

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Azithromycin No Better Than Vitamin C for Acute Bronchitis

A recent report advises that azithromycin (*Zithromax*) is no better than low-dose vitamin C for the treatment of acute bronchitis and should not be prescribed [*Lancet* 2002;359:1648-54]. The report says that each year in the U.S., about 10 million adults seek treatment for acute bronchitis, and that most of them are given antibiotics, although the pathogens involved are usually viruses. The authors point out that many experts condemn such practice because of weak or conflicting experimental evidence of clinical benefit, the lack of a strong biological rationale, and the increasing societal concern about widespread antibiotic resistance.

In a well-controlled trial, the researchers randomly assigned 220 patients with acute bronchitis (duration 2 to 14 days) to a total dose of 1.5 g azithromycin or vitamin C over five days. Patients also received albuterol inhaler and dextromethorphan. Measures used to compare the effects of the two treatments included time taken to return to work or usual activities and improvements in health-related quality of life. The results showed that azithromycin was no more effective than low-dose vitamin C. Given the lack of evidence that vitamin C is effective, the investigators concluded that azithromycin is ineffective and should not be prescribed for patients with acute bronchitis.

The principal investigator recommended that physicians avoid all antibiotics for the treatment of acute bronchitis, except if the condition changes and there is suspicion of pneumonia [*Reuters Health*, 10 May 2002]. He blamed the common use of azithromycin for acute bronchitis on a published open-label study that reported a 90% recovery rate, but the study did not include a placebo-treatment group.

First-Line Prevention of Recurrent Breast Cancer: Aromatase Inhibitor or Tamoxifen?

Last December, at a breast cancer symposium held in San Antonio, researchers presented results of a study comparing the aromatase inhibitor anastrozole (*Arimidex*) with tamoxifen in more than 9300 women who had breast cancer and undergone surgery and chemotherapy. They found a 17% relative reduction in risk of recurrence in those taking the aromatase inhibitor compared with those taking tamoxifen, but no difference in survival time. Those women taking anastrozole were less likely to develop endometrial cancer, have strokes or blood clots, or suffer other adverse effects. The *Arimidex* group had a higher incidence of muscle aches and osteoporotic fractures [*The New York Times on the Web*, 9 April 2002].

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CLINICAL PRACTICE (continued)

First-Line Prevention of Recurrent Breast Cancer (continued)

Despite the promising findings with anastrozole, a group of the nation's leading cancer specialists have determined that it is premature for postmenopausal women with early breast cancer to switch to aromatase inhibitors. Representing the views of the American Society of Clinical Oncology, the expert report firmly stated that tamoxifen should remain the standard of therapy that it has been for the last 16 years.

The panel unanimously agreed that the *Arimidex* findings were encouraging, but that 33 months was not long enough to judge the safety and effectiveness of aromatase inhibitors as a standard prevention for recurrence of breast cancer among postmenopausal women.

The maximum benefit of tamoxifen is seen after five years of treatment and it is conceivable that five years of anastrozole could be inferior to five years of tamoxifen. Aromatase inhibitors, however, could be a good choice at this time for a small group of women with a history of stroke or blood clots [*Ibid*, 19 May 2002].

Tamoxifen is the only FDA-approved drug for prevention of recurrent breast cancer and for primary prevention in high-risk women. *Arimidex* and the other marketed aromatase inhibitors—*Femara* (letrozole) and *Aromasin* (exemestane)—are approved for the treatment of advanced breast cancer.

New Guidelines for Treatment of Rheumatoid Arthritis

Updated guidelines from the American College of Rheumatology (ACR) for the management of rheumatoid arthritis, emphasize the value of early diagnosis and treatment to prevent joint damage [*Arthritis Rheum* 2002;46:328-346]. Prompting the update is the introduction of new therapeutic interventions that were not available in 1995, and new data from clinical trials and from epidemiologic studies showing that rheumatoid arthritis patients need to be treated earlier and more aggressively.

