

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Avoid Atenolol for Initial Treatment of Uncomplicated Hypertension

Evolving evidence continues to suggest that atenolol may not work as well to prevent myocardial infarction and stroke as other antihypertensive agents [*Prescriber's Letter* 2005;12:210410]. The LIFE trial compared losartan-based with atenolol-based therapy in more than 9000 patients with hypertension over the age of 55 with left ventricular hypertrophy [*Lancet* 2002;359:995-1003]. Blood pressure control was similar with the two regimens. Losartan-based therapy reduced the risk of the primary outcome (23.8% vs. 27.9%), a composite of cardiovascular mortality, myocardial infarction, and stroke, as compared with atenolol-based treatment, primarily reflecting a 25% difference in the risk of stroke.

The most recent study to evaluate the role of beta-blockers in treating hypertension, ASCOT, compared the incidence of coronary heart disease (CHD) events with atenolol plus a diuretic (bendroflumethazide) if needed, versus a calcium channel blocker (amlodipine) plus an ACE inhibitor (perindopril) if needed, in more than 19,000 patients with hypertension and at least three CHD risk factors. The study was stopped early because there was a greater reduction in all-cause mortality in the amlodipine-perindopril group than in the atenolol-diuretic group.

Preliminary results presented at the 2005 College of Cardiology Scientific Session showed that each regimen reduced systolic blood pressure to about the same extent. The primary endpoint, non-fatal MI and fatal coronary heart disease, was reduced by 10%, a difference that did not reach statistical significance. However, the relative risk of all-cause mortality was 14% lower with amlodipine-based therapy than with atenolol-based therapy ($p=0.005$). The amlodipine regimen also resulted in a significantly lower risk of cardiovascular mortality and of stroke.

The *Prescriber's Letter* observes that it is "unclear why atenolol seems less effective than other antihypertensive agents for improving outcomes or if it's specific to atenolol. Some experts suggest that atenolol's short half-life may be the culprit, especially if the drug is used only once a day." The author of the report suggests a thiazide diuretic for the initial treatment of uncomplicated hypertension, reserving a beta-blocker for patients with hypertension plus a compelling condition. For this purpose, metoprolol may be a better choice than atenolol.

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CLINICAL PRACTICE (continued)

Acupuncture Provides No Benefit for Patients with Migraine

Despite the widespread use of acupuncture to prevent migraine attacks, evidence of benefit is meager. A recent report in *JAMA* [2005;293:2118-25] concerns the efforts of German investigators to evaluate the efficacy of this procedure. The researchers enrolled 302 patients (88% women) with migraine headaches meeting internationally-accepted criteria and assigned them to one of three groups: acupuncture, sham acupuncture, or a waiting list control. Acupuncture and sham acupuncture were administered by specialized physicians and consisted of 12 sessions per patient over 8 weeks. The primary endpoint was the difference in headache days of moderate or severe intensity during the course of the trial, as determined by headache diaries.

The number of days of headache decreased by an average of 2.2 days from a baseline of 5.2 days in the acupuncture group compared with a decrease of 2.2 days from a baseline of 5.0 days in the sham acupuncture group and a decrease of 0.8 days from a baseline of 5.4 days in the waiting list control group. The proportion of responders (reduction in headache days by at least 50%) was 51% in the acupuncture group, 53% in the sham acupuncture group, and 15% in the waiting list group. The investigators conclude: "Acupuncture was no more effective than sham acupuncture in reducing migraine headaches although both interventions were more effective than a waiting list control."

DRUGS IN DEVELOPMENT

Prostate Cancer Vaccine Prolongs Life

A therapeutic vaccine for the treatment of prostate cancer, developed by Seattle-based Dendreon, has shown promise in a placebo-controlled trial in 127 men with advanced prostate cancer that no longer responded to hormone therapy. On average, the men who received the vaccine lived 26 months, compared with 21 months for those patients on placebo. Three years later, 34% of vaccine patients were still alive, compared with 11% of unvaccinated patients [*Reuters*, 18 February 2005].

