Restrictions Likely

COX-2s *from page 1*

use" to help guide their decisions regarding selective COX-2 inhibitors, said Dr. Tindall, who testified before the panel but was not a voting member.

At the unprecedented 3-day joint meeting of the FDA's Arthritis Drugs and Drug Safety and Risk Management advisory committees, there was nearly unanimous support for keeping celecoxib on the market but far narrower votes for rofecoxib and valdecoxib, reflecting the strength of the data on the cardiovascular risks seen with those two drugs.

All 32 panel members agreed that the three COX-2–selective NSAIDs approved in the United States significantly increased the risk of cardiovascular events, although to varying degrees, with the greatest risk evident for rofecoxib (Vioxx), voluntarily withdrawn from the U.S. market by Merck & Co. in September.

Summarizing the issues, the panel chair, Alastair Wood, M.D., noted that there are now several randomized controlled trials showing significant cardiovascular risks associated with the three approved COX-2–selective NSAIDs—celecoxib (Celebrex), rofecoxib, and valdecoxib (Bextra)—which is a "far larger randomized safety signal than we've seen with any of the drugs that have been withdrawn [by the FDA] for safety reasons."

The panel members agreed that celecoxib appeared to have the lowest risk and voted 31-1 that its overall risk-benefit profile supported continued marketing for the current indications in the United States.

On rofecoxib and valdecoxib, for which the evidence of cardiovascular risk was much stronger, the vote was divided, with rheumatologists tipping the balance toward support of the drugs' continued marketing.

For rofecoxib, the panel voted 17-15 that the overall risk-benefit profile supported marketing the drug but recommended eliminating the highest dose (50 mg), restricting the dose to 12.5 mg, and limiting rofecoxib to short-term use only.

For valdecoxib, the panel voted 17-13, with 2 abstentions, in favor of keeping it on the market, with a contraindication against its use in cardiac surgery patients, based on study findings of substantially increased risk of coronary events in coronary artery bypass graft (CABG) patients. Several panelists recommended against using valdecoxib for more than 6 months, because there are no data available on this drug for longer durations. And several said it should be considered a second-line drug.

What the committee made clear was that these drugs "should not be as widely used" and should be used only in more carefully selected patients, in whom the benefits would outweigh the risks, said John Jenkins, M.D., director of the FDA's office of new drugs. Although the close votes for rofecoxib and valdecoxib are "challenging to interpret," the agency will closely consider the comments of the panelists, he added at a press briefing.

At press time, the FDA was expected to make final decisions within weeks about how to proceed, based on its review of the panel's recommendations.The agency was expected to publicly announce the changes before implementing them.

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In addition to withdrawing the drugs or adding a black box warning to their labels, the FDA may consider making COX-2–selective NSAIDs second-line drugs, adding contraindications in selected patient populations, and requiring a patient medication guide to be dispensed with all prescriptions. Short of taking a drug off the market, another option is to restrict distribution through programs such as those currently in place for thalidomide and the antipsychotic clozapine.

Although the FDA does not have the authority to ban pharmaceutical advertisements, a black box warning makes it difficult to advertise a drug directly to consumers because of requirements for disclosing information about a drug's negative effects.

During the press conference, Dr. Wood, who was among those voting against keeping rofecoxib and valdecoxib on the market, said that essentially, the panels provided a "clear ranking" of the drugs. The uniform vote to keep celecoxib on the market and the split votes regarding rofecoxib and valdecoxib reflected the clear hazard seen with those two drugs.

Commenting on celecoxib specifically, Steven Abramson, M.D., chairman of the department of rheumatology and medicine at the Hospital for Joint Diseases, New York, said, "While I tend to think there is a cardiovascular signal that is COX-2 dependent, this is the weakest."

Cardiologist Steven Nissen, M.D., of the Cleveland Clinic Foundation, agreed, adding that the risk with celecoxib appeared to be dose dependent. Although there was no evidence of a signal associated with the 200-mg dose used in the vast majority of patients, the evidence of an increased risk came from the polyp-prevention trial, in which higher doses—400 mg/day and 800 mg/day—were used, he pointed out. The 800-mg dose was "very likely" to produce an excess risk, which was "probable" at the 400-mg dose, he said, advocating a black box warning of a dose-dependent increase in cardiovascular risk with this drug.

Dr. Nissen, who voted against supporting the marketing of rofecoxib, except possibly under a compassionate use program, referred to blood pressure increases and a signal for heart failure "clearly" outside those of other drugs in the class. Such signals were seen in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, at a daily dose of 25 mg—effects not seen at lower doses of celecoxib.

