

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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NEW DRUGS AND INDICATIONS

Natalizumab Therapy for Crohn's Disease

Crohn's disease involves persistent recruitment of leukocytes in gut tissue, with resultant inflammation. Natalizumab (*Tysabri*) is a humanized monoclonal antibody against alpha-4 integrin. It inhibits leukocyte adhesion and migration into inflamed tissue. Natalizumab has been shown to be effective against multiple sclerosis, another chronic inflammatory disease. Therefore, researchers conducted a 12-week induction trial of natalizumab in patients with moderate-to-severe Crohn's disease. Response was defined by a decrease in the Crohn's Disease Activity Index (CDAI) score of at least 70. Patients who manifested a response to natalizumab were eligible to enroll in a 48-week maintenance study [*N Engl J Med* 2005;353:1912-25].

In the induction phase of the study, natalizumab and placebo groups had similar rates of response (56% and 49%) and remission (37% vs. 30%). Continuing natalizumab in the maintenance phase of the study resulted in higher rates of sustained response (61% vs. 28%) and remission (44% vs. 26%) through week 36 than did switching to placebo. The proportion of patients suffering severe adverse events was similar in each group in both phases of the study. In an open label extension study, a patient treated with natalizumab died from progressive multifocal leukoencephalopathy.

The authors of the report conclude: "Induction therapy with natalizumab for Crohn's disease resulted in small, nonsignificant improvements in response and remission rates. Patients who had a response had significantly increased rates of sustained response and remission if natalizumab was continued every four weeks." Related commentary stresses that for natalizumab to add a new dimension to the treatment of inflammatory bowel disease, it must have an acceptable risk of adverse events. Of concern are the apparent unintended consequences of immunodeficiency. Furthermore, progressive multifocal leukoencephalopathy has developed in at least three patients receiving natalizumab, two of whom died. This development has prompted the manufacturer to halt sales of the antibody for the treatment of multiple sclerosis [*Ibid*, 1965-68].

Sildenafil Therapy for Pulmonary Arterial Hypertension

Sildenafil inhibits phosphodiesterase type 5, an enzyme that metabolizes cyclic guanosine monophosphate and thereby enhances the cyclic guanosine monophosphate-mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lung. Sildenafil, under the name *Revatio* was recently approved in the U.S. for the treatment of pulmonary arterial hypertension (PAH).

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NEW DRUGS AND INDICATIONS (continued)

Sildenafil Therapy for Pulmonary Arterial Hypertension (continued)

In a recently reported trial, researchers assigned 278 patients with symptomatic PAH to placebo or sildenafil (20, 40, and 80 mg) orally three times daily for 12 weeks [*Chest* 2005;128:161S]. The primary endpoint was the change in baseline to week 12 in the distance walked in six minutes. The distance walked in six minutes significantly increased from baseline in all sildenafil groups; mean placebo-corrected treatment effects were 45 m, 46 m, and 50 m for 20 mg, 40 mg, and 80 mg, respectively. All sildenafil doses reduced the mean pulmonary-artery pressure, improved the WHO functional class, and were associated with side effects such as flushing, dyspepsia,

and diarrhea. The incidence of clinical worsening did not differ significantly between patients treated with sildenafil and those treated with placebo.

Four other agents are currently approved for the treatment of PAH in the U.S. and Europe: intravenous epoprostenol, the inhaled prostacyclin analogue iloprost, the subcutaneously and intravenously administered prostacyclin analogue treprostinil, and the oral endothelin-receptor antagonist bosentan. Although these drugs are effective in many patients, adverse effects occur with all of them. Sildenafil appears to be an important addition.

CLINICAL PRACTICE

Appropriate Use of Antimicrobial Drugs

Among children presenting with sore throat, perhaps up to one-third have pharyngitis caused by group A beta-hemolytic strep (GABHS). Most sore throats, however, are due to upper respiratory viruses such as rhinovirus and adenovirus and do not warrant antibiotic treatment.

