

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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DRUG EVALUATION

Peginterferon Alfa-2a Plus Ribavirin for Chronic Hepatitis C Virus Infection

Until recently, the standard of care for patients with chronic hepatitis C was the addition of ribavirin to interferon-based therapies. However, some patients, particularly those with more resistant hepatitis C virus (HCV) genotypes, do not respond to these agents. Two types of pegylated interferons have been developed, peginterferon alfa-2b (*Peg-Intron*), which contains a linear polyethylene glycol (PEG) moiety, and peginterferon alfa-2a (*Pegasys*), which contains a branched PEG moiety. Both have demonstrated significantly superior efficacy to non-pegylated interferons in clinical trials. One study showed that peginterferon alfa-2b plus ribavirin produced significantly improved sustained virologic responses as compared with interferon alfa-2b plus ribavirin. Now, a study has reported on the comparative efficacies of peginterferon alfa-2a plus ribavirin, interferon alfa-2b plus ribavirin, and peginterferon alfa-2a alone for the treatment of chronic hepatitis C [*N Engl J Med* 2002;347:975-82].

A significantly higher proportion of patients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response—defined as the absence of detectable HCV RNA 24 weeks after stopping therapy—than did patients who received interferon alfa-2b plus ribavirin (56% vs. 44%) or peginterferon alfa-2a alone (56% vs. 29%). The proportions of patients with the relatively resistant HCV genotype 1 who had sustained virologic responses were 46%, 36%, and 21% for the three regimens. Responses to therapy were lower in patients with both HCV genotype 1 and high baseline levels of HCV RNA, especially so for peginterferon alfa-2a alone. Safety profiles of the treatment regimens were similar; the incidence of influenza-like symptoms and depression was lower in the groups receiving peginterferon alfa-2a than the group receiving interferon alfa-2b plus ribavirin. The efficacies of peginterferon alfa-2b plus ribavirin and peginterferon alfa-2a plus ribavirin have not yet been compared.

Controversy Over Use of Tamoxifen for Breast Cancer Chemoprevention

The best strategy to decrease the toll taken by breast cancer continues to be controversial. Recent studies have challenged the putative benefits of self-examination and mammography. Chemoprevention may prove to be a better approach. A report by the International Breast Cancer Intervention Study (IBIS) investigators in a

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DRUG EVALUATION (continued)

Controversy Over Tamoxifen for Breast Cancer Prevention (continued)

recent issue of *The Lancet* [2002; 360:817-24], provides data from the fourth randomized trial of tamoxifen as a chemopreventive agent for breast cancer. The previous trials have reported mixed results.

The randomized, double blind, placebo-controlled trial enrolled 7152 women aged 35 to 70 years, who were at increased risk of breast cancer. After median follow-up of 50 months, breast cancers were diagnosed in 1.93% of women in the tamoxifen group and in 2.83% in the placebo group, a relative risk reduction of 32%. Calculations based on the absolute difference of 0.90% suggest that 111 women at increased risk need to be treated with tamoxifen to prevent one case of breast cancer. The large number of women who must be treated but will derive no benefit is worrisome be-

cause tamoxifen is not benign. In the latest study, endometrial cancer was increased and thromboembolic events were significantly increased with tamoxifen. There was also a significant excess of deaths from all causes in the tamoxifen group.

A commentary on the report points out, “A cardinal requirement of chemopreventive agents is that they must be safe. Because they are given to many people, most of whom will not get the targeted condition, the agents must have a low profile of adverse effects. Tamoxifen clearly does not have a safety profile that would allow it to be used by enough women to have a large impact on the overall incidence of breast cancer” [*Ibid*, 813-14].

Aldosterone Blocker Further Reduces Cardiac Hypertrophy

Aldosterone causes vascular inflammation and tissue changes throughout the body but especially in the myocardium. Consistent with our understanding of the effects of aldosterone, new findings presented at the European Society of Cardiology Congress demonstrate that the selective aldosterone blocker eplerenone, newly approved for the treatment of hypertension, plus enalapril reduced left ventricular (LV) mass in patients with LV hypertrophy and hypertension compared with enalapril alone.

