

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

by Milo Gibaldi, Ph.D., School of Pharmacy

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Written by Milo Gibaldi, Ph.D.

Edited by Nelda A. Murri, Pharm. D.

Prepared by Sandra Walston, M.C.

(206) 598-6612/nelda@u.washington.edu

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NEW DRUGS AND INDICATIONS

FDA Approves Fulvestrant for Metastatic Breast Cancer

AstraZeneca has received permission to market *Faslodex* (fulvestrant), an injectable selective estrogen receptor antagonist for second-line treatment of hormone receptor positive metastatic breast cancer. It is the only estrogen receptor antagonist demonstrated to be effective after tamoxifen failure. Three aromatase inhibitors—anastrozole (*Arimidex*), exemestane (*Aromasin*), and letrozole (*Femara*)—are approved for advanced breast cancer in postmenopausal women following failed therapy with tamoxifen.

Two well-controlled trials enrolling 950 postmenopausal women and comparing once-monthly intramuscular fulvestrant with daily doses of oral anastrozole served as the basis for approval. Enrollees had locally advanced or metastatic breast cancer refractory to antiestrogen or progestin treatment. The tumor response rate in the North American trial was 17% for each treatment. In the trial conducted in Europe, response rates were 20.3% with fulvestrant and 14.9% with anastrozole. Fulvestrant modestly extended time to progression compared with anastrozole, from 103 days to 165 days in the North American trial and from 156 days to 166 days in the European trial.

As a postmarketing commitment, AstraZeneca will monitor potential medication errors resulting from name confusion with the drug maker's injectable prostate cancer drug *Zoladex* (goserelin). Fulvestrant is contraindicated in pregnant women and should not be used in patients on anticoagulants. A *Faslodex* filing for first-line use is expected next year [*The Pink Sheet*, 29 April 2002].

Voriconazole Is a Suitable Alternative for Empirical Antifungal Therapy

The risk of fungal infection increases greatly in patients with neutropenia and persistent fever. Because of the poor outcomes associated with established infections, empirical antifungal therapy with conventional amphotericin B or liposomal amphotericin B has become the standard of care. Amphotericin B, however, is associated with dose-limiting nephrotoxicity and other adverse reactions. Liposomal amphotericin B is equally effective and significantly safer, but the high cost of the product has limited its use. Antifungal triazoles are also promising agents for empiric antifungal therapy, especially the latest generation of agents that includes voriconazole (*Vfend*). An advisory committee to the FDA unanimously recommended approval of both oral and intravenous formulations

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NEW DRUGS AND INDICATIONS (continued)

Voriconazole Alternative for Empirical Antifungal Therapy (continued)

of voriconazole for the treatment of acute invasive aspergillosis. Investigators recently reported the results of a study testing whether voriconazole might be as effective as conventional or liposomal amphotericin B for empiric antifungal therapy [*N Engl J Med* 2002;346:225-34].

A total of 837 patients were evaluated. Success rates were 26.0% with voriconazole and 30.6% with liposomal amphotericin B. The small advantage was not statistically significant. On the other hand, there were fewer docu-

mented breakthrough fungal infections in patients treated with voriconazole than in those treated with liposomal amphotericin B (1.9% vs. 5.0%), and the voriconazole group had fewer cases of severe infusion-related reactions and of nephrotoxicity. A related editorial observed, "Therapeutic decision-making must involve considerations of both efficacy and safety issues; given alternatives, we might accept some gaps in efficacy in favor of lower toxicity. Now that we have alternatives to conventional amphotericin B, one may at least ask whether a 'best' antifungal agent exists" [*Ibid*, 280-81].

Bosentan Improves Pulmonary Arterial Hypertension But Worsens Heart Failure

Pulmonary arterial hypertension is a debilitating, potentially life-threatening disease. Beneficial effects have been reported with continuous intravenous infusion of epoprostenol, a prostaglandin, but treatment requires hospitalization. There is increasing evidence that endothelin-1, a potent endogenous vasoconstrictor and smooth-muscle mitogen, plays a role in pulmonary arterial hypertension, and that bosentan (*Tracleer*), an orally effective antagonist of endothelin receptors, may be beneficial.

