, however, must be balanced against potential harms such as increased risk of thromboembolic disease and endometrial cancer [*Ann Intern Med* 2002;137:52-54, 56-58, 59-67]. How helpful the guidelines will be to physicians and patients remains to be seen.

CLINICAL PRACTICE (continued)

Treatment of Persistent Pain in the Elderly

Experts considering the best way to treat persistent pain in elderly patients, as a consequence of arthritis, back disorders, or other causes, seem to agree that acetaminophen is a good first step for mild to moderate conditions. In a highly controversial step, however, both the American Geriatrics Society and the American Pain Society have come out in favor of COX-2 inhibitors if acetaminophen is not satisfactory for persistent pain. Although the COX-2 inhibitors are no more effective than traditional NSAIDs, the societies stressed the need to avoid the chronic use of NSAIDs in older, frail patients because of the high risk of gastrointestinal bleeding.

However, whether COX-2 inhibitors are safer is uncertain. There is no evidence to support the use of *Celebrex* (celecoxib). *Vioxx* (rofecoxib) was proved safer than naproxen in a general population. Further-

more, any gastrointestinal benefit of using a COX-2 inhibitor is likely to be reduced or disappear in patients taking low-dose aspirin to prevent heart disease. Some experts think that the chronic use of all NSAIDs, including COX-2 inhibitors, should be avoided in the elderly.

What are the alternatives? According to the *Prescriber's Letter* [2002;9:37] physicians might consider trying salsalate (*Disalcid*) or choline magnesium trisalicylate (*Trilisate*), both of which are safer than traditional NSAIDs and cost less than COX-2 inhibitors. Opioids—hydrocodone, oxycodone, or morphine—are preferred for moderate to severe pain. Gabapentin and some other anticonvulsants relieve neuropathic pain. The newsletter also recommends a trial of glucosamine for patients with joint pain.

Updated Recommendations for Antiretroviral Treatment of Adult HIV Infection

The partial restoration of CD4 cells during suppression of HIV replication with potent antiretroviral agents has resulted in dramatic reductions in morbidity, mortality, and health care utilization. However, the toxicity of many regimens and the emergence of drug resistance calls for new treatment strategies to address these challenges. These strategies include both new antiretroviral drugs, and approaches to enhance host cellular immune control of HIV replication. Evolution in the treatment arena over the past few years has prompted the need for a reevaluation of treatment guidelines, especially in determining when to initiate therapy. The task was undertaken by the USA Panel of the International AIDS Society [*JAMA* 2002; 288:222-35].

Data support the premise that CD4 cell count is the major determinant of initiating therapy. In previously untreated patients, antiretroviral drugs should be prescribed before the CD4 cell counts fall to 200/ μ l or less, because studies have shown an increased mortality when therapy is initiated in patients with counts below 200/ μ l. However, the ideal CD4 count above 200/ μ l at which to start therapy is unclear. That serious illness and other complexities are seen in some patients with CD4 levels above 200/ μ l, supports the use of a CD4

cell count threshold higher than 200/ μ l. In patients with CD4 counts above 350/ μ l, the risk of three-year clinical progression is low. Initiation of therapy offers few benefits but potentially decreases quality of life, increases risk of serious adverse drug effects, and limits future treatment options. However, initiation of therapy may be considered in such patients who also have a viral load above 50,000 to 100,000 copies/ml, or a rapidly declining CD4 cell count, even if it is above 350/ μ l. Therapy continues to be recommended in all patients with symptomatic established infection regardless of CD4 cell count.

The choice of initial therapy should be individualized based on efficacy and durability of antiretroviral activity, tolerability, and adverse effects. There is little difference in clinical activity in trials between regimens that contain two nucleoside reverse transcriptase inhibitors (NRTIs) with either a nonnucleoside reverse transcriptase inhibitor (NNRTIs) or a single (or ritonavir-boosted) protease inhibitor. The panel singled out the protease inhibitor combination of lopinavir and ritonavir as an important addition to the list of approved agents. Triple NRTI regimens, especially those that include abacavir, have become an alternative initial therapy.

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Updated Recommendations for Antiretroviral Treatment (continued)

The panel recommends close monitoring of antiretroviral therapy with an emphasis on assessment of adherence to the prescribed therapy, CD4 cell counts and viral load, and drug resistance. Substituting individual antiretroviral agents is frequently indicated because of drug-specific toxic effects. Wholesale changes may be needed in the event of treatment failure due to drug-resistant virus. When a decision is made to change therapy because of sustained virological failure, the new regimen should be one with the highest likely ef-

fectiveness, as predicted by the patient's drug history and resistance test results, as well as the highest likelihood of tolerability and adherence.

