

# drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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## CONTENTS

### NEW DRUGS & INDICATIONS

- FDA Approves Natalizumab for Multiple Sclerosis
- New Biologic Agent Reduces the Risk of Oral Mucositis
- Seeming Successor to *Neurontin* Approved for Neuropathic Pain

### DRUG EVALUATION

- Statins, LDL Cholesterol, Inflammatory Proteins, and Coronary Artery Disease
- As-Needed Antiarrhythmic Treatment for Atrial Fibrillation
- Cholinesterase Inhibitor Improves Parkinson's Disease-Associated Dementia
- Taking an Aromatase Inhibitor at Outset More Effective for Breast Cancer
- Antihypertensive Agents in Patients with Coronary Disease and Normal BP

### DRUG SAFETY

- FDA Warns of Serious Side Effects of *Bextra*
- New Dosing Recommended for *Procrit* in Cancer Patients
- Osteoporosis Looms in Men Treated for Prostate Cancer

### PUBLIC HEALTH

- Immunizing Children May Prevent Flu Deaths in Elderly

#### Drug Therapy Topics Supplement

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## NEW DRUGS AND INDICATIONS

### FDA Approves Natalizumab for Multiple Sclerosis

A new type of biologic therapy has been granted expedited approval for patients with relapsing-remitting forms of multiple sclerosis. Natalizumab (*Tysabri*) is a humanized monoclonal antibody; it is thought to work by binding to immune system cells and preventing them from entering and damaging the brain [[www.fda.gov/bbs/topics/news/2004/NEW01141.html](http://www.fda.gov/bbs/topics/news/2004/NEW01141.html), 24 November 2004].

The FDA based approval on preliminary results from two ongoing well-controlled trials. In the first study, comparing natalizumab with placebo, patients on the drug had a 66% reduction in frequency of relapses. The second trial enrolled patients who were still experiencing relapses despite treatment with interferon beta-1a (*Avonex*). In these patients, the addition of the new agent reduced the frequency of relapses by 54% over the reductions produced by *Avonex* alone.

Natalizumab is given intravenously once a month. The most frequently reported important adverse effects have been serious infections, transient hypersensitivity reactions, depression, and gallstones. Common side effects included limited infections, headache, mild depression, joint pain, and menstrual disorders.

Natalizumab was co-developed by Biogen and Elan. Experts think that it will quickly reach first-line status for relapsing-remitting MS. Biogen, a drug company that also makes *Avonex*, is eager to demonstrate that the combination of *Avonex* and *Tysabri* is more effective than *Tysabri* alone. There is no evidence, as yet, to support this suggestion.

### New Biologic Agent Reduces the Risk of Oral Mucositis

Oral mucositis is a serious complication of cancer therapy. The condition is particularly common in patients receiving chemotherapy and radiation in preparation for hematopoietic bone marrow transplantation. Patients with mucositis have excruciating pain and often are incapable of swallowing, even fluids. In the most severe presentations, patients require parenteral nutrition. Many studies in animals and humans have sought a way of preventing and treating oral mucositis but with little avail.

In a recent report, investigators describe the use of the recombinant keratinocyte growth factor (KGF), palifermin, for this purpose in patients with leukemia or

(Continued on Supplement page 2)

## NEW DRUGS AND INDICATIONS (continued)

### New Biologic Agent Reduces the Risk of Oral Mucositis (continued)

lymphoma who were receiving high doses of chemotherapy and radiation treatments associated with bone marrow transplantation [*N Engl J Med* 2004;351:2590-98]. KGF stimulates the growth of cells on the surface layer of the mouth, stomach, and colon. This is thought to lead to a faster healing process of mouth ulcers.

In the study, intravenous palifermin or placebo was given to 212 patients for three days before cancer treatment began and three days after treatment. In the control group, 98% of patients developed severe mucositis. The same resulted in only 63% of patients who received the drug. The relative reduction in the most severe (grade 4) form of mucositis was even greater.

The researchers also found that patients receiving palifermin used significantly less morphine for pain and for fewer days than did placebo recipients. The most common adverse effect of the drug was a skin rash.