Bosentan's benefits have been confirmed in a recent report showing that the dual endothelin-receptor blocker significantly improved the exercise capacity of patients with pulmonary arterial hypertension [*N Engl J Med* 2002;346:896-903]. The investigators randomized 213 patients to receive bosentan or placebo for at least 16 weeks. At that time, bosentan-treated patients were able to walk farther than patients who received placebo. A higher dose of bosentan appeared to have a more pronounced effect than a lower dose but was associated with a higher incidence of abnormal hepatic function. Bosentan also was associated with improvements in a dyspnea index and a function scale, and with a delay in

clinical worsening. The most common side effect of bosentan was headache.

A related editorial comments that while the findings suggest a therapeutic role for bosentan, the duration of the trial was not sufficient to determine if treatment increases survival. Nevertheless, the author of the editorial finds it "conceivable that the continuous intravenous administration of epoprostenol through a central catheter will soon be history" [*Ibid*, 933-35].

However, not all the news on bosentan is good. A trial investigating it for the treatment of heart failure found that bosentan led to an early worsening of the condition [*Scrip*, 27 March 2002]. The lead investigator of the trial reported at the American College of Cardiology meeting in Atlanta, "For some reason that we do not understand, patients treated with this drug developed fluid retention within the first two weeks," adding that "analyses suggest that this early fluid retention has an adverse prognostic effect" [*Ibid*]. Whether further trials are conducted with lower doses of bosentan combined with increased use of diuretics remains to be determined.

FDA Approves *Orfadin* to Treat Hereditary Liver Disease

Children with a rare and rapidly lethal liver disease—hereditary tyrosinemia—can now be treated with *Orfadin* (nitisinone), the first drug that promises to help them live years longer [*The New York Times on the Web*, 23 January 2002]. Hereditary tyrosinemia type-1 (HT-1) is a genetic metabolic disorder that causes progressive liver failure and liver cancer in young children. Fewer than 100 American children, and a few hundred more worldwide are thought to have

the disorder. The condition is not tested for at birth, so often infants die undiagnosed.

When these children break down the amino acid tyrosine, their genetic defect causes them to produce carcinogenic toxins. Current therapy calls for a low-protein diet to minimize tyrosine intake, which helps but does not stop the disease. Many of these children do not survive infancy. *Orfadin* may greatly improve the situa-

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Orfadin to Treat Hereditary Liver Disease (continued)

tion. In an ongoing study of 180 patients who began the drug in infancy, 88% have survived four years and counting, far better than the usual 29% survival rate with diet alone. *Orfadin*'s manufacturer, Rare Disease Thera-

peutics, estimates cost of treatment at \$12,000 a year for an infant, up to \$60,000 a year for an older child. For families that cannot afford the therapy, the company will provide it free or at reduced cost.

Intravenous Zometa for Long-Term Maintenance of Osteoporosis

Oral bisphosphonates—alendronate (*Fosamax*) and risedronate (*Actonel*)—are effective agents for the management of osteoporosis. In general, however, their low bioavailability and potency require frequent administration on an empty stomach. Seeking a more convenient way to prevent bone loss, investigators studied the benefits of infrequent administration of intravenous *Zometa* (zoledronic acid)—a bisphosphonate recently approved for malignant hypercalcemia—in 351 postmenopausal women for one year, comparing a single dose with three-monthly and six-monthly doses and with placebo. They found that the annual infusion

of *Zometa*, as well as the other dosage regimens, increased bone mineral density by about 5%, the same increase observed on daily oral dosing of oral bisphosphonates with proven efficacy against fractures. The most common side effects associated with *Zometa* were musculoskeletal pain, nausea, and fever, most of which were reported as mild. Before recommending the use of *Zometa* in postmenopausal women, the authors of the report emphasize the need for a larger study to demonstrate an effect of *Zometa* on fracture rate [*N Engl J Med* 2001;346:653-61].

DRUG SAFETY

■ **Vioxx Linked to Nonbacterial Meningitis.** Merck's COX-2 inhibitor, *Vioxx* (rofecoxib), has been linked to five cases of nonbacterial meningitis [*Archives Internal Medicine*, March 25]. The cases are among seven reported to the FDA from May 1999, when *Vioxx* was approved, through February 2001, but two are inadequately documented. All seven patients were taking *Vioxx* when they developed meningitis, 1 to 12 days after initiating therapy. Symptoms included headache, stiff neck, eye pain, fever and chills. Based on these cases, the FDA has required Merck to add meningitis to the growing list of potential side effects included on the *Vioxx* product label. Since February 2001, meningitis also has been reported in five other *Vioxx* patients, but those reports have not been evaluated in detail. No one has died in any of the cases, but all required hospitalization.