The ACR recommends that initial treatment should be chosen based on prognosis. Patients who present at a young age, with high rheumatoid factor titer, elevated erythrocyte sedimentation rate, swelling of more than 20 joints, or extra-articular manifestations have a poor prognosis. They should receive aggressive treatment

with disease modifying antirheumatic drugs (DMARDs) as soon as the diagnosis is made. Thereafter, patients should be reassessed periodically for evidence of disease activity or progression and for adverse effects associated with treatment.

New, FDA-approved medications are two anti-tumor necrosis factor (TNF) agents, etanercept and infliximab, anakinra, a recombinant human form of interleukin-1 receptor antagonist, and leflunomide. Another new treatment modification is the use of DMARDs in combination. The experts who formulated the new guidelines do not see them as controversial, either among health care providers or third party payers. "The insurers are already funding the TNF inhibitors and other new biologics" [*Reuters Health*, 21 February 2002].

Treatment Guidelines for Bipolar Disorder

The American Psychiatric Association has updated guidelines for treating bipolar disorder, a common and serious mental disorder with a suicide rate, if left untreated, of 10% to 15%. A summary of these guidelines is available to subscribers of *Prescriber's Letter* at www.prescribersletter.com.

The treatment of bipolar disorder was greatly improved with the introduction of the mood stabilizer lithium, which was found to help treat or reduce the frequency of both manic and depressive episodes. But

lithium has many drawbacks. In the last decade, anti-convulsants have become an important class of drugs for bipolar disorder. Carbamazepine and valproic acid were found to have mood stabilizing properties. Valproic acid came to be favored over carbamazepine because it is better tolerated, especially in the divalproex (*Depakote*) formulation. Valproic acid may even be better than lithium for certain patients. Another important change in the treatment of bipolar disorder is the use of atypical antipsychotics such as risperidone

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Treatment Guidelines for Bipolar Disorder (continued)

(*Risperdal*) and olanzapine (*Zyprexa*). Olanzapine is approved for acute treatment—for up to eight weeks.

Lithium or valproic acid is the usual first-line mood stabilizer for most patients. Carbamazepine is often considered an alternative to valproic acid but it is not as well tolerated. Oxcarbazepine (*Trileptal*) has not been as well studied but it is finding increased use because many patients tolerate it better than they do carbam-

azepine. Other new anticonvulsants such as lamotrigine (*Lamictal*) are also finding use in bipolar disorder.

Atypical antipsychotics are currently considered as adjuncts. They are most often used short-term. Patients with bipolar disorder often need a rapid anti-anxiety effect to help until the mood stabilizer kicks in. Benzodiazepines are often used in this setting. An antidepressant is added to lithium or lamotrigine for severe depressive episodes, but it should never be used alone.

CDC Issues New Guidelines for Treating STDs

A report in the *Prescriber's Letter* [June 2002] summarizes the changes the CDC has made in developing new guidelines for the treatment of sexually transmitted disease (STDs). Quinolones are no longer recommended to treat gonorrhea acquired in California or Hawaii. Quinolone-resistant infection is common in Asia and is now spreading to the West Coast. Patients who acquired gonorrhea in these states or in Asia should receive cefixime or ceftriaxone. In most states, however, the CDC continues to recommend the use of ciprofloxacin, ofloxacin, or levofloxacin for initial therapy. Azithromycin or doxycycline should be added if chlamydia is not ruled out. Annual screening for chlamydia is recommended for all sexually active

women under age 25 and women over 25 if they have new or multiple sex partners. Homosexual men should be tested annually for HIV, chlamydia, syphilis, and gonorrhea, and vaccinated against hepatitis A and B. Patients should be cautioned not to rely on spermicides containing nonoxynol-9 to prevent STDs. Frequent use can cause genital or rectal lesions that might facilitate HIV transmission.

A copy of the new guidelines can be downloaded at www.cdc.gov/std. *Prescriber's Letter* subscribers can obtain a concise chart that summarizes the latest treatment for STDs from www.prescribersletter.com.