A related editorial said that the work, if supported by additional studies, “will fundamentally change targeted therapies for radiochemically-induced mucositis.” At the end of 2004, the FDA approved palifermin (Amgen’s *Kepivance*) to reduce the chance that patients with blood cancers will develop mucositis. The drug has not been studied in patients with other types of cancer.

### FDA Approves Seeming Successor to *Neurontin* for Neuropathic Pain

An end-of-year communication from the FDA announced the approval of *Lyrica* (pregabalin) for the management of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia (PHN). *Neurontin* (gabapentin) is also approved for the treatment of PHN. Pregabalin is the second FDA-approved treatment for diabetic neuropathy [*MD Consult*, 4 January 2005], following duloxetine (*Cymbalta*) approval in August 2004.

Debilitating neuropathic pain affects about 1 in 6 patients with diabetes. The pain is often described as “burning, tingling, sharp, stabbing, or pins and needles in the feet, legs, hands, and arms” [*Ibid*]. PHN is a complication of shingles, a resurgence of herpes zoster. “Constant stabbing, burning, or electric-shock-like sensations” are terms used to characterize the associated pain [*Ibid*].

Clinical trials in patients with one condition or the other showed *Lyrica* provided rapid and clinically significant pain reduction in “a significant portion of patients,” with pain relief beginning as early as the first week of treatment. According to the manufacturer, pain relief was sustained in studies of up to 12 weeks’ duration. The most common adverse effects of treatment included dizziness, drowsiness, dry mouth, peripheral edema, blurred vision, weight gain, and difficulty with concentration, but the discontinuation rate due to adverse effects was low.

Over Pfizer’s protests, the FDA is likely to classify pregabalin as a controlled substance, but in a category with lower potential for misuse or abuse relative to controlled substances in other categories. Pregabalin is currently under review by the FDA for the adjunctive treatment of partial seizures in adults.

## DRUG EVALUATION

### Statins, LDL Cholesterol, Inflammatory Proteins, and Coronary Artery Disease

Atherosclerosis is now recognized to have an important inflammatory component. A recent study showed that high levels of the inflammatory proteins interleukin-6 and, in particular, C-reactive protein (CRP) were significantly related to an increased risk of coronary heart disease in both men and women [*N Engl J Med* 2004;351:2599-610].

In parallel, statins once thought to merely inhibit synthesis of cholesterol and, thereby, development of atheroma, now appear to inhibit inflammatory processes directly. Two articles in a recent issue of the *Journal* confirm that reducing the inflammatory component of cardiovascular disease through the use of

(Continued on Supplement page 3)

## Statins, LDL Cholesterol, Inflammatory Proteins, and Coronary Artery Disease

statins improves clinical outcome. What's more, improvement is independent of the reduction in serum cholesterol levels.

One report [*Ibid*, 2005;352:29-38] described a study in which 502 patients with documented coronary disease underwent intravascular ultrasonography. Patients received moderate statin therapy (pravastatin 40 mg/day) or intensive treatment (atorvastatin 80 mg/day). Ultrasonography was repeated after 18 months. CRP levels were measured at baseline and follow-up.

Pravastatin reduced LDL cholesterol from 150 to 110 mg/dl, whereas a reduction from 150 to 79 mg/dl was observed in the atorvastatin group. Pravastatin had no effect on CRP levels while atorvastatin reduced the levels of the inflammatory protein from a geometric mean of 2.8 to 1.8 mg/l. The correlation between the reduction in LDL cholesterol levels and that in CRP levels was weak but significant. Univariate analysis found that the percent change in the levels of LDL cholesterol and CRP were related to the degree of progression of atherosclerosis. After adjustment for the reduction in lipid levels, the decrease in CRP levels was independently and significantly correlated with rate of progression.

A related editorial observed, "The notion that the anti-inflammatory effects of statins ameliorate cardiovascular disease suggests that it should be possible to create other anti-inflammatory agents, perhaps tailored to the specific immunologic abnormalities in atheroma" [*Ibid*, 73-75].