Other NSAIDs, including ibuprofen and naproxen, have been linked to rare cases of meningitis. The FDA also has received six poorly documented cases of meningitis associated with the COX-2 inhibitor *Celebrex* (celecoxib). According to the FDA, "As with other NSAIDs, rofecoxib should be considered in the differential diagnosis of aseptic meningitis" [*The Pink Sheet*, 1 April 2002].

The timing of the *Archives*' article is unfortunate for Merck, coming shortly after the FDA required Merck

to add a warning against cardiovascular events to the *Vioxx* label and the company announced the temporary withdrawal of a new drug application for its second-generation COX-2 inhibitor *Arcoxia*. One reason for Merck's decision to reevaluate the NDA is that *Arcoxia* shows a cardiovascular profile similar to *Vioxx*, including a higher rate of thrombotic events compared with naproxen.

■ **More Warnings on Nucleoside RTI Stavudine.** Bristol-Myers Squibb has issued another "Dear Healthcare Professional" letter warning of the potential for lactic acidosis as a complication of therapy with its nucleoside HIV-reverse transcriptase inhibitor (RTI) stavudine (*Zerit*). As a result of mounting reports, the U.S. label now recommends that therapy with *Zerit* be stopped immediately in patients with suspected lactic acidosis or if motor weakness develops. It also recommends that the drug not be reintroduced in patients with confirmed lactic acidosis. Lactic acidosis is an infrequent event but seems to be more often associated with antiretroviral combinations that include stavudine. Obesity, female gender, and prolonged nucleoside exposure are risk factors. Fatal lactic acidosis has been reported in pregnant women taking stavudine in combination with didanosine (*Videx*). The use of these agents during pregnancy is discouraged [*Scrip*, 3/5 April 2002].

DRUG EVALUATION

Postmenopausal Hormone Therapy and Quality of Life

The common perception that postmenopausal hormone therapy improves quality of life in women is not supported by solid evidence. Indeed, the high rates of discontinuation of hormone therapy in the first few years of use cast doubt on this assumption [*JAMA* 2002;287:641-42]. A recent study presents important information regarding hormone replacement therapy (HRT) and quality of life in a segment of postmenopausal women. It may have implications for all postmenopausal women.

Investigators compared the effects of HRT and placebo on quality of life parameters—physical activity, energy/fatigue, mental health, and depressive symptoms—among postmenopausal women with established coronary disease participating in a well controlled cardioprotection trial of combined conjugated equine estrogens and medroxyprogesterone [*Ibid*, 591-97].

Women who received HRT rather than placebo had larger declines in physical function and a trend toward

increased symptoms of fatigue, but experienced an improvement in depressive symptoms. Since the mean age of the group was 67 years, most women (84.3%) did not have vasomotor flushing symptoms at baseline. Greater declines in physical function and energy were observed among these women, while no changes were noted for mental health or depressive symptoms. Although baseline quality-of-life parameters were worse among women who reported vasomotor flushing, HRT in these women was associated with improvement in mental health and reduction in depressive symptoms without significant effects on physical function or energy level.

Given that HRT improves perimenopausal symptoms, such as hot flashes, improved quality of life among symptomatic women is not an unexpected finding. The report's primary contribution is that the majority of women without vasomotor symptoms at baseline experienced a decrease in physical function and no improvement in mental health with HRT.

Better Outcomes with Angiotensin Receptor Blocker Than With β -Blocker in Hypertensive Patients

Up until now, β -blockers and diuretics are the best-documented interventions for prevention of cardiovascular morbidity and death in patients with hypertension. Patients treated with these agents, however, still have significantly higher rates of cardiovascular complications than people without hypertension. Left ventricular hypertrophy (LVH), which is only modestly affected by β -blockers or diuretics, is a cardinal manifestation of pre-clinical cardiovascular disease and an independent risk factor for all cardiovascular complications in hypertension. Blocking angiotensin II could be especially effective in reversing LVH, and reversal has possible benefits that are independent of blood pressure. The Life Trial, initiated nearly ten years ago, aimed to establish whether selective blocking of angiotensin II improves LVH beyond reducing blood pressure and, consequently, decreases cardiovascular morbidity and mortality.