The panel also noted several new agents in development, derived from current drug classes (e.g., the NRTIs amdoxovir and emtricitabine, the NNRTIs DPC-083 and TMC-125, and the protease inhibitors atazanavir and tipranavir) and new drug classes including entry inhibitors (e.g., enfuvirtide) and integrase inhibitors.

NEW DRUGS AND INDICATIONS

Iressa for Advanced Non-Small Cell Lung Cancer

Patients with lung cancer have almost certainly learned about *Iressa* (gefitinib), because it has been the subject of laudatory coverage in the media. *Iressa*, an oral inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, has not been approved in the U.S. but is in clinical trials for the treatment of non-small cell lung cancer (NSCLC). *Iressa* is available from AstraZeneca on a "compassionate use" basis.

EGFR is a cell surface receptor with an intracellular tyrosine kinase domain that, when activated, initiates signaling events that regulate cell proliferation and survival. Most NSCLC express EGFR, often at high levels. Gefitinib is a highly selective inhibitor of the EGFR tyrosine kinase.

Iressa has been studied as monotherapy for patients with advanced NSCLC in noncomparative trials published only as abstracts. One study enrolled 210 patients and found a response rate of 18.4% with 250 mg/day and 19% with 500 mg/day in patients who had failed one or two previous chemotherapy regimens, at least one of which contained a platinum derivative; overall survival was about eight months. Another study enrolled 216 patients who had failed at least two chemotherapy

regimens that contained a platinum derivative and docetaxel, given concurrently or sequentially, and reported a response of 11.8% in patients who received the low dose of *Iressa* and 8.8% of those who received the high dose; median survival was about six months.

The results of clinical trials comparing standard platinum-based chemotherapy alone with chemotherapy plus *Iressa* as first-line treatment in more than 2000 patients with advanced NSCLC, scheduled to be presented at an international medical oncology meeting in October, show that the addition of *Iressa* did not improve survival or quality of life. According to the *Medical Letter*, "Oral monotherapy with gefitinib (*Iressa*) in patients with advanced NSCLC refractory to conventional treatment, produced tumor responses in less than 20% of patients and decreased symptoms in about 40% without causing serious adverse effects. Used as first-line treatment in combination with standard chemotherapy, gefitinib apparently did not improve survival or quality of life" [*Medical Letter* 2002;44:77-78]. The FDA is now considering the fate of *Iressa*, following a positive recommendation from an advisory committee favoring third-line use.

New Indication for Bosentan

The dual endothelin receptor antagonist *Tracleer* (bosentan), recently approved for the oral treatment of pulmonary arterial hypertension, has now been shown to be effective in the prevention of digital ulcers in patients with scleroderma [*Scrip*, 21 August 2002]. The drug's manufacturer intends to seek a second orphan drug designation for *Tracleer* in this additional patient population.

Scleroderma is a serious connective tissue disorder. In about 25% of patients, fibrosis in the extremities leads to spasm in blood vessels, especially in response to changes in temperature. Affected digits manifest pain, ulceration, and infection, and suffer a severe loss of function. Some fear that bosentan is too expensive as a prophylactic for digital ulcers.

NEW DRUGS AND INDICATIONS (continued)

FDA Approves Preservative-Free Influenza Vaccine for Pediatric Use

Aventis Pasteur announced FDA approval to market *Fluzone* (a preservative-free, pediatric dose, influenza virus vaccine). For the first time, physicians will have the option of offering a preservative-free formulation of the influenza vaccine to infants aged 6 to 35 months. The new product is expected to ensure continued public confidence in the influenza vaccine for young children. With this development, the Centers

for Disease Control and Prevention's Advisory Committee on Immunization Practices may strengthen its current encouragement to annually immunize healthy children aged 6 to 23 months, because they are at substantially increased risk for influenza-related hospitalizations. Unfortunately, Aventis Pasteur can provide only a limited quantity of pediatric *Fluzone* for the 2002-2003 season.

FDA Approves Trial for Interferon in the Treatment of West Nile Virus

A New York hospital has received FDA approval to begin the first trial of *Intron-A* (interferon alfa-2b) to treat patients infected with West Nile virus. The study will enroll 40 patients nationally, wherever they are hospitalized. All patients 50 years old or older are eligible; younger patients will be eligible only if they have developed encephalitis. The study seeks to determine

whether interferon can decrease the duration of illness and severity of neurological symptoms and prevent death. The randomized nonblinded trial will treat half the patients with *Intron-A* and the other half with standard hospital care. Whether Schering-Plough pursues an expanded trial if the preliminary data are promising remains to be seen [*Reuters Health*, 22 August 2002].