### As-Needed Antiarrhythmic Treatment for Atrial Fibrillation

In many patients with recurrent atrial fibrillation, long-term oral prophylaxis with antiarrhythmic drugs may not be the most appropriate first-line treatment. An alternative strategy, called the pill-in-the-pocket approach, calls for patients to take a single oral dose of an antiarrhythmic drug at the time of onset of palpitations. Researchers have assessed the feasibility and safety of this strategy with either flecainide or propafenone, outside the hospital, to terminate atrial fibrillation of recent onset in patients with mild heart disease who have infrequent, well-tolerated antiarrhythmic episodes. Only patients who responded to and tolerated the study drugs were enrolled [*N Engl J Med* 2004;352:2384-89].

During a mean follow-up of 15 months, 165 patients had a total of 618 episodes of arrhythmia; of

The other report described a similar study that evaluated relationships among LDL cholesterol, cholesterol, and CRP achieved after moderate or intensive statin therapy and the risk of recurrent myocardial infarction or death from coronary causes among 3745 patients with acute coronary syndrome [*Ibid*, 20-28]. The investigators found that patients in whom statin therapy resulted in LDL cholesterol levels of less than 70 mg/dl had lower event rates than those with higher levels (2.7 vs. 4.0 events per 100 person-years). A nearly identical difference was observed between those who had CRP levels of less than 2 mg/l after statin therapy and those who had higher levels (2.8 vs 3.9 events per 100 person-years).

For patients with post-treatment LDL cholesterol levels greater than 70 mg/dl, the rates of recurrent events were 4.6 among those with CRP levels of more than 2 mg/l and 3.2 events per 100 person-years among those with CRP levels of less than 2 mg/l. Patients with LDL cholesterol levels of less than 70 mg/dl and CRP levels of less than 1 mg/l after statin therapy had the lowest rates of recurrent events (1.9 per 100 person-years).

The researchers conclude, "Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant levels of LDL cholesterol." They recommend that "strategies to lower cardiovascular risk with statins should include monitoring CRP as well as cholesterol."

those episodes, 92% were treated 36 ± 93 minutes after onset of symptoms. Treatment was successful in 94% of episodes; the average time to resolution was 113 ± 84 minutes. Among the 165 patients with recurrent episodes, the drug was effective during all the arrhythmic episodes in 84% of them. Only 7% of patients reported adverse effects. Monthly visits to the emergency department and hospitalization were significantly lower during follow-up than during the year before the index episode.

The authors of the report conclude that, in selected patients with recurrent atrial fibrillation, pill-in-the-pocket treatment is safe and effective, with a high rate of compliance, a low rate of adverse events, and a marked decrease in utilization of healthcare resources.

## DRUG EVALUATION (continued)

### Cholinesterase Inhibitor Improves Parkinson's Disease-Associated Dementia

The average prevalence of dementia among patients with Parkinson's disease is about 40%. Cholinergic deficits are the most consistent findings associated with symptoms. Preliminary studies suggest that cholinesterase inhibitors, now deemed first-line therapy for Alzheimer's disease, may also be beneficial in patients who have dementia associated with Parkinson's disease. These observations led to a placebo-controlled study to evaluate the efficacy and safety of rivastigmine in such patients [*N Engl J Med* 2004;351:2509-18].

A total of 541 patients in whom mild-to-moderate dementia developed at least two years after a diagnosis of Parkinson's disease were randomly assigned to receive placebo or 3-12 mg/day rivastigmine for 24 weeks; 410 completed the study. Primary efficacy variables were the scores for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC).

Outcomes were better among patients treated with rivastigmine than among those who received placebo. Differences were similar to those reported in trials of rivastigmine for Alzheimer's disease. Clinically significant improvements in the scores for the ADCS-CGIC were noted in 19.8% of patients in the rivastigmine group and 14.5% of those in the placebo group; worsening was observed in 13.0% and 23.1%. The most frequent side effects of the drug were nausea, vomiting, and tremor.

The investigators conclude, "In patients with Parkinson's disease, dementia is a major prognostic factor for progressive disability and nursing home placement, and thus our findings may have implications for clinical practice." A related editorial suggests that cholinesterase inhibitors "can now be added to the list of medications that may benefit these patients" [*Ibid*, 2547-49].

