Drug Monitor

Three-in-One Pill for HIV

A new "triple-threat" drug for HIV infection, approved on the FDA fast track, combines the active ingredients of three well established, highly active antiretroviral drugs: the nonnucleoside reverse-transcriptase inhibitor efavirenz (Sustiva; Bristol-Meyers Squibb, New York, NY) and the nucleoside reverse-transcriptase inhibitors emtricitabine (Emtriva; Gilead Sciences Inc., Foster City, CA) and tenofovir disoproxil fumarate (Viread; Gilead Sciences Inc.). The drug, known by the trade name Atripla, represents the first single-tablet, once-daily combination treatment available for HIV-1 infection. It may be taken alone or in combination with other antiretroviral drugs.

Atripla represents another breakthrough as well—it's the result of the first collaboration between drug manufacturers in the HIV/AIDS field: Bristol-Myers Squibb, Gilead Sciences, and Merck (Whitehouse Station, NJ; which holds the rights to efavirenz in some territories). Atripla was approved under a new drug application, which allows it to be considered for purchase in the 15 countries included in the President's Emergency Plan for AIDS Relief.

In a 48-week clinical trial of the combination treatment (which used separate formulations of the drugs), 80% of 244 HIV-infected adults had a marked reduction in viral load (HIV RNA levels of less than 50 copies/mL). Patients receiving this treatment also experienced a substantial increase in the number of healthy CD4 cells (mean increase, 190 cells/mm^3). The most common adverse effects were headache, dizziness, abdominal pain, nausea, vomiting, and rash. Potentially serious adverse effects include lactic acidosis, liver toxicity, renal impairment, and depression. In patients with chronic hepatitis B infection (not an approved indication for Atripla), stopping Atripla can result in severe flare-ups of the disease.

Sources: FDA News Release P06-96. July 12, 2006.

N Engl J Med. 2006;354:251–260.

Who Needs Perioperative Beta-Blockade?

Perioperative beta-blockade is recommended for patients at cardiac risk who are undergoing major noncardiac surgery. But it might be unnecessary for some patients, charge researchers from the multicenter Diabetes Postoperative Mortality and Morbidity (DIPOM) Trial Group.

In the study, which involved nine hospitals in Copenhagen, Denmark, researchers randomly assigned 921 patients with diabetes who were over age 39 and scheduled for major noncardiac surgery to receive either metoprolol 100 mg controlled and extended release (462 patients) or placebo (459 patients). The intervention started on the day before surgery and lasted up to eight days postoperatively in each group. Follow-up lasted from six to 30 months.

Metoprolol significantly reduced the mean heart rate by 11% and mean blood pressure by 3%, but it had no significant effect on mortality or cardiac morbidity. The number of deaths was 74 in the metoprolol group and 72 in the placebo group, and the number of cardiac events was 46 in the metoprolol group and 45 in the placebo group.

Based on their findings, the researchers conclude that the evidence is insufficient to recommend perioperative beta-blockers for diabetic patients at risk for cardiac morbidity. Moreover, they say that it's premature for policy making organizations to use perioperative beta-blocker treatment as a measure of hospital quality.

Source: *BMJ.* 2006;332:1482. doi:10.1136/bmj.332.7556.1482.

Combination Chemotherapy for Elders with Colorectal Cancer

Of all patients diagnosed with colorectal cancer, many are elderly and most require cytotoxic chemotherapy—either as an adjuvant postoperative therapy or to treat disease recurrence. Elders who undergo chemotherapy, however, are more likely than younger patients to experience "unpredictable" toxicities, say researchers from the Southern Italy Cooperative Oncology Group Trial 0108, and no consensus has yet been reached regarding the best strategies for managing colorectal cancer in older patients.