The study enrolled 55 patients with cardiac hypertrophy as well as systolic and diastolic hypertension. Patients were randomly assigned to receive eplerenone, enalapril, or a combination of the two drugs for nine

months. All treatments significantly reduced LV mass compared to baseline, but the combination reduced LV mass considerably more than either agent alone. Diastolic pressure was reduced similarly in all three treatment groups, but systolic blood pressure was reduced to a greater extent in the combination group [*Reuters Health*, 4 September 2002].

An earlier study demonstrated that spironolactone, the only aldosterone blocker approved in the U.S., added to standard therapy—an ACE inhibitor, loop diuretic, beta blocker, and digoxin—substantially reduced the risk of both morbidity and death among patients with severe heart failure [*N Engl J Med* 1999;341:709-17].

DRUG SAFETY

Stronger Warning Label for OTC Acetaminophen, Aspirin, and NSAIDs

Citing evidence that thousands of Americans unwittingly take toxic, potentially fatal, doses of acetaminophen each year, a panel of experts urged, by a vote of 21-1, stronger warnings for the analgesic, the main ingredient in about 200 nonprescription products, including *Tylenol*. In light of the billions of doses of acetaminophen taken each year, its risks are low—about 100 people die and more than 2000 are hospital-

ized annually as a result of unintentional overdose—but the panel held that the risks could be lowered. The principal reason for unintentional overdosing is the failure of consumers to recognize that their cough-cold, fever, and headache medications each contain acetaminophen [*Reuters Health*, 20 September 2002].

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Warning Label for Acetaminophen, Aspirin, and NSAIDs (continued)

The advisors called for every package of medication containing acetaminophen to prominently state that it contains the ingredient, and suggested warnings that taking more than the recommended dose could cause liver damage. The maker of *Tylenol* is already taking these steps. The expert panel also asked for warnings to consumers not to use more than one product containing acetaminophen at the same time. Although the evidence is imperfect, acetaminophen's label also cautions consumers who imbibe three or more alcoholic beverages a day to consult their doctors before taking the drug. The advisory panel opted to leave this caveat unchanged.

Meeting with the expert panel, McNeil, the maker of *Tylenol*, the top brand of acetaminophen, provided panel members with data showing that acetaminophen is safe at recommended dosages—up to 4 g per day in divided doses. Ordinarily, serious hepatotoxicity occurs only following substantial overdose, either a single dose of 15 g or multiple doses of about 12 g/day [*Scrup*, 25 September 2002]. High alcohol consumption or liver disease, however, appears to increase susceptibility.

Although the panel's discussion centered on unintentional overdoses, a large number of the cases of

acetaminophen toxicity are the result of suicide attempts. The FDA estimates that these destructive efforts lead to about 350 deaths each year. Attempting to commit suicide by ingesting large quantities of acetaminophen seems to be a still greater problem in the UK, where the government now requires blister packaging to limit the number of tablets that can be accessed quickly.

At the same session, the FDA advisory panel also recommended that additional warnings about gastrointestinal (GI) bleeding and renal toxicity be added to the labeling of all products containing aspirin and other OTC NSAIDs. Even low-dose aspirin used for cardioprotection merits a more explicit warning. Current labeling varies by product depending on when it was switched to OTC status. Some product labels caution about allergies, others advise patients with stomach problems to use the product only under a physician's care. All contain a poorly documented warning about alcohol use. The panel agreed with the FDA that the risk of GI bleeding for those who use the maximum recommended daily dose of NSAIDs is about six per thousand, about twice that of nonusers. The impact on the large user population is substantial.