### Taking an Aromatase Inhibitor from the Outset More Effective for Breast Cancer

The standard adjuvant therapy for postmenopausal women with hormone-receptor-positive localized breast cancer is treatment with tamoxifen, a selective estrogen-receptor modulator, for five years. This paradigm, however, has been challenged and is already changing. Based on convincing evidence, cancer specialists now recommend that women take an aromatase inhibitor at some point in their treatment. However, it is not yet clear whether taking an aromatase inhibitor from the outset is more effective than initiating therapy with tamoxifen.

Supporting the need for a change in initial therapy is a report from the ATAC Trialist Group suggesting that aromatase inhibitors should replace tamoxifen as first-line treatment for postmenopausal women with breast cancer [*Lancet*, 2005;365:60-62]. The researchers followed more than 9000 women in 20 countries for 68 months. They found that women who took anastrozole (*Arimidex*), one of three aromatase inhibitors available in the U.S., for five years had a lower rate of recurrence and fewer side effects than those who used tamoxifen.

Treatment with anastrozole was associated with longer disease-free survival, time to recurrence, and distant metastases. The most pronounced effect was a 42% reduction in the development of contralateral breast cancers. Advantages were even more pronounced among patients who were hormone-receptor-positive. Benefits were observed at all times after the first year of follow-up. Also to the good, the research group noted significant reductions in the incidence of endometrial cancer, thromboembolic events, and ischemic cerebrovascular events in the anastrozole group; withdrawals due to adverse events were also significantly less common. However, patients treated with the aromatase inhibitor did experience more arthralgias and fractures than women on tamoxifen.

The authors of the report conclude that "Anastrozole should be preferred initial treatment for postmenopausal women with localized hormone-receptor-positive breast cancer." Other experts, however, find this conclusion premature. The question remains as to whether an aromatase inhibitor from the outset is more effective than 3 to 5 years of tamoxifen, followed by an aromatase inhibitor.

## Antihypertensive Agents in Patients with Coronary Disease and Normal BP

A recent report calls attention to the uncertainty that still exists regarding optimal use of antihypertensive agents in patients with coronary artery disease (CAD) [*JAMA* 2004;292:2217-26]. Is there benefit for patients with “normal blood pressure”?

The report describes a well-controlled trial that compared the effects of amlodipine (10 mg) or enalapril (20 mg) with placebo in 1991 patients with CAD (> 20% stenosis) and diastolic blood pressure < 100 mm Hg. The primary endpoint was the incidence of cardiovascular events for amlodipine vs. placebo.

Baseline blood pressure averaged 129/78 mm Hg; it increased negligibly in the placebo group and decreased by about 5/2.5 mm Hg in each of the active treatment groups. Cardiovascular events—cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris or congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease—occurred in 23.1% of placebo-treated patients, in 16.6% of amlodipine-treated patients, and in 20.2% of enalapril-treated patients. Differences between the enalapril and placebo groups or the enalapril and amlodipine groups

did not reach conventional statistical significance. The investigators estimated that for every 16 patients with CAD and normal blood pressure given amlodipine to lower blood pressure, one cardiovascular event could be prevented.

In a subgroup of 274 patients in whom atherosclerosis progression was estimated by intravascular ultrasound, there was a trend toward less progression in the amlodipine group compared with the placebo group. Compared with baseline, those in the placebo group manifested progression, those in the enalapril group showed a trend toward progression, and those in the amlodipine group showed no progression.

The authors of the report conclude, “Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events.” Similar, but smaller and nonsignificant, treatment effects were observed with enalapril. Intravascular ultrasound demonstrated evidence of slowing of atherosclerosis progression [*Ibid*]. A related editorial emphasizes that “the findings provide direction for future trials with patients randomized to various strata of blood pressure targets below 140 mm Hg systolic.”

## DRUG SAFETY

### FDA Warns of Serious Side Effects of *Bextra*

On 10 December 2004, *MD Consult* advised that the FDA would require new warnings concerning the use of *Bextra* (valdecoxib), a COX-2 selective NSAID indicated for the treatment of osteoarthritis, rheumatoid arthritis, and dysmenorrheal pain. The new label will include a boxed warning strengthening earlier concerns about the risk of life-threatening skin reactions, and a new bolded warning contraindicating the use of *Bextra* in patients undergoing coronary artery bypass graft surgery.

