

Natalizumab reduces relapse and disability in MS

Clinical question Is natalizumab safe and effective for the treatment of relapsing multiple sclerosis (MS)?

Bottom line Natalizumab reduces the likelihood of relapse and progression of disability in patients with relapsing MS (RMS). Although no cases of progressive multifocal leukoencephalopathy (PML) were seen in this study and the drug was well tolerated, a meta-analysis estimates the risk of PML at approximately 1 per 1,000 patients treated for 18 months. (Level of evidence = 1b)

Polman CH, O'Connor PW, Havrdova E, et al, for the AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:899-910.

Synopsis Natalizumab is a selective adhesion-molecule inhibitor that is thought to block binding of leukocytes to vascular cells in the brain, thereby attenuating the inflammatory response seen in RMS. However, it has been linked to PML, a fatal and rapidly progressive neurodegenerative condition. In this study, 942 patients were randomly assigned (allocation concealed) in a 2:1 ratio to receive either natalizumab, 300 mg by IV infusion every 4 weeks, or placebo. Relapses were assessed by a neurologist blinded to treatment assignment and could be treated with high-dose corticosteroids. Patients underwent MRI at baseline and after 1 year and 2 years. Groups were balanced at the start of the study, and analysis was by intention to treat. Approximately 9% in each group withdrew from the study, but half these patients continued to undergo regular monitoring. After 2 years, the cumulative probability of progression of disability was lower in the natalizumab group (17% versus 29%; $P < .001$; number needed to treat [NNT] = 9). The probability of relapse was also decreased (0.26 versus 0.81 relapses/patient/year; $P < .001$). There were also fewer new or enlarging lesions detected by MRI in the natalizumab group; the percent of patients remaining relapse free at 1 year (77% versus 56%; NNT = 5) and 2 years (67% versus 41%; NNT = 4) was higher in the natalizumab group. There was no difference between groups in the risk of infection, and no cases of PML were detected. The only adverse events more common in the natalizumab group were fatigue (27% versus 21%) and allergic reaction (9% versus 4%). Patients were excluded from this study if they were taking interferon. A second study found similar benefits in a group of 1,171 randomized to natalizumab plus interferon or interferon alone for up to 2 years, although two patients developed PML (*N Engl J Med*. 2006;354:911-923). A third study compiled data from 3,417 patients who had received natalizumab in clinical trials and concluded that the overall risk of PML was 1 per 1,000 patients treated for 18 months (95% CI, 0.2-2.8 per 1,000) (*N Engl J Med*. 2006;354:924-933).

Glucosamine/chondroitin has mixed benefits for OA

Clinical question Is glucosamine or chondroitin (or both) effective for osteoarthritis (OA) of the knee?

Bottom line Glucosamine/ chondroitin provides modest if any symptomatic benefit for patients with mild OA of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (Level of evidence = 1b)

Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med*. 2006;354:795-808.