Working on the hypothesis that substituting the generally better tolerated capecitabine for the more traditional 5-fluorouracil/leucovorin (5-FU/LV) therapy, in combination with oxaliplatin, might benefit elderly patients with metastatic colorectal cancer, the researchers conducted an uncontrolled, open-label trial involving 76 patients aged 70 or older. Patients received a median of six cycles of treatment, each consisting of an initial IV dose of oxaliplatin on day 1, followed by two daily, oral doses of capecitabine on days 2 through 15. Cycles were repeated every three weeks, and the oxaliplatin dose was increased in subsequent cycles if there was no toxicity above grade 1 after the first cycle.

About three fourths of the group achieved some level of disease control.

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Of the 76 patients, two had a complete response and 29 had a partial response, for an overall response rate of 41%. Tumors shrank in another 12 patients, though this did not qualify as a major response. In addition, 18 (46%) of 39 patients with symptoms at baseline experienced symptom improvement during the trial.

The response rate translated to a median progression free survival of 8.5 months and a median overall survival of 14.4 months. Surprisingly, the researchers say, patients over age 75 had an even better response rate than those aged 75 or younger.

Only four patients (5%) developed grade 3 or higher hematologic toxicity during treatment, and none developed grade 4 neutropenia. A low incidence of thrombocytopenia was observed when oxaliplatin doses were raised above 100 mg/m^2. The researchers attribute this tolerability to the fact that capecitabine and oxaliplatin do not have overlapping toxicities, the conservative step-up dosage schedule used in the trial, and the limited number of cycles delivered.

According to the researchers, their results suggest that "combination therapy should not be denied to elderly patients who have been selected carefully on the basis of performance status and comorbidities and who are willing to receive palliative treatment for their cancer." Ongoing phase III trials promise to show more definitively the feasibility of replacing 5-FU/LV with capecitabine in combination regimens for metastatic colorectal cancer. The switch would eliminate the need for a central venous catheter and, thus, the risks of catheter-related infection and thromboembolism. Moreover, the capecitabine-oxaliplatin regimen requires only one clinic visit during each cycle, for the infusion of oxaliplatin—a benefit that might be appreciated particularly by elders.

Source: *Cancer.* 2006;104:282–289.

Lidocaine During Labor

Can a local anesthetic help reduce perineal pain during delivery? Researchers from University of Bristol, United Kingdom compared the effectiveness of lidocaine with a placebo spray in 185 women during spontaneous vaginal delivery.

Although the women, all in second-stage labor, found the lidocaine spray acceptable, it wasn't associated with any reduction in perineal pain. Mean pain scores were similar in both groups. If anything, the researchers say, there was a slight trend toward worse pain.

The lidocaine spray may have other benefits, however. Women who received lidocaine were less likely to have second-degree perineal trauma and to experience dyspareunia during the two months after delivery. The researchers suggest that the spray might allow a more controlled delivery of the fetal head, thus preventing trauma.

Source: *BMJ.* 2006;333:117. doi:10.1136/bmj.38878.833241.7C (published online June 28, 2006).

Preventing Eptifibatide-Related Bleeding

Advanced age puts patients at higher risk for bleeding when they're treated with eptifibatide during and after percutaneous coronary intervention (PCI). According to findings from the Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-Platelet and Anti-Thrombotic Agents–Thrombosis In Myocardial Infarction-30 (PROTECT–TIMI-30) trial, age was the only independent correlate of bleeding events.

The researchers also found a high rate of bleeding (20%) associated with the inappropriate administration of the full eptifibatide dose to 45% of patients whose reduced creatinine clearance (50 mL/min or less) indicated the use of a lower dose. But this association appeared to be largely mediated by the incorporation of age into creatinine clearance calculations. To avoid missing patients who need a reduced eptifibatide dose, the researchers recommend using creatinine clearance or glomerular filtration rate rather than creatinine level alone.

Most of the bleeding events occurred more than six hours after eptifibatide initiation. It remains unclear, however, whether early termination of the infusion would preserve or reduce the ischemia-related efficacy of the drug, the researchers say. They advise prospective, randomized trials investigating the effects of a shorter infusion. ●

Source: *J Am Coll Cardiol.* 2006;47:2374–2379.