NEW DRUGS AND INDICATIONS

Zevalin Approved for Non-Hodgkin's Lymphoma

The FDA has approved *Zevalin* (ibritumomab tiuxetan) for the treatment of relapsed or refractory low-grade, follicular, or transformed B-Cell non-Hodgkin's lymphoma (NHL). *Zevalin* is the first radioimmunotherapy to gain FDA approval. Approval is limited to treatment of *Rituxan* (rituximab)-refractory NHL, but *Zevalin* has also received accelerated approval—contingent on completion of two additional studies—for chemotherapy-relapsed or refractory B-cell NHL.

Zevalin is a monoclonal antibody linked to the radioisotope yttrium-90. It targets the CD20 antigen on the surface of B cells and B-cell tumors, induc-

ing cellular damage in the target and neighboring cells. *Zevalin* can also be linked to indium-111 for use as an imaging agent. The *Zevalin* therapeutic regimen consists of *Rituxan* preceding indium-111 *Zevalin* followed seven to nine days later by a second infusion of *Rituxan* prior to yttrium-90 *Zevalin*. The purpose of administering *Rituxan* twice is to remove cancerous cells in the blood and lymphatics so that the therapeutic dose of *Zevalin* goes directly to the tumor site. Like other antibodies, *Zevalin* carries the risk of severe or fatal infusion-related reactions. The drug's maker estimates that there are approximately 300,000 NHL patients in the U.S.; about 25-30% of them are eligible for *Zevalin*.

DRUG EVALUATION

Coronary Angioplasty More Effective Than Thrombolytic Therapy

Studies have demonstrated that primary percutaneous coronary intervention (angioplasty) is more effective than thrombolytic therapy after acute myocardial infarction. But up until now, angioplasty has been limited to hospitals that have on-site cardiac surgery programs, and most acute MI patients have not had access to this intervention. Given the dilemma of having a better therapy but with limited access, researchers conducted a randomized trial to determine at hospitals without on-site cardiac surgery whether treatment of acute MI with primary angioplasty is superior to therapy with a thrombolytic agent [*JAMA* 2002; 287:1943-51].

Eleven community hospitals without extant angioplasty programs participated in the study. After instituting a formal angioplasty development program in these hospitals, the investigators enrolled 451 thrombolytic-eligible patients with acute MI of less than 12 hours' duration and assigned them to receive primary angio-

plasty or accelerated tissue plasminogen activator (alteplase). The main outcome measures were a six-month composite incidence of death, recurrent MI, and stroke, and median hospital length of stay.

At six weeks (10.7% vs. 17.7%) and at six months (12.4% and 19.9%), the incidence of the composite end point was reduced in the primary angioplasty group compared with the thrombolytic-therapy group. The greatest impact of primary angioplasty was a 50% decrease in recurrent MI. Median length of stay was also reduced in the primary angioplasty group compared with the drug-treatment group (4.5 vs. 6.0 days).

Based on these findings, research cardiologists are urging the nation to change its system for emergency care of heart attacks. Added to results of earlier reports, the new findings offer compelling evidence for angioplasty becoming the standard of care for acute MI associated with ST-segment elevation on electrocardiogram.

Safety of COX-2 Inhibitor Challenged

Studies have demonstrated that COX-2 inhibitors are no more effective in relieving pain and inflammation than conventional NSAIDs. Furthermore, the FDA has found no evidence that the leading COX-2 inhibitor, celecoxib (*Celebrex*), offers a better gastrointestinal safety profile than NSAIDs and prohibits Pharmacia, the drug's manufacturer, from making such claims. Nevertheless, thousands of physicians have written millions of prescriptions for *Celebrex* based on the belief that it is safer than NSAIDs. One reason for this perception is misleading data from the CLASS trial published in *JAMA* [2000;284:1247-55].

According to the report, the study, funded by Pharmacia, determined the occurrence of clinically relevant upper gastrointestinal ulcer complications and symptomatic ulcers in patients with arthritis during the first six months of treatment with celecoxib, ibuprofen, or diclofenac. A comparison of celecoxib with the two NSAIDs combined showed no significant difference with respect to ulcer complications but did demonstrate a significantly lower incidence of ulcer complications plus symptomatic ulcers in the celecoxib group versus the pooled NSAID groups. The authors of the report concluded that celecoxib was associated with a lower inci-

dence of complications than were traditional NSAIDs. Results from the report were widely disseminated. Less widely publicized were lethal criticisms of the study.