The main trial enrolled 9222 patients, 55 to 80 years old, with primary hypertension (sitting blood pressure 160-200/95-115 mm Hg) and evidence of LVH. Patients were randomly assigned for at least four years to losartan or atenolol, to which diuretics and other antihypertensive drugs could be added as needed

to normalize blood pressure. Losartan (*Cozaar*) was the first available selective angiotensin II receptor antagonist receptor, and atenolol, a β -blocker, is recognized as a first-line treatment for hypertension. The primary end point of the study was a composite of death, myocardial infarction, or stroke [*Lancet* 2002;359:995-1003].

Blood pressure was reduced similarly in the two groups. The composite end point was reached at a rate of 23.8 per 1000 patient-years of follow-up in the losartan group and at a rate of 27.9 per 1000 patient-years in the atenolol group, a statistically significant 13% decrease in relative risk. The difference was due mainly to a 25% reduction in the frequency of stroke in the losartan group. The rates of heart attack and cardiovascular mortality, however, were not significantly different between groups. Surprisingly, the incidence of new onset diabetes was 25% lower in patients assigned to losartan than in patients assigned to atenolol.

The report concludes, "Losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and is better tolerated. Losartan seems to confer benefits beyond reduction in blood pressure" [*Ibid*]. A commentary notes that most

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Better Outcomes with Angiotensin Receptor Blocker (continued)

patients in both groups were also receiving hydrochlorothiazide, that diuretics are more effective in preventing stroke than β -blockers, and that the combination of an angiotensin receptor blocker (ARB) and hydrochlorothiazide does not produce more side effects than placebo. "Thus a treatment strategy based on this combination provides at least equal cardioprotection to β -blockers and more protection from strokes, with fewer side effects" [*Ibid*, 990-991]. The authors of the commentary also postulate that the observed effects in the LIFE study could probably be obtained by any ARB.

In a separate analysis of the 1195 diabetic hypertensive patients who participated in the LIFE study, the

results favoring losartan are still more impressive. In this higher risk group there was a 24% reduction in risk of the primary end point; losartan reduced all-cause mortality by 39%, cardiovascular mortality by 37%, and hospital admission for heart failure by 40% [*Ibid*, 1004-10].

An investigator participating in the LIFE trial told the press, "the results were a mandate for change that would encourage many doctors to initiate treatment with *Cozaar*" [*The New York Times on the Web*, 20 March 2002]. Merck, the maker of *Cozaar*, sponsored the study. A limitation was that the study population was overwhelmingly white, while hypertension is a major health problem for blacks.

Requip Slows Parkinson's Progression; Mirapex is Also Effective

Data presented at a neurology meeting indicates that the dopamine D₂/D₃ agonist ropinirole (*Requip*) slows the progression of Parkinson's disease compared with standard therapy. The loss of functioning dopamine neurons in ropinirole patients was 35% less than in those receiving levodopa [*Scrip*, 19 April 2002].

Last year, guidelines for the treatment of Parkinson's disease were updated to recommend dopamine agonists—ropinirole, pramipexole (*Mirapex*), and pergolide—as initial therapy for early disease instead of levodopa because they caused fewer side effects. The experts who developed the guidance recommended the use of dopamine agonists for the first few years after diagnosis before switching to levodopa.

The new data are from a positron emission tomography study in 186 untreated Parkinson's disease patients randomized to two years' treatment with ropinirole or levodopa. At the end of study, changes in the

area of brain affected by the disease—the substantia nigra and putamen—showed a 13% loss of function in the ropinirole group and a 20% loss of function in the levodopa group. Similar data showing that pramipexole is associated with a slower rate of neuron loss in the brain than is levodopa have been published in *JAMA* [2002;287:1653-1661].

Loss of dopamine is an indicator of disease progression, but the clinical significance of these findings needs further evaluation. While patients treated with ropinirole were dramatically less likely to experience dyskinesias, there was no difference between the treatment groups in terms of symptom control. Indeed, the motor component of one rating scale favored the levodopa group. Further complicating the clinical picture, trial design allowed patients experiencing insufficient therapeutic benefit with either levodopa or ropinirole to supplement assigned medication with adjunctive levodopa.

Methotrexate and Mortality in Rheumatoid Arthritis Patients

U.S. researchers have assessed mortality outcomes of 1240 patients with rheumatoid arthritis who were seen at an outpatient arthritis center. The average length of follow up was six months. By the end of study 191 patients had died. Patients who began treatment with methotrexate (n=588, average dose=13 mg/week) had worse prognostic factors for mortality than patients who received other treatments. Nevertheless, the unadjusted mortality hazard ratio of methotrexate compared with no methotrexate was 0.8 and statistically significant.