Experts recommend penicillin as the antibiotic of choice for children with sore throat due to GABHS, but also cite amoxicillin and erythromycin (for penicillin-allergic patients), and first-generation cephalosporins as acceptable alternatives. They also recommend a GABHS test prior to treating children with an antibiotic to reduce unnecessary exposure.

In a recent report, investigators measured rates of prescribing of antimicrobial drugs and the effect on prescribing of a GABHS test among children presenting with a sore throat [*JAMA* 2005;294:2315-22]. They determined that physicians prescribed antibiotics in 53% of an estimated 7.3 million annual visits for sore throat and nonrecommended antibiotics to 27% of children who received an antibiotic.

Probably the result of a major educational campaign continuing for many years, antibiotic prescribing decreased from 66% of visits in 1995 to 54% of visits in 2003. This decrease was the consequence of a

decrease in the prescribing of recommended antibiotics from 49% to 38%. Regarding GABHS testing, physicians performed a test in 53% of visits and in 51% of visits at which an antibiotic was prescribed. GABHS testing was not associated with a lower antibiotic prescribing rate overall.

The data indicate that physicians prescribed antibiotics to children with sore throat in excess of the maximum expected prevalence of GABHS. Although there was a decrease in the proportion of children receiving antibiotics between 1995 and 2003, this was due to decreased prescribing of agents recommended for GABHS. The use of nonrecommended antimicrobials (e.g. amoxicillin/clavulanic acid, clarithromycin, and azithromycin) remained the same over the nine-year study, at an unacceptably high level of 27% among those who received antimicrobials.

Finally, although GABHS testing was not associated with a lower rate of antibiotic prescribing overall (48% tested versus 51% not tested), testing was associated with a lower rate of antibiotic prescribing (47% tested vs. 73% not tested) for children with diagnosis codes of pharyngitis, tonsillitis, and streptococcal sore throat. We can do better with greater use of GABHS testing.

Combination Use of Triptans and NSAIDs for Migraine

The management of migraine is patient-specific and challenging. Available therapies are migraine-specific agents such as triptans and nonspecific analgesics such as NSAIDs. Triptans are thought to prevent the release of inflammatory substances from nerve endings and alter the pain signal transmission. NSAIDs act by inhibiting prostaglandin synthesis.

Triptans are considered first-line agents but monotherapy is ineffective in many patients. In light of the different mechanisms of action of triptans and NSAIDs, combination therapy is plausible. It might increase patient response and even reduce symptom recurrence. A recently reported clinical trial addressed these hypotheses [*Headache* 2005;45:983-91].

The well-controlled study assessed the efficacy of sumatriptan alone and naproxen alone against a combination of the two agents in a total of 965 patients with a diagnosis of migraine with or without aura and at least two but not more than six migraine attacks per month. Each patient treated one migraine attack of moderate or severe intensity with one of four treatment options: sumatriptan 50 mg and naproxen 500 mg; sumatriptan 50 mg, naproxen 500 mg; or placebo.

The primary endpoint of sustained pain response—no pain greater than mild at two hours, taking no rescue medication for 24 hours after dosing and having no recurrence of moderate or severe pain within the 24-hour window—was reached in 46% of the sumatriptan/naproxen group compared with 29% in the sumatriptan group, 25% in the naproxen group, and 17% in the placebo group. Pain relief at two hours was achieved in 65% of patients in the combination group, 49% in the sumatriptan group, 46% in the naproxen group, and 27% in the placebo group.

The investigators also observed a significant difference between headache recurrence rates in the 24 hours following treatment. Recurrence occurred in only 29% of those treated with the combination of sumatriptan and naproxen. Comparatively, recurrence rates were 41%, 47%, and 38% in the sumatriptan, naproxen, and placebo groups respectively. The researchers surmise that the long half-life of naproxen (18 hours) coupled with the potency of sumatriptan may explain the increased response and lower recurrence rate seen with combination therapy. The results indicate the use of both a triptan and an NSAID for patients experiencing migraine that is not effectively relieved by triptan monotherapy.