An article in the *Washington Post* in August 2001 and two letters to *JAMA* published in November 2001 called attention to the fact that complete information available to the FDA contradicted these conclusions. The journal article reporting the results of CLASS actually referred to the combined analysis of the results of the first six months of two separate and longer trials. The protocols of these trials differed markedly from the published report.

Two comparisons were originally planned—celecoxib versus ibuprofen and celecoxib versus diclofenac. In both trials, the prespecified primary outcome was ulcer-related complications, not symptomatic ulcers, and the maximum duration of follow up was 15 months and 12 months, respectively. The protocol explicitly specified that celecoxib would be claimed to be different only if both overall (celecoxib versus both NSAIDs) and pairwise (celecoxib versus each NSAID) comparisons were statistically significant for ulcer-related complications.

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Safety of COX-2 Inhibitor Challenged (continued)

Analysis according to the prespecified protocol showed similar numbers of complications in the three groups. Almost all the ulcer complications that had occurred during the second half of the trials were in users of celecoxib. This finding supports the FDA's concerns that COX-2 inhibitors could interfere with the benefits of COX 2 in ulcer healing, leading to a long-term increase of complications. The results are contrary to the published conclusions. They were available when the manuscript was submitted, but were neither cited in the article nor reported to *JAMA* [*BMJ* 2002;324:1267-88].

The published report had a substantial impact on prescribing. About 30,000 reprints of the article were purchased from the publisher. A search of the Science Citation Index found 169 articles citing the report. This

wide distribution and citation coincided with the sales of *Celebrex* increasing from \$2.6 billion in 2000 to \$3.1 billion in 2001 [*Ibid*].

In contrast with the CLASS trial, the VIGOR trial found a small but unequivocal benefit of another COX-2 inhibitor, rofecoxib (*Vioxx*), over the traditional NSAID naproxen. Potential reasons for these different outcomes are the use of concurrent low-dose aspirin in about 20% of patients in the CLASS trial but in no patient in the VIGOR trial, the use in the CLASS trial of diclofenac, which has greater COX-2 selectivity than naproxen, the use of higher than usual doses of celecoxib in the CLASS trial, and the greater COX-2 selectivity of rofecoxib over celecoxib [*Ibid*].

Expert Committee Downgrades Benefits of Hormone Replacement Therapy

On considering the evidence, an international team of women's health experts is discouraging the use of hormone replacement therapy (HRT) for many postmenopausal conditions. A report of the team's action in *JAMA* [2002;287:1923-24] noted, "Coronary heart disease, fractures, depression, urinary incontinence—all cited in the past as primary reasons to initiate HRT—are losing favor as valid indications for it, as evidence from high-quality clinical trials accumulates."

In 1992, three major organizations—the American College of Physicians, the American College of Family Medicine, and the U.S. Preventive Services Task Force—announced support for guidelines that urged physicians to prescribe HRT for women with or at risk of heart disease and osteoporosis. The guidelines relied almost exclusively on observational studies and clinical experience, the results of which are now considered suspect. A decade later there has been a dramatic shift

in best clinical practices for treating patients during menopause.

Four years ago, results from the first large, randomized clinical trial of HRT for secondary prevention of cardiovascular disease shocked the medical world. Not only did HRT fail to reduce the risk of coronary heart disease, it actually increased risk over placebo by nearly 50% during the first 18 months of the study. It remains true that HRT helps prevent bone loss, but whether that benefit translates into reduced risk of fracture remains uncertain as convincing data are lacking. Given estrogen's adverse effect profile—three-fold increased risk of thrombosis and increased risk of gall bladder disease, breast cancer, and cancer of the uterus (in the absence of a progestin)—patients are probably better off with other drug options. The experts also cite the lack of evidence supporting the use of HRT to retard early Alzheimer's disease.

Gleevec Now Considered First-Line for CML

The striking superiority of Novartis's tyrosine kinase inhibitor *Gleevec* (imatinib)—in terms of complete hematologic response, complete cytogenetic response, and tolerance of therapy—over interferon alfa in a recent trial in newly diagnosed chronic myeloid leukemia (CML) patients attracted a great deal of attention at the Orlando, Florida meeting of the American Society of Clinical Oncology. The results prompted the

investigators to declare that the drug should now be considered the standard of care for early CML.