After correcting for differences in disease severity, the mortality hazard ratio for methotrexate use was 0.4.

Other disease-modifying agents—sulfasalazine, penicillamine, hydroxychloroquine, and gold—did not have a significant effect on mortality. The hazard ratio of methotrexate use for cardiovascular death was 0.3, whereas that for other causes of death was 0.6 and not significant. The data suggest that methotrexate may provide a substantial survival benefit for patients with rheumatoid arthritis, largely by reducing cardiovascular mortality. The authors of the report suggest that the survival benefit of methotrexate might be a standard against which new disease-modifying antirheumatic drugs should be compared [*Lancet* 2002;359:1173-77].

CONTROVERSIES AND DILEMMAS

Erythromycin-Resistant Streptococci in Schoolchildren

Group A streptococci are the most frequent cause of bacterial pharyngitis in children and adults. Penicillin V remains the drug of choice for treatment. Erythromycin is recommended for those who are allergic to penicillin. Azithromycin is not recommended as first-line treatment for pharyngitis due to group A streptococci. However, many practitioners find the five-day regimen of one dose of azithromycin per day attractive. Furthermore, azithromycin and other macrolides are frequently prescribed for nonstreptococci pharyngitis and other upper respiratory infections, thereby posing a mounting risk of drug resistance.

During a longitudinal study of schoolchildren in Pittsburgh, researchers observed the sudden emergence and rapid spread of erythromycin resistance in pharyngeal isolates of group A streptococci.

Their findings are reported in *The New England Journal of Medicine* [2002; 346:1200-1206].

In the first two years of the study, the investigators obtained 2200 throat cultures from 100 children and 322 were positive for streptococci. All of the isolates were sensitive to erythromycin. In the third year, from October 2000 and May 2001, 1794 cultures were obtained, of which 318 were positive for streptococci. In contrast to the earlier findings, 48% of the isolates demonstrated erythromycin resistance.

The authors recommend that macrolide antibiotics not be used for the routine treatment of pharyngitis due to group A streptococci until more epidemiologic information is available or unless susceptibility testing is first performed. A related editorial urges investigation of the prevalence of macrolide resistance throughout the U.S. [*Ibid*, 1243-45].

ALTERNATIVE MEDICINE

St. John's Wort for Depression Trial Proves Inconclusive

Millions of people have been treating their notion of mental depression with the herbal product St. John's Wort. Many are convinced that the product works as well or better than more costly prescription drugs. A new study, however, funded by the NIH, challenges but does not clearly reject that premise [*JAMA* 2002; 287:1807-14]. In the study, 340 patients with moderately severe major depression were randomly assigned to receive an extract of the plant's "active ingredient," hypericum, sertraline (*Zoloft*), or placebo.

After eight weeks, St. John's Wort showed no benefit over placebo in improving patients' overall mood or in resolving depression. But neither did sertraline. In fact, a complete response occurred in 31.9% of the placebo-treated patients, compared with 23.9% of the hypericum-treated patients and 24.8% of the sertraline-treated patients. Sertraline was better than placebo in only one scale, which was a secondary measure in the study. Both treatments were associated with significantly more adverse events than was the placebo.

An investigator in the study said that with sertraline, all the trends were positive, but they did not rise to the

level of statistical significance, not unexpected in light of the middling doses of sertraline used in the study and the substantial placebo effect. On the other hand, the trial found a complete absence of trends suggestive of efficacy for St. John's Wort. A review of placebo response in studies of major depression appears in the same issue of the journal [*Ibid*, 1840-47]. The authors of that report concluded, "The response to placebo in published trials of antidepressant medication for major depressive disorder is highly variable and often substantial and has increased significantly in recent years.... These observations support the view that the inclusion of a placebo group has major scientific importance in trials of new antidepressant medication" [*Ibid*].

Correction

New Drug for BPH. A report in the May 2002 DTT Supplement concerned a new 5-alpha reductase inhibitor for the treatment of benign prostatic hyperplasia. Other drugs for BPH were also cited including alfuzosin, which is not available in the U.S. Not cited is the widely prescribed tamsulosin (*Flomax*). The omission is regretted.