The vaccine, called *Provenge*, is made by mixing a synthetic version of prostatic acid phosphatase (PAP)

with dendritic cells harvested from the patient. The preparation is designed to stimulate the immune system to attack the 95% of prostate cancer cells that generate PAP.

The only approved chemotherapy for patients with advanced disease, *Taxotere* (docetaxel), extends life by about 2.5 months. *Provenge* appears to be more effective in this regard and seems to be less toxic than chemotherapy. The availability of the therapeutic vaccine would allow testing of combination therapy.

A Vaccine to Prevent Shingles and Its Aftermath

In the U.S., herpes zoster, or shingles, affects hundreds of thousands of people annually, most of whom are older than 50. The increased incidence and severity of herpes zoster and postherpetic neuralgia among older adults are closely linked to a progressive age-related decline in cell-mediated immunity to varicella-zoster virus, the agent that causes chicken pox. Previous studies have shown that chicken pox vaccines can elicit a substantial increase in cell-mediated immunity to varicella-zoster virus. These observations led investigators to propose that immunization of older persons would boost their cell-mediated immunity and thereby protect against herpes zoster and its complications.

To test their hypothesis, a group of researchers, constituting the Shingles Prevention Study Group, enrolled 38,546 adults at least 60 years of age with a history of chicken pox in a placebo-controlled trial of an investigational live attenuated varicella-zoster virus vaccine (zoster vaccine), administered subcutaneously at the start of the study. The median duration of herpes zoster surveillance was about three years [*N Engl J Med* 2005;352:2271-84].

A total of 957 confirmed cases of herpes zoster were identified; outbreaks occurred twice as often in placebo groups as compared with the zoster vaccine
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A Vaccine to Prevent Shingles and Its Aftermath (continued)

group (642 cases vs. 315 cases). Resurgence of the virus resulted in 27 cases of postherpetic neuralgia among vaccine recipients and in 80 cases among placebo recipients. Reactions at the injection site, generally mild, were more frequent among vaccine recipients.

The minimum potency of the zoster vaccine administered to subjects in this study was at least 14 times

greater than the minimum potency of Merck's chicken pox vaccine, *Varivax*. There is no evidence that the chicken pox vaccine marketed throughout the world would be effective in protecting older adults from herpes zoster; its use is not recommended. While herpes zoster is almost never life threatening, the burden of illness resulting from this condition is considerable and sometimes awesome. Many would welcome the emergence of an effective vaccine.

DRUG EVALUATION

Colony-Stimulating Factor Provides Benefit in Treatment of Crohn's Disease

Sargramostim (*Leukine*) is a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), used to promote myeloid-cell recovery after chemotherapy. Crohn's disease is a chronic inflammatory disease occurring throughout the gastrointestinal tract, the treatment of which emphasizes immunosuppressive agents. Recent evidence suggests that the disorder may actually be the result of a breakdown of a defensive barrier in the gut. Loss of this protective layer of cells may permit persistent exposure of lamina propria cells to luminal microbes and microbial product, resulting in a chronic inflammatory process mediated by T cells. Therefore, treatment directed at augmenting the intestinal innate immune defense rather than suppressing a secondary inflammatory response may be effective in the treatment of Crohn's disease. Colony-stimulating factors may help maintain the function of the defensive barrier and exogenous GM-CSF may augment host defense and reduce inflammation associated with Crohn's disease.

Investigators have evaluated this possibility in a well-controlled trial in 124 patients with moderate-to-

severe active Crohn's disease who received 6 µg of sargramostim per day or placebo subcutaneously for 56 days. Antibiotics and aminosalicylates were permitted but not corticosteroids or other immunosuppressant agents [*N Engl J Med* 2005;352:2193-201].