Compared with celecoxib and rofecoxib, there is much less information on valdecoxib, with data from only two trials available. Dr. Wood said he was uncertain whether the available data supported continued marketing of valdecoxib, which has a clear risk and no evidence of GI benefit. Referring to comments made at the meeting about patient choices, he said "it seems highly improbable" that valdecoxib is safer than celecoxib, given the size of the signal in the CABG study.

The FDA has the authority to require a black box warning and to state what would be necessary to remove it, which would encourage the companies to do the appropriate studies, panelists said.

The panel agreed that some type of warning should be added to the labels of the more than 20 nonselective NSAIDs approved in the United States, for which safety has not been studied in long-term, large, placebo-controlled trials. But several panelists recommended against using the same warning for all nonselective NSAIDs. Data suggest "naproxen is more beneficial than some of the others," but it is associated with GI risks, so patients using naproxen could take a proton pump inhibitor (PPI). There are not many data on naproxen given with a PPI, but there are "certainly data in other settings" supporting this approach, said Dr. Wood, professor of medicine and pharmacology at Vanderbilt University, Nashville. ■

Statins Associated With Onset of Radiographic Osteoarthritis

BY HEIDI SPLETE
Senior Writer

A new study puts a twist in the theory that statins could conveniently serve dual purposes in patients with inflammatory diseases that affect both the joints and heart.

Findings from the investigation, involving 5,678 women aged 65 and older, suggest that the use of statins appeared to modestly increase a woman's risk of developing new relatively severe radiographic hip osteoarthritis.

However, statin use did not appear to affect the progression of disease in patients who already had osteoarthritis, reported Mary S. Beattie, M.D., and her associates at the University of California, San Francisco (J. Rheumatol. 2005;32:106-10).

The rationale for the study was based on the fact that while statins are increasingly recognized for their broad anti-inflammatory effects, they have also been shown to increase the production of nitric oxide, which could have a deleterious effect on the cartilage matrix, the investigators said.

The researchers monitored the women, all of whom were white and aged 65 and older, for radiographic evidence of new-onset disease as well as for the progression of established radiographic hip osteoarthritis (RHOA) over an 8-year period. All the women had already been participants in a multicenter study of osteoporotic fractures.

Overall, 7% (397) of the women were statin users, and these women demonstrated nearly twice the risk of developing severe disease, defined radiographically as a summary grade of 3 or greater on the modified Croft scale.

'Obesity is the common denominator for the presence of high cholesterol and hip osteoarthritis in women, and this may explain the results.'

At baseline, 4,933 women had no RHOA in either hip; 566 women had developed new, radiographic evidence of disease in 630 hips by the fifth follow-up visit. Of the 745 women who had RHOA in 936 hips at baseline, the disease worsened in 484 hips among 420 women.

Evidence of new-onset radiographic disease was deemed present if any of five criteria were met: a summary grade of 2 or greater; a minimum joint space (MJS) of 1.5 mm or less; joint space narrowing superolaterally of 2 or greater and superomedially of 3 or greater; or definite osteophytes in any location.

Radiographic progression was deemed present if the MJS decreased by 0.5 mm or more; summary grade increased by 1 or greater; or the osteophyte score increased by 2 or more.

Only 26 (6.5%) of the statin users showed signs of progressive disease. There was a moderate, but not statistically significant, trend toward a decreased risk of OA progression among statin users.

Women who showed signs of progressive RHOA were less likely to be taking vitamin D, compared with women whose disease did not progress (42.6% vs. 51.5%); however, the odds ratio was not statistically significant. There were no significant differences between those with and without RHOA in terms of age, BMI, and walking for exercise.

The study findings are limited by the fact that the investigation included only white women and a small number of statin users.

Evidence suggests that the use of statins can slightly improve symptoms among rheumatoid arthritis patients, Christopher J. Penney, M.D., of the University of Calgary (Alta.), noted in an accompanying editorial.

"The quite modest effect of statins in the management of human rheumatic disease may be related to the dose or to the differences between mouse, man, and test tube," he said, adding that more prospective trials of statins are needed to determine whether the effects are clinically significant (J. Rheumatol. 2005;32:17-9).

"Obesity is the common denominator for the presence of high cholesterol and hip osteoarthritis in women, and this may explain the results of this trial," Roy D. Altman, M.D., an osteoarthritis specialist in Agua Dulce, Calif., said in an interview.

The researchers alluded to the relationship between obesity and hip osteoarthritis in women by adjusting for height and weight, but they did not specifically adjust for BMI, noted Dr. Altman, a member of the Rheumatology News editorial advisory board. ■