DRUG SAFETY

More Evidence of Olanzapine-Diabetes Link

Further evidence of an association between the atypical antipsychotic agent olanzapine (*Zyprexa*) and diabetes has been reported in the *BMJ* [2002; 325:243-48]. The findings of a case-control study suggest that patients with schizophrenia taking olanzapine are at increased risk of developing type 2 diabetes as compared with nonusers of antipsychotic medication and those taking conventional antipsychotic drugs. Compared with nonusers of antipsychotic agents, patients who received olanzapine were nearly six times more likely to develop diabetes. Compared with conventional antipsychotic drugs, olanzapine increased the risk of diabetes about 4-fold. The study also examined the risk of diabetes with risperidone (*Risperdal*), and found that patients taking the product had a nonsignificant increased risk compared with nonusers of antipsychotic agents and those taking conventional antipsychotic drugs.

Physicians should keep a close eye on weight gain and glucose levels in patients on any atypical antipsychotic agent, but olanzapine appears to pose a special problem. The potential mechanism for this association

is not known, but may be related to the serotonergic system. Inhibition of 5HT_{1A} sites can decrease insulin output by reducing pancreatic beta-cell responsiveness, while 5HT_{2A/C} receptor agonists can cause hyperglycemia [*Scrip*, 9 August 2002]. Lilly rejects the proposition that diabetes is more of a problem with olanzapine than with other atypical agents. Indeed, there is no evidence of this in head-to-head studies.

Adverse Effects of HIV Medication

Serious side effects compromise the adherence of HIV-infected patients to prescribed highly active antiretroviral therapy (HAART). *The Prescriber's Letter* [2002; 9:180818] has prepared a succinct document discussing the prominent adverse effects of HIV medications.

Lactic acidosis can occur during treatment with nucleoside or nucleotide reverse transcriptase inhibitors (RTIs). Risk factors for this toxicity are obesity, female gender, pregnancy, and prolonged use of these classes of RTIs. Hepatotoxicity—a 3 to 5 times increase in serum transaminases—has been reported in patients receiving HAART that includes a nonnucleoside RTI or a protease inhibitor. Among the nonnucleoside

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DRUG SAFETY (continued)

Adverse Effects of HIV Medication (cont.)

RTIs, nevirapine has the greatest potential for causing clinical hepatitis. Nevirapine probably should be avoided in HIV patients with hepatitis B or C infection.

Hyperglycemia, new-onset diabetes, and exacerbation of preexisting diabetes have been reported among patients receiving HAART and are strongly associated with protease inhibitor use. Fasting glucose levels should be checked every 3 to 4 months during the first year of treatment for all patients starting anti-HIV therapy that includes a protease inhibitor, and especially for those with diabetes. HAART is also associated with elevation of total and low-density lipoprotein serum cholesterol, as well as increases in fasting trig-

lycerides. Dyslipidemias occur primarily with protease inhibitors, but some evidence suggests that the toxicity may be drug-specific rather than class-specific. Elevated lipid levels might be associated with accelerated atherosclerosis and cardiovascular complications.

Decreased bone density is now recognized as a complication of HIV infection that might be linked to HAART. It appears to be more closely but not exclusively associated with protease inhibitors. Recommending adequate intake of calcium and vitamin D is reasonable for all patients receiving HAART. When fractures occur or osteoporosis is documented, more specific therapy with bisphosphonates or raloxifene might be indicated.

DRUG EVALUATION

Risperidone Controls Behavior in Autistic Children

The results of a recently reported study suggest that the atypical antipsychotic agent risperidone is effective and well tolerated for the treatment of tantrums, aggressive behavior, and self-injurious behavior in autistic children [*N Engl J Med* 2002;347:314-21]. In the study, 101 autistic children, 5 to 17 years of age, were randomly assigned to risperidone or placebo. Risperidone was initiated at a dose of 0.5 mg/day and increased to a maximum dose of 2.5 mg/day. After eight weeks of therapy, children in the risperidone group showed a 57% reduction in a standardized irritability score compared with a 14% reduction in the placebo group.

The research team defined a positive response to therapy as a minimum reduction of 25% on an irritability score and a rating of much improved or very

much improved on a standardized clinical global impressions-improvement scale. This response was seen in 69% of the children who received risperidone compared with 12% of the children who received placebo. About two thirds of patients who had a positive response to risperidone maintained the benefits at six months. Compared with children on placebo, children on risperidone had an increased appetite and gained more weight, and complained more frequently of fatigue, drowsiness, dizziness, drooling, and constipation. But the side effects were mild and usually resolved within a few weeks. The report attracted attention because the search for safe and effective psychotropic medication that might benefit children with autism has been frustrating.