Disappointingly, there was no significant difference in the rate of the primary endpoint of a clinical response defined by a decrease of at least 70 points on the Crohn's Disease Activity Index (CDAI). The endpoint was observed in 54% of patients on sargramostim and 44% in the placebo group. Although the trial would ordinarily be considered negative, the rates of prespecified secondary outcomes, a clinical response defined by a decrease from baseline of at least 100 points and remission (CDAI score < 150 points) on day 57 were significantly higher in the sargramostim group than in the placebo group (48% vs. 26%, and 40% vs. 19%, respectively). The investigators also report significant improvement in quality of life in the active treatment group, as compared with the placebo group. The study raises interesting possibilities.

Statins May Decrease the Risk of Colorectal Cancer

In vitro data support a role for the use of HMG-CoA reductase inhibitors (statins) in colorectal cancer. HMG-CoA reductase is overexpressed in colorectal-cancer cells and statins induce apoptosis in cancer cell lines. The incidence of cancer has been reported in several well-controlled trials designed to assess the safety and efficacy of statins among patients with cardiovascular disease. The outcomes have been decidedly mixed, but the small number of cancer cases observed in these studies limits their statistical power to detect

associations. To clarify the situation, investigators have evaluated data collected in a population-based case-control study of patients who received a diagnosis of colorectal cancer and matched controls in a 1:1 ratio. Nearly 4000 subjects were interviewed as to statin use [*N Engl J Med* 2005;352:2184-92].

The researchers found that the use of statins for at least five years was associated with a significantly re-

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DRUG EVALUATION (continued)

Statins May Decrease Risk of Colorectal Cancer (continued)

duced relative risk of colorectal cancer (odds ratio, 0.50). The association remained significant after adjustment for the use of aspirin or other NSAIDs, family history of colorectal cancer, ethnic group, and level of vegetable consumption, among other pertinent factors (odds ratio, 0.53). The use of fibric acid derivatives was

not associated with a reduced risk of colorectal cancer (odds ratio, 1.08).

The investigators urge further investigation of the overall benefits of statins in preventing colorectal cancer, recognizing that the impact may be modest because the absolute risk reduction is likely to be low.

Long-Term Antibiotic Treatment Does Not Alter Cardiac Events in At-Risk Patients

An observed association between chlamydia and atherosclerosis spurred a host of researchers to examine the possibility that antibiotic treatment might have a favorable effect on the course of coronary heart disease (CHD). Indeed, this strategy is being applied in some patients despite the absence of an established benefit. Two recent studies appear to put that possibility to rest [*N Engl J Med* 2005;352:1637-45; 1646-54].

In a randomized, prospective trial, investigators assigned more than 4000 patients with stable coronary artery disease to receive either azithromycin 600 mg or placebo weekly for one year. The participants were followed for an average of 3.9 years. Azithromycin had no effect on the primary endpoint, a composite of death due to coronary heart disease, nonfatal myocardial infarction, coronary revascularization, and hospitalization for unstable angina. About 20% of the patients in each group experienced a cardiac event. The results did not differ when the participants were stratified according to *Chlamydia pneumoniae* status at baseline.

In the other study, investigators enrolled 4162 pa-

tients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and assessed the efficacy of long-term treatment with gatifloxacin in a well-controlled trial. Patients received gatifloxacin 400 mg daily for two weeks, followed by a 10-day course every month for the duration of the trial. A survival analysis showed that the rates of primary-endpoint events at two years—death from all causes, myocardial infarction, unstable angina requiring hospitalization, revascularization and stroke—were 23.7% in the gatifloxacin group and 25.1% in the placebo group ($p=0.41$). No benefit was seen in any of the prespecified subject groups, including patients with elevated titers to *C. pneumoniae* or C-reactive protein.

Thus, the body of evidence suggests that antibiotics that are effective against chlamydia are not useful for secondary prevention of coronary disease. At the same time, evidence that infection can be a stimulus for atherothrombosis continues to mount. A related editorial urges that future research “should focus on expanding our limited knowledge base with regard to proatherogenic mechanisms...” [*Ibid*, 1706-08].