Pediatric Pneumococcal Vaccination Cuts Adult Disease Rates

A report in *JAMA* [2005;294:2043-51] finds that the targeting of young children with newly approved 7-valent pneumococcal conjugate vaccine (PCV-7) impressively reduces rates of invasive disease among older adults. Unlike the 23-valent vaccine given to adults, PCV-7 affects pneumococcal carriage and transmission. “Therefore, the epidemiology of invasive pneumococcal disease in adults could change with the introduction of PCV-7 vaccination of children” [*Reuters Health*, 26 October 2005].

To determine the impact of PCV vaccination of children which was introduced in 2000, investigators at the Minnesota Department of Health analyzed data from eight U.S. geographic areas with a popula-

tion of greater than 28 million people for the period from 1998 to 2003. They report that during the study period, rates of invasive pneumococcal disease among people 50 years or older decreased from 40.8 to 29.4 cases per 100,000, a 28% reduction. Furthermore, for adults 65 years or older, the rate in 2003 was 41.7 cases per 100,000, already reaching the U.S. Department of Human Services’ goal of 42 cases per 100,000.

The authors of the report in *JAMA* recommend: “Policy makers elsewhere who are considering whether to incorporate PCV-7 into their routine infant immunization programs and who are weighing its cost-effectiveness should consider the benefits seen in older adults.”

DRUG SAFETY

Acetaminophen Poisonings Rising Sharply in U.S.

A new study shows that the percentage of acute liver failure cases due to acetaminophen overdose has increased from 1998 to 2003, with unintentional overdose now accounting for half of these cases [*Hepatology* 2005;42:1364-72]. The reasons for this situation are the narrow therapeutic index of acetaminophen coupled with its ubiquity in cough and cold preparations and analgesic combinations.

Acetaminophen is best known under the trade name *Tylenol*, which is widely used for pain and fever. Consumers who purchase generic versions of *Tylenol* may not be aware of its contents because they are often labeled "Aspirin Free Pain Relief." Furthermore, many consumers are unaware that acetaminophen is also found in several hundred cold remedies as well as in other prescription and nonprescription combination products. These products include *Excedrin*, *TheraFlu*, and some forms of *Midol*, *Alka-Seltzer*, and *Nyquil*, as well as narcotic analgesics such as *Vicodin* and *Percocet*. Consequently, people can inadvertently ingest far more than the maximum recommended dose of acetaminophen.

The study involved data analysis on 662 consecutive patients treated for acute liver failure. Over the five-year study period, the percentage of acute liver failure due to acetaminophen rose from 28% to 51%. Among the 275 cases determined to be acetaminophen-related, 48% were identified as unintentional overdose and 44% as suicide attempts. Clinical outcomes were similar in each group.

The maximum recommended dose of acetaminophen is 4 g per day, typically two 500 mg tablets or capsules four times daily. Consistent use of 7.5 g per day, and sometimes less, may be hazardous. Efforts to stem this serious problem include attempts to require more prominent labeling of the contents of combination products and discussions on limiting the quantity of acetaminophen per package.

Early Findings Suggest *Paxil* Increases Birth Defect Risk

The FDA is advising patients that *Paxil* (paroxetine) should ordinarily not be taken during pregnancy. Prompting the move are preliminary results suggest-

ing that the SSRI antidepressant increases the risk of birth defects when taken during the first three months after conception.

Two studies showed that women who took *Paxil* during the first trimester were 1.5 to 2.0 times as likely to have a baby with a heart defect as women who took other antidepressants or women in the general population. GlaxoSmithKline added data from one of the studies to *Paxil*'s prescribing information in September and since then has added details from the second study [*Reuters*, 9 December 2005].

Risk of Death in Demented Elderly on Antipsychotic Medication

Antipsychotic agents are disproportionately used in the elderly and are prescribed for more than 25% of Medicare patients in nursing homes. They are prescribed for dementia, delirium, psychosis agitation, and affective disorders.