Tirofiban Is as Effective as Abciximab in the Long Term

The superiority of abciximab (*ReoPro*) over tirofiban (*Aggrastat*) at 30 days following administration during percutaneous coronary revascularization with stent placement, appears to disappear at six months. The two glycoprotein IIb/IIIa platelet receptor inhibitors provide similar long-term protection against a composite end point of death, myocardial infarction, and target vessel revascularization [*Lancet* 2002;360:355-60]. The findings derive from a study that enrolled a total of 4809 patients who were undergoing elective or

urgent stent implantation. The composite end point occurred in 14.8% of the patients in the tirofiban group and in 14.3% of the patients in abciximab group. The incidence of heart attacks was slightly higher in the tirofiban group, but the incidence of revascularization was slightly lower. None of the differences were significant. The investigators concluded, "While the more expensive drug (abciximab) is better up front, it provides little long-term advantage compared with tirofiban" [*Reuters Health*, 2 August 2002].

Simvastatin Quickly Lowers C-Reactive Protein Levels

In recent years, research has suggested that inflammation ranks high as a possible cause of heart disease. Inflammation also causes complications after heart attacks and heart surgery. A new study provides the strongest evidence to date that statins not only lower cholesterol, they also independently reduce levels of an important inflammatory factor, C-reactive protein, within just two weeks [*Circulation* 2002;106:1447-52].

In a well-controlled, crossover study, 40 subjects with elevated LDL cholesterol received simvastatin for 14 days and then placebo for 14 days, or placebo first and then simvastatin. Simvastatin prompted a significant reduction in LDL cholesterol at 7 days and addi-

tionally at 14 days. By day 14, C-reactive protein levels were significantly lower during the simvastatin phase than during the placebo phase. Analysis revealed no association between the reductions in cholesterol levels and the reductions in C-reactive protein levels.

The lead investigator told *Reuter's Health* [27 August 2002], "The speed with which simvastatin lowers C-reactive protein levels raises the question of whether statins may prove useful for the acute treatment of coronary events." He added, "I wouldn't promote its use on the basis of one study, but the evidence for its usefulness is increasing over time."

Men with BPH May Benefit from Combination Therapy

Benign prostatic hyperplasia (BPH), with its attending urinary urgency, frequency, and nighttime urination, affects about nine million men in the U.S. A news release from the National Institutes of Health in May reported that two drugs commonly used to treat BPH, the 5-alpha-reductase inhibitor finasteride (*Proscar*) and the alpha-1 receptor blocker doxazosin (*Cardura*), are more effective in combination than alone to prevent progression.

A trial sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases found that, compared to placebo, finasteride and doxazosin together reduced the risk of BPH progression by 67%.

The risk of progression was reduced by 39% with doxazosin alone and 34% with finasteride alone. Combination therapy was also more effective than either drug alone in reducing the risk of urinary retention and the risk of invasive therapy, and finasteride was more effective than doxazosin in this regard. An abstract of the to-be-published report is available at www.niddk.nih.gov.

The *Prescriber's Letter* recommends that combination therapy be used first line for men at higher risk for BPH progression, those who are over 50 with low urine flow, high PSA levels, or enlarged prostates [2002; 9:180714].

CONTROVERSIES AND QUANDARIES

NIH Trial to Test Chelation Therapy

The National Institutes of Health is investing, some say foolishly, \$30 million into a major clinical trial of a controversial cardiovascular therapy that has little scientific rationale. The NIH's National Heart Lung and Blood Institute (NHLBI) and National Center for Complementary and Alternative Medicine (NCAAM), announced joint funding of a 5-year study to determine whether chelation therapy can help patients with heart disease.

EDTA, the active component of chelation therapy, binds with minerals in the body and is a long-established treatment for heavy metal poisoning. In the past 20 years, it has also become a widely

used "alternative" treatment for arterial plaque through its purported ability to draw off calcium. Skeptics say chelation is scientifically implausible and that the only supporting evidence is anecdotal. Current thinking is that calcium plays only a small role in plaque. Furthermore, EDTA is water-soluble and, therefore, could not penetrate fatty membranes and affect calcium in plaques. In the face of these arguments, advocates of chelation therapy say that EDTA is also an antioxidant and provides its putative benefit by decreasing oxidation of plaque-forming cholesterol. Opposing this claim is the idea that chelation may actually promote oxidation by producing free radicals [*Science* 2002;297:1109].