Patients taking *Bextra* for labeled indications have reported Stevens-Johnson syndrome and toxic epidermal necrolysis, potentially fatal skin reac-

tions. These reactions occurred usually, but not always, within two weeks of initiating therapy. Patients should be advised to discontinue the drug at the first appearance of a skin rash, mucosal lesion, or any other signs of an allergic response. *Bextra* is a benzenesulfonamide; patients with a history of allergic reaction to sulfonamides may be at greater risk of skin reactions.

### New Dosage Recommendations for Use of *Procrit* in Cancer Patients

In December, at the behest of the FDA, Ortho Biotech notified oncologists, hematologists, and other health care professionals of important changes to the safety and dosing sections of the

(Continued on Supplement page 6)

## DRUG SAFETY (continued)

### New Dosing for *Procrit* (continued)

product label for *Procrit* (erythropoietin). The new information recommends that the target hemoglobin level in patients with cancer should be individually determined but should not exceed 12 g/dl in men or women. The dose should be withheld if the hemoglobin level reaches 13 g/dl. Dosing interruption and modification are recommended if the rate of increase of hemoglobin level exceeds 1 g/dl over a two-week period.

The new recommendations arise from studies that permitted or required dosing to achieve hemoglobin levels greater than 12 g/dl. An excess of thrombotic vascular events and deaths were reported in these studies.

Another label change, made at the request of the drug manufacturer, is the addition of an alternative dosing regimen—40,000 IU subcutaneously weekly. Up until now, the only dosing regimen specified in the *Procrit* labeling for the cancer chemotherapy indication was 150 IU/kg

given subcutaneously three times per week [*MD Consult*, 10 December 2004].

### Osteoporosis Looms in Men Treated for Prostate Cancer

A review of the medical records of 184 men with prostate cancer who had received androgen deprivation therapy (ADT) with goserelin injections for at least one year reveals that physicians generally do not take steps to prevent or treat osteoporosis [*Cancer*, 2004;103:237-41].

The chart review found that dual energy X-ray absorptiometry scans had been ordered for less than 10% of patients in the past three years; similar numbers were receiving calcium and vitamin D supplements. Oral bisphosphonates were prescribed for only 5% over the previous year. None were receiving estrogen or calcitonin. The only risk factor that generally led to treatment for osteoporosis was the presence of bone metastasis. The authors of the report suggest that “guidelines for bone mineral density measurement and treatment interventions are necessary for patients undergoing ADT.”

## PUBLIC HEALTH

### Immunizing Children May Prevent Flu Deaths Among the Elderly

The influenza vaccine shortage in the United States has forced a debate about the best vaccination strategy to employ. Mounting data suggest that there are more effective ways to combat the annual attack of this disease than what the country does now, steering the vaccine to healthy infants and people 50 or older, as well as people with chronic illness, the groups that suffer the most hospitalizations and deaths. A report in *Science* [2004;306:1123] cites a study published online on November 2 in *Vaccine*, which concludes that vaccinating school-age children could have a greater impact on slowing the spread of influenza virus and reducing disease than current practice.

Vaccine experts have long recognized that immunizing a high percentage of people in a community can decrease the circulation of the pathogen and create a “herd protection” that extends to the unvaccinated. This appears to apply to the flu vaccine. Since the 1998-1999 flu season, researchers have offered an intranasal influ-

enza vaccine to everyone between the ages of 18 months and 18 years residing in two Texas towns. They achieved penetration rates of 20% to 25% of the eligible population. Each year, the investigators estimated serious flu-related disease in all age groups. For purposes of control, they also analyzed three other communities in which less than 1% of the children received flu vaccine.

In the two reference communities, the investigators found that each year they vaccinated school-age children, serious cases of influenza in adults at least 35 years of age were 8% to 18% lower than in the comparison communities. An author of the report noted, “With the current policy you only try to control mortality. If you want to control flu, our hypothesis is to focus on kids” [*Ibid*]. A mathematical model suggests that vaccinating just 30% of school-age children in a community reduces the likelihood of epidemic spread of influenza from 90% to 65%. If 70% are vaccinated, the likelihood drops to 4%.