In April, the FDA issued an advisory that the use of atypical antipsychotic medication increases mortality in elderly people with dementia. Now, investigators report that conventional (first-generation) drugs pose a similar if not greater risk of death [*N Engl J Med* 2004;353:2335-41].

The retrospective cohort study involved 22,890 patients (65 years of age or older) who began receiving an antipsychotic agent between 1994 and 2004. The data included 9142 patients who began using a conventional antipsychotic drug (e.g., chlorpromazine, perphenazine) and 13,748 patients who began using an atypical agent (e.g., olanzapine, risperidone).

In the first 180 days of use, 17.9% of those using a conventional agent died, compared with 14.6% of those who used an atypical antipsychotic. The greatest difference in adjusted death rates occurred during the first 40 days of use when the hazard ratio was 1.56. The most common causes of death were cardiovascular—sudden death or heart failure—and infections, primarily pneumonia. The principal author of the report told *Reuters Health* [1 December 2005] that physicians need to thoughtfully weigh the risks and benefits because there are often no other good alternatives for elderly persons with delirium and dementia.

DRUG EVALUATION

Does Pioglitazone Offer Secondary Prevention of Macrovascular Events in Patients with Diabetes?

Patients with type 2 diabetes are at high risk of myocardial infarction and stroke. There is indirect evidence that the insulin-sensitizing glitazones, which are selective agonists of peroxisome proliferator-activated receptor gamma (PPAR gamma), might reduce macrovascular complications. To test this possibility, a group of international researchers undertook a well-controlled trial in 5238 patients with type 2 diabetes who had evidence of macrovascular disease (e.g., prior MI or stroke). Patients were assigned to pioglitazone, titrated up to 45 mg, or matching placebo in addition to their other medications. The average duration of observation was nearly three years [*Lancet* 2005;3656:1279-89].

At the conclusion of the study, 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint—all-cause mortality, non-fatal MI, stroke, and acute coronary syndrome (disease endpoints) as well as endovascular or surgical intervention in the coronary or leg arteries (procedure endpoints). The difference did not reach pre-defined statistical significance.

The secondary endpoint was a composite of all-cause mortality, non-fatal MI, and stroke. During the observation period, 301 patients in the pioglitazone group and 358 patients in the placebo group reached this endpoint ($p=0.027$). The authors of the report concluded that in patients with type 2 diabetes, who are at high risk for cardiovascular events, pioglitazone improves cardiovascular outcome, and reduces the need to add insulin to glucose-lowering agents compared with placebo.

Not emphasized in the report is the bad news concerning pioglitazone. In those patients assigned to the glitazones, the incidence of edema not attributable to heart failure was four times greater, and that of heart failure two times greater, than reduction of cardiovascular events. Furthermore, body weight increased more than with any other antihyperglycemic agent, including insulin [*Ibid*, 1241-42]. Additional studies are needed to identify those patients with the most favorable benefit-to-risk ratio.

Herceptin Appears to Halve Risk of Breast Cancer Recurrence in Some Women

Two recently published papers summarize the results of three trials of the monoclonal antibody trastuzumab, (*Herceptin*), both of which suggest that the drug, used as adjuvant therapy after surgical treatment of primary breast cancer, halves the recurrence of breast cancer [*BMJ* 2005;331:986].

One paper concerned an analysis of the combined results of the National Surgical Adjuvant Breast and Bowel Project trial plus the North Central Cancer Treatment Group trial [*N Engl J Med* 2005;353:1673-84]. The other presented the findings of the Herceptin Adjuvant (HERA) trial [*Ibid*, 1659-72]. Both papers report significant benefits of therapeutic antibody treatment for women with HER2-positive metastatic breast cancer, an aggressive form of breast cancer that affects about one of five women with the disease.

The paper on the HERA study appears to demonstrate that using *Herceptin* after standard chemotherapy reduced the risk of disease recurrence for women with

early stage HER2-positive breast cancer by 46%. The authors say: “As compared with observation after primary therapy (including surgery with or without radiotherapy and neoadjuvant or adjuvant chemotherapy) trastuzumab given after primary therapy reduced the rate of breast cancer recurrence, particularly distant recurrence.”