New Safety Information on Accutane

Roche Laboratories has advised health care professionals of several recent changes to the *Accutane* (isotretinoin) label. *Aggressive and/or violent behaviors* have been added to the list of events that isotretinoin may cause, based on postmarketing safety reports. No mechanism of action has been established for these events. A new section has been added advising caution when prescribing isotretinoin to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. The revised label also notes that in clinical studies of pediatric patients treated with isotretinoin, 29% developed back pain and 22% experienced arthralgias.

Also notable is the imminent launch of the first generic version of *Accutane*. *Accutane* costs \$275 to \$370 a month, depending on dosage. The generic version is expected to be 25% to 30% less expensive than *Accutane*. The price will fall still further when several rival generic drug firms launch their products. The generic manufacturers must observe the same strict rules as Roche does regarding the use of isotretinoin to prevent pregnant women from taking it and to keep women from getting pregnant while on the drug. Generic manufacturers' greatest challenge is to ensure that practitioners and patients recognize that isotretinoin is the same as *Accutane*, which is widely perceived to be linked with birth defects [*The Wall Street Journal Online*, 12 November 2002].

NEW DRUGS AND INDICATIONS

FDA Approves Novel Drug for Cholesterol Reduction

Following a rapid review, the FDA has approved ezetimibe (*Zetia*), the first in a new class of cholesterol-lowering agents that work by inhibiting the intestinal absorption of cholesterol. This mechanism of action makes ezetimibe complementary to statins. Patients who take ezetimibe with a statin can achieve additional reductions in LDL cholesterol and total cholesterol. Ezetimibe, in single 10-mg daily doses, taken with or without food, was generally well tolerated in clinical trials.

A press release issued by Schering-Plough and Merck cited a branch chief at the National Heart, Lung, and Blood Institute who noted that 60% of the estimated 13 million patients taking statins continue to have LDL cholesterol higher than recommended levels. He added, "As the first breakthrough to treat cholesterol since statins were introduced 15 years ago, *Zetia* provides physicians

with a new option to get more of these patients to goal."

In a pivotal study, patients who had not reached their LDL cholesterol goal on a stable dose of a statin alone had ezetimibe or placebo added. Adding the new drug to ongoing statin treatment provided a 36mg/dl additional reduction in LDL cholesterol, compared with a 6mg/dl reduction with the addition of placebo. Most of the response was seen within two weeks of adding ezetimibe. The additive reduction provided by ezetimibe was generally consistent across all statins tested, including simvastatin (*Zocor*) and atorvastatin (*Lipitor*). Furthermore, the study showed that 72% of the patients who were not at goal on their statin dose at baseline reached goal when ezetimibe was added, compared with 19% of patients who reached goal with the addition of placebo.

Extended-Release *Augmentin* for Acute Sinusitis and Community-Acquired Pneumonia

GlaxoSmithKline has received approval to market an extended-release version of *Augmentin* (amoxicillin/clavulanate). The new approval covers *Augmentin XR* for the treatment of adults with acute bacterial sinusitis or community-acquired pneumonia (CAP) caused by beta-lactamase producing bacteria such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* with reduced susceptibility to penicillin. *Augmentin XR*

is the first drug product to receive approval for both acute sinusitis and CAP caused by penicillin-resistant *S. pneumoniae*. Regular *Augmentin* is facing generic competition, but GSK has initiated legal proceedings to prevent this. GSK said that it would not seek to switch patients from *Augmentin* to *Augmentin XR* because the two formulations are approved for different indications.

CLINICAL PRACTICE

Digoxin Therapy May Pose Risk for Women with Heart Failure

A major trial in the setting of heart failure determined that digoxin therapy did not reduce overall mortality. However, digoxin did decrease the risk of hospitalization for worsening heart failure and the overall risk of hospitalization during three years of follow-up [*N Engl J Med* 1997;336:525-33]. Since these results were published, several societies and associations have issued clinical guidelines that strongly endorse the use of digoxin for patients with heart failure.