CLINICAL TRIALS

FDA Recognizes Burden on Clinical Trial Review Boards

In response to queries from the FDA, experts say that “the growth in the number and complexity of clinical trials has put great strain on institutional review boards” [*BMJ* 2005;330:748]. IRBs were established to approve and review biomedical research in humans, but their workload has grown so much that a new approach is needed, particularly for the recording of adverse events.

A former director of the U.S. Office of Human

Research Protections told the regulatory agency, “What we need to do now goes beyond tweaking the existing system... There is an urgent need and a compelling justification to create and implement a comprehensive national adverse event reporting system that takes advantage of currently available information technologies.” Meeting with clinical trial experts, the FDA learned that there is consensus for creating data safety monitoring boards for all multicenter trials.

DRUG SAFETY

SSRI Antidepressants Linked to Complications in Newborns

Babies born to women taking fluoxetine or a related antidepressant in the last trimester of pregnancy were three times as likely to develop drug-related symptoms as those born to women who did not use the drugs or took them only in early pregnancy. The findings derive from an extensive literature review as well as unpublished data from the FDA advisory committee meeting of June 2004 [*JAMA* 2005;293:2372-83].

For the most part, affected neonates display central nervous system, motor, respiratory, and gastrointestinal signs. Symptoms are usually mild and persist for no more than a week or two. Medical management has consisted primarily of supportive care in nurseries. A severe syndrome, consisting of seizures, dehydration, excessive weight loss, or hyperpyrexia is rare in term

infants. There have been no reported neonatal deaths attributed to these medications.

The FDA and involved drug manufacturers have recently agreed to a class labeling change for serotonin reuptake inhibitors—selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors—to include information about potential adverse events in neonates exposed *in utero*. The new labeling cautions physicians and patients about neonatal complications associated with late pregnancy exposure. The label lists the clinical features of the drug-related neonatal syndrome, suggests a withdrawal or toxicity mechanism, and states that tapering the antidepressant in the third trimester might be considered as an option to reduce or prevent these symptoms.

Heart Risk Increased with Duration of Use of Anti-HIV Drugs

Since the introduction of highly active antiretroviral therapy (HAART) in the mid 1990s, elevation in blood lipids and potentially increased risk of heart disease have preoccupied physicians. New findings, from a large observational study, summarized in *JAMA*, show that the risk of myocardial infarction (MI) increases with longer exposure to HAART [*JAMA* 2005;293:2081].

The findings derive from a survey that included more than 76,000 patient-years of follow-up. A total of 277 patients experienced a first MI, a rather high rate given the average age of the population, about 40 years old. Incidence increased from 1.39 per 1000 patient-

years in those who had not been exposed to antiretroviral drugs to 2.53 in those exposed to the drugs less than one year, and 6.07 in those exposed to the drugs for at least six years. The investigators estimated a 1.17-fold increased risk of a first MI per additional year of exposure to HAART. Whether some combinations of antiretroviral drugs are more likely to increase cardiovascular risks than others remains uncertain.

The researcher presenting the report, at the 12th Annual Retrovirus Conference, told *JAMA*, “The take-home message is that it’s very important that patients with modifiable risk factors be carefully monitored and every effort made to minimize these factors.”

Expert Panel Urges Restricted Use of *Natrecor* in Heart Failure

An independent panel recommended that *Natrecor* (nesiritide), a recombinant form of human B-type natriuretic peptide (hBNP), be restricted to acutely ill hospitalized patients and endorsed Johnson & Johnson’s plans for additional studies. The panel’s report strongly advised that *Natrecor* not be given to patients in outpatient clinic visits, a use that has strongly boosted sales; J&J has not discouraged this practice. The panel also suggested that in-hospital use of *Natrecor* be limited to patients with shortness of breath at rest and that alternative therapy be considered.