The report on the combined interim analysis of two phase III trials of trastuzumab plus chemotherapy shows that the addition of drug reduces the risk of recurrence by 52% in women with early stage, operable HER2-positive breast cancer compared with women who received chemotherapy alone. After four years of follow-up, 15% of women treated with trastuzumab plus chemotherapy had breast cancer recurrence, compared with 33% of women given chemotherapy alone. A survival analysis of the results after a median of 24 months suggests a 49% increase in overall survival, or a hazard ratio of 0.67, equivalent to a 33% reduction in the risk of death.

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DRUG EVALUATION (continued)

Herceptin Appears to Reduce Breast Cancer Recurrence (continued)

While the results are nothing short of stunning, the early termination of the trials for reasons of perceived benefit of one treatment over the other has provoked controversy. According to Canadian trialists, “When randomized controlled trials identify larger than expected treatment effects, investigator may conclude before completing the trial as planned, that one treatment is superior to the other” [*JAMA* 2005;294:2203-09]. In these situations, data interpretation must be viewed with skepticism.

Analysis indicates that the risk of overestimating treatment effects is not uniform across all truncated randomized controlled trials. Indeed, the Canadian

trialists found a strong association between number of events and the magnitude of treatment effects. “[T]his association remained very strong across a number of cutpoints for calculations up to almost 200 events. These findings suggest that the risk of overestimating treatment effects decreases markedly when the number of events is very large” [*Ibid*].

In the HERA trial, at the first interim analysis (median follow-up of one year), 347 events were observed. In the other trials, 394 events had been reported, triggering the first scheduled interim analysis. Thus, the large number of events in these trials lends credence to the reported interim treatment effects.

Atorvastatin Bests Simvastatin for Secondary Prevention after MI

Yet another study supports the idea that when it comes to low-density lipoprotein cholesterol (LDL-C), lower is better. The IDEAL study was a prospective, randomized multicenter trial with a median follow-up of 4.8 years, which enrolled 8888 patients aged 80 years or younger with a history of acute myocardial infarction. Patients were assigned to receive a high dose of atorvastatin (80 mg daily) or a usual dose of simvastatin (20 mg daily). The main outcome measure was the occurrence of a major coronary event—coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation [*JAMA* 2005;294:2437-45].

Mean LDL-C at baseline was 122 mg/dl. During treatment, mean LDL-C levels were 104 mg/dl in the simvastatin group and 81 mg/dl in the atorvastatin

group. This difference led to an 11% trend in reduction in the primary endpoint but did not reach statistical significance ($p=0.07$). However, there were significant reductions in nonfatal acute MI and in the secondary composite endpoints of any coronary heart disease event.

There are several possible reasons why statistical significance was not reached for the primary endpoint. One explanation might be an insufficient difference in levels of LDL-C between the groups. A second possible explanation was that the duration of the study was only a median of 4.8 years. A third possibility is that the effect of simvastatin on HDL-C would attenuate the differences produced by improved effects of atorvastatin on LDL-C.

Tamoxifen Therapy Also Reduces Heart Disease Mortality

In breast cancer patients, adjuvant therapy with tamoxifen for five rather than two years appears to reduce the risk of death from coronary heart disease [*J Natl Cancer Institute* 2005;97:1609-10]. The results are based on a study of 4175 women with breast cancer who were recurrence-free after two years of tamoxifen. The group included 2046 women who were randomized to continue therapy for three more years and 2129 randomly assigned to discontinue use.

Five years of tamoxifen therapy was linked to re-

duction in all-cause mortality, breast cancer-specific mortality, and with a decreased risk of contralateral breast cancer. As reported previously, the longer duration therapy was associated with risk of endometrial cancer. Use of tamoxifen for five years decreased coronary heart disease (CHD) mortality by 33% relative to two years of therapy ($p=0.22$). At 10-year follow-up, CHD-specific mortality was 2.1% and 3.5% in the five and two-year tamoxifen groups, respectively.