In the open label study, 1106 patients were randomized either to imatinib or interferon plus cytarabine (Ara-C). The primary end point was time to progression, defined as either death, progression to accelerated or blast phase, rapidly increasing white

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Gleevec Now Considered First-Line for CML (continued)

blood cell counts, or loss of either a complete hematologic or major cytogenetic response. The estimated rate of progression-free survival at 12 months was 97.2% for *Gleevec* compared with 80.3% for the interferon arm. Notably, 68% of patients treated with *Gleevec* had no detectable leukemia as compared with 7% of interferon-treated patients. The percentage of

patients whose disease progressed to the terminal stages of leukemia was only 1.5% among those treated with imatinib compared with 7% of patients treated with interferon [*Scrip*, 24 May 2002]. Less than 1% of *Gleevec* patients had severe side effects, compared with 23% of interferon patients [*Reuters Health*, 22 May 2002].

DRUG SAFETY

Drug for Irritable Bowel Syndrome Returns to Market

For the first time, the FDA is allowing a drug to go back on the market after it was withdrawn for safety reasons. The drug, alosetron (*Lotronex*), is expected to be available in the fall. *Lotronex* was withdrawn in November 2000, less than 10 months after its marketing for the treatment of women with diarrhea-dominant irritable bowel syndrome (IBS), because it was linked to severe intestinal problems and several deaths. But thousands of patients who found the drug to be of benefit protested the withdrawal. Their pleas persuaded the FDA to reconsider.

This time around, *Lotronex* will have far more restrictions, leaving considerable responsibility with physicians, pharmacists, and patients to use the drug correctly and to watch for early signs of intestinal problems. A physician who wishes to prescribe *Lotronex* must enroll in a program run by GlaxoSmithKline, the drug's maker, that requires them to "self attest" that they know how to diagnose and treat IBS, how to prescribe *Lotronex*, and how to recognize and treat complications. Physicians must also agree to explain the drug's risks and benefits to patients, provide each patient with a pamphlet about the drug, and report serious adverse events to GlaxoSmithKline or the FDA.

Patients who want *Lotronex* must sign an agreement acknowledging its risk of serious constipation problems and of ischemic colitis. They must also pledge to call their physicians immediately if they develop any symptoms considered to be dangerous. Physicians in the program will be given special stickers to apply to prescriptions for *Lotronex*, and the drug's labeling will alert pharmacists not to fill prescriptions that do not bear a sticker. The new directions for

Lotronex use reduce the starting dose in half, to 1 mg a day. *Lotronex* is now indicated only for women with very severe conditions that have not responded to other drugs, a group that constitutes less than 5% of all people with IBS [*The New Times on the Web*, 8 June 2002].

Plasma Troponin Levels May Predict Chemotherapy-Related Cardiotoxicity

A report in the *Annals of Oncology* [2002;13:710-715] suggests that measuring plasma troponin I levels soon after high-dose chemotherapy may allow physicians to predict which patients will develop cardiac dysfunction. The investigators measured troponin I levels immediately after chemotherapy in 211 women with high-risk breast cancer. Patients were considered troponin-positive if the level was at least 0.5 ng/ml. Left ventricular ejection fraction was determined before chemotherapy and several times after treatment for up to 12 months.

Seventy patients were troponin-positive, and over time their ejection fraction decreased. Ejection fraction remained unchanged in troponin-negative patients. In troponin-positive patients, the decrease in ejection fraction was strongly related to the maximum troponin level following chemotherapy. The investigators told *Reuters Health* [3 May 2002], "The innovative aspect of this new marker is that it gives us information long before functional impairment can be detected with other techniques."

In another study, researchers found that anthracycline-induced cardiotoxicity typically begins several months after treatment. Moreover, the longer the delay, the worse the disease appears to be. Therefore, current recommendations to only monitor cardiotoxicity during and shortly after treatment should be revised [*Annals of Oncology* 2002;13:699-709].