The report follows publication of analyses in *JAMA* [2005;293:1900-05] suggesting that patients

taking the drug were at increased risk of nephrotoxicity and death. The *JAMA* study found that patients who took *Natrecor* were 80 percent more likely to die within a month than patients who took older drugs. *Natrecor*, introduced in 2001, was the first drug approved for acute decompensating heart failure, an important cause of hospital admissions. Many patients given the drug have experienced rapid relief of symptoms. But *Natrecor* has never been studied outside of the hospital setting. Since the report, demand for *Natrecor* has fallen 30% [*The Wall Street Journal*, 14 June 2005].

Insulin Increases Risk of Death in Patients with Heart Failure

A recent publication presents surprising findings, suggesting that patients with advanced heart failure and insulin-treated diabetes have a much greater risk of dying compared with similar patients not receiving insulin [*Am Heart J* 2005;149:168-74]. Among a cohort of 554 patients with advanced heart failure, about 25% had diabetes. Nearly a third of these patients were on insulin therapy and the rest were non-insulin-treated.

One-year mortality rates were 10.3% for patients with normal blood glucose levels and 14.2% for non-insulin-treated patients, compared with 37.9% for insulin-treated diabetic patients. On multivariate analysis, insulin therapy was a highly-significant independent

predictor of mortality. The hazard ratio was 4.30. In an interview with *Reuters Health* [16 February 2005], the principal investigator stressed “the urgent need for further investigation to see whether we should try to avoid insulin in these patients.”

Correction

Low-Dose Aspirin in Primary Prevention of Cardiovascular Disease in Women: The lead story in the May 2005 DTT Supplement incorrectly reported a 34% reduction in the risk of ischemic stroke among low-dose aspirin users in the Women’s Health Study. The actual finding was 24%.

BIOMARKERS

Exhaled Nitric Oxide Guides Treatment of Chronic Asthma

Despite a deeper understanding of the underlying pathology and the availability of effective therapies, asthma remains a major health problem in the U.S. Although treatment guidelines abound, their application can be challenging because of the variable nature of the disease and poor compliance with home-based measurements of pulmonary function. Consequently, clinicians often fail to determine, for example, the appropriate dose of inhaled corticosteroid for an individual patient.

Biomarkers associated with asthma and used to judge control include the degree of hypersensitivity to methacholine or histamine and eosinophil counts in sputum. The amount of nitric oxide in exhaled air (FENO) is a recent addition to the list. All of these measures show favorable changes when inhaled corticosteroids are administered. Of the three, however, assessment of FENO may be the most reproducible, the least time-consuming, the least invasive, and the easiest to perform. The magnitude of FENO is increased in proportion to bronchial wall inflammation. Increases in FENO are associated with deteriorating control, and FENO levels decrease in a dose-dependent manner with anti-inflammatory therapy.

In a recently reported prospective, randomized controlled trial, researchers compared dose adjustment of an inhaled corticosteroid, fluticasone, using a FENO-based algorithm, or an algorithm based on

standard criteria of disease severity—symptoms, bronchodilator requirements, and pulmonary function test results [*N Engl J Med* 2005;352:2163-73]. After optimizing the corticosteroid dose in each group, the investigators followed 94 patients with mild-to-moderate asthma for up to 12 months.

At the end of the study, the mean daily dose of inhaled corticosteroid was remarkably different in the two groups, 370 µg per day for the FENO group and 642 µg per day for the control group. The rates of exacerbation of asthma, the primary endpoint, were 0.49 episodes per patient per year in the FENO group and 0.90 in the control group, representing a nonsignificant reduction of 46%. The need for oral prednisone, pulmonary function, and levels of airway inflammation (sputum eosinophils) did not differ between the two groups. The authors of the report conclude, “With the use of FENO measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control.”

A related editorial notes that a reduction of inhaled corticosteroid to the lowest effective dose is in the patient’s best interest once control of asthma is achieved. Without specific guidance, however, physicians often opt to continue treatment in patients who appear to be doing well when, in fact, the dose should be changed [*Ibid*, 2233-35].