Synopsis A previous meta-analysis of glucosamine and chondroitin for OA found a consistent benefit to treatment and good safety (*JAMA*. 2000;283:1469-1475). However, many of the studies were small, did not report allocation concealment, were manufacturer sponsored or conducted, or had other limitations that could lead to bias. In the current study, 1,583 patients with clinical and radiographic evidence of OA of the knee were randomized (allocation concealed) to placebo; glucosamine HCl, 500 mg 3 times daily; chondroitin, 400 mg 3 times daily; both glucosamine and chondroitin; or celecoxib, 200 mg once daily. Most previous studies used glucosamine sulfate, although the importance of this substitution is of uncertain clinical significance. The mean age of patients was 58 years, 63% were women, and most were American Rheumatology Association functional class II (able to perform usual self-care and vocational activities, but limited in avocational activities). The use of up to 4,000 mg acetaminophen was allowed (other than on the day of evaluation), and patients were followed for 24 weeks. With 1,583 patients, there was an 85% probability of identifying a clinically significant 15% improvement between the active treatment and placebo groups. The dropout rate was approximately 20% in each group, fairly high for such a short study. The primary outcome of a 20% decrease in the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score, a validated pain score, was achieved by 60% of patients taking placebo, 64% taking glucosamine, 65% taking chondroitin, 67% taking glucosamine plus chondroitin, and 70% taking celecoxib. Only the comparison between celecoxib and placebo was significant. A review of the 14 secondary outcomes revealed trends toward greater benefit with glucosamine and chondroitin or celecoxib, but these benefits were statistically significant only for two of these outcomes. The authors saw an interaction between the degree of pain and response to the study drugs. Although there was essentially no trend toward benefit, significant or otherwise, for patients with mild pain, a significant benefit was seen for the 354 patients with moderate or severe pain (WOMAC score = 301-400). In these patients, a 20% decrease in the WOMAC pain score occurred for 54% receiving placebo, 79.2% receiving glucosamine plus chondroitin, and 69.4% taking celecoxib ($P = .002$ for placebo versus glucosamine plus chondroitin; number needed to treat = 4). The benefit for glucosamine/chondroitin in these patients with more severe disease was actually larger than that for celecoxib. Similarly large benefits were seen for 8 of 14 secondary outcomes. There was no important difference between groups regarding adverse events.

FOBT screening does not reduce all-cause mortality

Clinical question Does fecal occult blood testing (FOBT) reduce all-cause mortality?

Bottom line Screening for colorectal cancer using FOBT does not reduce all-cause mortality. We have to remember this—and the similar controversial results regarding mammography—as we evaluate any new screening tests that well-meaning disease advocates would like to inflict on our (currently) healthy patients. (Level of evidence = 1a)

Moayyedi P, Achkar E. Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. *Am J Gastroenterol*. 2006;101:380-384.

Synopsis The most important outcome of any screening study is all-cause mortality. After all, the whole idea behind screening is that we do something to otherwise healthy persons with the implicit promise that it will help them live a longer life. Is that true of FOBT? The authors combined data from the three large published randomized trials of FOBT: one Danish, one British, and

one American. All studies compared FOBT, performed every 2 years, with no screening. The British and Danish studies used unrehydrated FOBT in adults aged 45 to 75 years; the American study used rehydrated FOBT in adults aged 50 to 80 years. All three studies followed subjects for a mean of 12 years; which means that 245,217 subjects were followed up for more than 3 million patient years. Overall, there was a 13% relative reduction in colorectal cancer mortality. In absolute terms, dividing the total colorectal cancer deaths by total participants, that is a less impressive 0.82% versus 0.94% ($P=.002$; number needed to treat = 833 for 12 years). But here's the interesting finding: When you look at all-cause mortality, there was actually a 1.9% relative increase in noncolorectal cancer deaths and no overall difference between groups in all-cause mortality (26.51% if screened and 26.46% if unscreened). Potential explanations for this paradox include unintended consequences of screening (eg, failure of patients to adopt a healthier lifestyle because they have been screened or mortality from follow-up colonoscopy) and better identification of colorectal cancer as a cause of death in screened patients.

Dexamethasone reduces nausea after laparoscopic cholecystectomy

Clinical question Does preoperative dexamethasone reduce nausea in patients undergoing elective laparoscopic cholecystectomy?

Bottom line Preoperative dexamethasone appears to reduce postoperative nausea in patients undergoing elective laparoscopic cholecystectomy. (Level of evidence = 2b)

Feo CV, Sortini D, Ragazzi R, et al. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg*. 2006;93:295-299.

Synopsis More than 100 patients undergoing elective laparoscopic cholecystectomy were randomly assigned to receive either 8 mg IV dexamethasone or a saline placebo 90 minutes before surgery was performed under general anesthesia. The authors do not describe analyzing their data by intention to treat. Only 8% of patients who were treated with dexamethasone experienced nausea, compared with 27% of control patients (number needed to treat = 5.3, 95% CI, 3.0-26.5). If these data are not based on intention to treat, they are most likely biased in favor of treatment.

Aspirin and statins cost-effective only for those at high risk

Clinical question In men without a history of cardiovascular disease, is low-dose aspirin, a statin, or both cost-effective in preventing cardiovascular events?