The initial analysis of data from this study did not examine the effects of digoxin separately on men and women, a potentially important omission because men and women differ with respect to the risk, causes, and prognosis of heart failure. In this light, investigators have revisited the database and conducted a post hoc subgroup analysis to assess whether there were sex-based differences in the effect of digoxin therapy

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Digoxin Therapy Risk for Women with Heart Failure (continued)

among the 6800 patients participating in the study [*Ibid*, 2002;347:1403-11].

The subgroup analysis determined that the mortality rate of women treated with digoxin was higher than that of women who received placebo (33.1% vs. 28.9%), whereas the mortality rate of men treated with digoxin was slightly lower than that of men who received placebo (35.2% vs. 36.9%). Multivariate analysis found that women taking digoxin had an adjusted hazard ratio for death of 1.23 (95% CI 1.02-1.47). The apparent benefit of digoxin in men was not statistically significant. Digoxin reduced the rate of hospitalization for worsening heart failure for both men and women, but the difference was statistically significant only for men. The investigators say that

their finding is important for practice given that the only benefit of digoxin therapy is a small reduction in hospitalization. The study also underscores the importance of investigations of sex-based variations in treatment effectiveness.

A related editorial questions whether the evidence is sufficient to abandon digoxin therapy for women. The authors contend that the digoxin dose used in the study was too high for women, producing higher serum concentrations in women than in men and introducing the possibility of digoxin toxicity [*Ibid*, 1394-95]. They recommend that women with heart failure continue to receive digoxin therapy but at a dose that will result in a serum concentration lower than 1.0 ng/ml (approximately 0.7 ng/ml).

Thrombolytic Therapy, Balloon Angioplasty, Stents, and CABG

One of the longest running debates in cardiology has concerned the best reperfusion therapy in patients with evolving acute myocardial infarction (MI). Recognition that most cases of acute MI are caused by thrombotic occlusion of a ruptured plaque resulting in diminished blood flow in a coronary vessel, led to efforts to restore flow to interrupt the infarct process. This concept was verified in large trials of thrombolytic therapy showing that timely reperfusion results in myocardial salvage and enhanced survival. Moreover, the time from symptom onset to thrombolytic administration was related to reduced infarct size and mortality.

The introduction of percutaneous transluminal coronary angioplasty (PTCA) provided an alternative method for the emergent recanalization of an occluded infarct artery. Proponents of this “primary” strategy to reperfusion therapy argued that, compared with thrombolytic therapy, coronary angioplasty results in higher rates of vessel patency and blood flow. In addition, avoiding thrombolytic agents virtually eliminates the risk of intracranial hemorrhage. Proponents of thrombolytic therapy maintained that primary angioplasty resulted in delays to treatment, had not been adequately tested, and was only available in a few hospitals.

Results from many randomized trials comparing primary angioplasty with thrombolytic therapy have settled this debate, demonstrating reduced mortality, reinfarction, recurrent ischemia, unplanned revascular-

ization, stroke, and intracerebral bleeding, and early hospital discharge with the invasive approach. Moreover, whereas the efficacy of pharmacologic reperfusion appears to have been optimized, the introduction of new devices, including coronary stents, and the improved deployment of drug regimens during the angioplasty procedure, has significantly improved the early safety profile and long-term results of percutaneous intervention in acute MI.

Nevertheless, there are those who maintain that still earlier reperfusion with thrombolytic therapy might improve outcomes. A recent report in *The Lancet* contains the latest skirmish in the “primary PTCA versus thrombolytic therapy wars” [*Lancet* 2002;360:825-29]. The well-designed and executed trial enrolled 840 patients with acute MI with ST-segment elevation. After receiving heparin and aspirin, the patients were randomized to prehospital thrombolysis with accelerated dosing of tissue plasminogen activator (alteplase) or to primary PTCA (balloon angioplasty). The primary endpoint was a composite of death, nonfatal reinfarction, and nonfatal disabling stroke at 30 days.