Bottom line From the viewpoint of cost to a third-party payer, the costs of aspirin alone are reasonable in men at low-risk for coronary heart disease (CHD); the addition of a statin to aspirin therapy in these men is above what is considered to be reasonable cost for prevention. However, the combination of aspirin and a statin is cost-effective when men are at high risk (10% or above). (Level of evidence = 2a)

Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. *Ann Intern Med*. 2006;144:326-336.

Synopsis Although both aspirin and statin drugs, separately, are effective for preventing a first CHD event, there is no direct evidence that the combination is more effective than either alone. The researchers conducting this analysis determined the cost-effectiveness of the combination from the perspective of a third-party payer, and we can use this analysis to understand the relative benefits of the two treatments. The researchers started with a base-case scenario of a 45-year-

old man with a 10-year risk of CHD of 7.5% treated with aspirin, statin therapy, both, or neither for 10 years. The outcome was the development of a CHD event—stroke, MI, or death—over the 10 years. The Markov model used in this analysis also assumed that all patients would be treated with both drugs after 10 years and then estimated their life-time cost-utility ratio. They also considered the major risks of treatment—GI, and myopathy-related death, derived from results of clinical trials. For men at low risk, lifetime aspirin therapy increases their lifespan an average of 3 days (adjusted for quality of those days, or “quality-adjusted days”). Men at moderate (7.5%) risk gained an average of 17 quality-adjusted days, and men at moderate to high risk (10%) gained 24 quality-adjusted days. When a statin was theoretically added to aspirin treatment, the average increase in lifespan was 13 days for low-risk men (an additional 10 days over aspirin alone), 35 days for moderate risk (an additional 18 days), and 45 days (an additional 21 days) for men at moderate to high risk. In men at low risk, the cost per quality-adjusted life-year is a very reasonable \$9,800 for aspirin alone but \$164,700 for the combination. At moderate risk, combination therapy is a reasonable \$56,200 (though the range, depending on the sensitivity analysis, was \$26,100 to \$246,276). At moderate to high risk, the cost per quality-adjusted life-year was \$42,500 (range = \$20,600-\$188,000).

100% humidity no better than other options for croup

Clinical question Is the use of high humidity or low humidity best for treating moderate to severe croup?

Bottom line In children with moderate to severe croup, the use of controlled delivery of 100% humidity results in no greater improvement in croup scores than the use of controlled delivery of 40% humidity or humidity by blow-by technique. (Level of evidence = 1b)

Scolnik D, Coates AL, Stephens D, et al. Controlled delivery of high vs low humidity vs mist therapy for croup in emergency departments: a randomized controlled trial. *JAMA*. 2006;295:1274-1280.

Synopsis Children with croup are often treated with humidity by standard blow-by technique, which results in water droplets too large to reach the larynx. The investigators wished to evaluate whether delivering particles sized for laryngeal deposition (5-10 micron) is beneficial. A total of 140 otherwise healthy children, aged 3 months to 10 years, presenting to a pediatric emergency department with moderate to severe croup were enrolled. Subjects randomly received (concealed allocation assignment) 30 minutes of humidity using traditional blow-by technique (commonly used placebo), controlled delivery of 40% humidity (optimally delivered placebo), or controlled delivery of 100% humidity with water particles of mass median diameter 6.21 micron. Complete follow-up occurred for all patients. Researchers assessing outcomes were blinded to treatment group assignment. Using intention-to-treat analysis, improvement in the Westley croup scores from baseline to 30 minutes and from baseline to 60 minutes was similar in all three treatment groups. In addition, no differences were found between the treatment groups in secondary outcomes including pulse; respiratory rates and oxygen saturation changes; proportion of excellent responders; croup scores of 0 at study conclusion; or proportion receiving dexamethasone or epinephrine or requiring additional medical care or hospitalization. The study was 80% powered to detect a 1-point difference in croup scores.

Levels of evidence are explained at www.infopeoms.com/levels.html.

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