The median delay between onset of symptoms was 130 minutes in the prehospital-thrombolysis group and 190 minutes in the primary-angioplasty group. Rescue angioplasty was required in 26% of the patients assigned to thrombolytic therapy. The rate of the primary

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CLINICAL PRACTICE (continued)

Thrombolytic Therapy, Balloon Angioplasty, Stents, and CABG (continued)

endpoint was 8.2% of patients who received thrombolytic treatment and 6.2% of those who underwent PTCA; the difference in risk was not statistically significant.

The trial, however, ended before the planned recruitment of 1200 patients, the number necessary to demonstrate a 40% relative reduction in the primary endpoint. Moreover, the results demonstrate a trend toward a 24% relative reduction of the composite endpoint favoring the interventional strategy, driven by strong reductions in reinfarction and stroke. Although the authors of the report conclude, "A strategy of primary angioplasty was not better than a strategy of prehospital fibrinolysis in patients presenting with early myocardial infarction" [*Ibid*], the results of their study do not contradict earlier findings that favor coronary angioplasty [*Ibid*, 814-15].

There has also been considerable interest in properly defining the comparative efficacy of PTCA and coronary artery bypass grafting (CABG). Trials in the early 1990s demonstrated similar survival. Bypass resulted in more Q-wave myocardial infarctions during hospitalization and a longer length of stay. Angioplasty resulted in more frequent repeat revascularization procedures, and less complete symptomatic relief. These

studies positioned angioplasty as a preferred treatment for single vessel or simple two-vessel disease but not for more technically complex disease.

Routine stent placement resulted in an impressive decrease in the risk of emergency bypass, and allowed more technically complex disease to be approached percutaneously. The lines of demarcation for patients suited for bypass or angioplasty became blurred. There have been three major randomized trials of surgery versus percutaneous intervention (PCI) with stent implantation. All three showed no difference in late mortality. The CABG patients had more symptomatic relief, and the PCI patients had a greater need for repeat revascularization. However, compared with balloon angioplasty, the need for repeat revascularization has been cut in half for PCI patients [*Ibid*, 961-62].

How do these findings apply to current practice, and will drug-releasing stents further narrow the gap in eligibility for percutaneous revascularization? Until these new and promising stents are available and rigorously compared with CABG, surgery is likely to remain as the preferred choice for complex anatomical subsets. A sirolimus-containing stent is expected to reach the market early next year.

Severity-Based Treatment of Pediatric Asthma

The prevalence of pediatric asthma has risen sharply over the past 30 years. Several treatment guidelines have been published in recent years. The major goals of each include the prevention of chronic symptoms, the prevention of acute exacerbations, and the maintenance of healthy activity levels and pulmonary function. According to a recent Contempo Update in *JAMA* [2002;288:745-47], the treatment of pediatric asthma is best approached in a step-wise manner based on the patient's degree of asthma severity.

The commentary suggests that patients with mild intermittent asthma require no long-term control but should carry a short-acting inhaled bronchodilator to be used as needed for symptoms. Use of the inhaler more than twice a week, however, indicates disease progression. Those with mild persistent asthma should use

either cromolyn or nedocromil, or low-dose inhaled corticosteroid, or possibly a leukotriene antagonist. Patients with moderate persistent asthma, characterized by daily symptoms and reduced pulmonary function, should be treated with low- to medium-dose inhaled corticosteroid and nedocromil, a long-acting beta agonist, or a leukotriene antagonist. Those with severe persistent asthma need high-dose inhaled corticosteroid and a long-acting beta agonist and/or leukotriene antagonist and/or sustained release theophylline and/or oral corticosteroid. All patients with asthma should use a short-acting inhaled bronchodilator as needed for symptoms [*Ibid*]. Note that the place of leukotriene antagonists in the treatment of pediatric asthma, especially as monotherapy, is still evolving. The use of these agents should be reconsidered if prompt relief is not achieved.