Treat Atherosclerosis Risks in Lupus Patients

Many risk factors were present within 1 year of diagnosis and increased in prevalence over 3 years.

BY JEFF EVANS
Senior Writer

WASHINGTON — Awareness of the increased risk of atherosclerosis in patients who have lupus may be rising, but even experts in lupus treatment are not adequately treating patients who have known risk factors for the condition, Dr. Murray B. Urowitz reported at the annual meeting of the American College of Rheumatology.

Premature atherosclerosis in patients with systemic lupus erythematosus (SLE) may develop as a result of a combination of disease- and therapy-related factors, classic coronary artery disease risk factors, and genetic factors. Many of these factors are present within the first year after diagnosis of SLE, said Dr. Urowitz, director of the Centre of Prognosis Studies in the Rheumatic Diseases at Toronto Western Hospital.

He and his colleagues in the Systemic Lupus International Collaborating Clinics (SLICC), a group of 30 investigators located at 27 centers around the world, conducted an analysis of 935 SLE patients who had been enrolled in the multicenter registry within 15 months of diagnosis during 2000-2006.

Follow-up data at 3 years were available for 278 patients. These patients had a mean SLE disease activity index-2k (SLEDAI-2k) score of 5.49 at enrollment and an adjusted mean SLEDAI-2k over 3 years of 4.94.

Of 101 patients who had hypercholesterolemia at enrollment, 25 received treatment for the condition. After 3 years, 167 patients had ever had hypercholesterolemia, but only 63 (38%) had received treatment.

"For some unknown reason . . . there is some reluctance to begin therapy with cholesterol-lowering medications in our patients," Dr. Urowitz said at the meeting.

"We can no longer say that we are busy looking at the initial treatment of patients with lupus. This is now 3 years into the illness," he said. These findings are coming from "the 'august' SLICC group who call themselves 'lupologists.' "

Premature atherosclerosis in patients with SLE may develop as a result of a combination of disease- and therapy-related factors.

In comparison, the percentage of hypertensive patients who received treatment increased from enrollment (87 of 109 [80%]) to the 3-year follow-up (144 of 162 [89%]) even though the prevalence of hypertension increased.

Other risk factors for coronary artery disease increased in prevalence during the 3 years, including the percentage of patients who currently or had ever smoked (from 14% to 19% and from 37% to 42%, respectively), the percentage of patients who reported a family history of coronary artery disease (from 18% to 25%), as well as the percentage of those with diabetes mellitus or who had become postmenopausal.

Risk factors relating to body composition also increased during follow-up, such as the percentage of patients with a body mass index in the overweight or obese range (from 31% to 46%), a waist-to-hip ratio greater than 0.8 (from 32% to 55%), and low physical activity (from 37% to 55%). Since enrollment, more of the patients had taken corticosteroids (from 71% to 79%), antimalarials (from 60% to 77%), or immunosuppressives (from 38% to 59%).

"All risk factors increased in prevalence over 3 years, so you're not off the hook when they start [treatment]; this doesn't tell the whole story. You must continue to follow up patients," said Dr. Urowitz, professor of medicine at the University of Toronto. ■

Etoricoxib, Diclofenac Pose Similar Cardiovascular Risks

BY CATHERINE HACKETT
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CHICAGO — Prolonged treatment with the COX-2 inhibitor etoricoxib carried no increased cardiovascular risk, compared with the traditional NSAID diclofenac in a pooled analysis of nearly 35,000 arthritis patients, reported Dr. Christopher Cannon at the annual scientific sessions of the American Heart Association.

For arthritis patients "who need to take one of these types of agents long term, either one will have the same risk profile for thrombotic events such as heart attack or stroke," he said at a press conference.

The Multinational Etoricoxib and Diclofenac Arthritis Long-Term (MEDAL) program is a prespecified pooled analysis of three studies. The largest was MEDAL, performed in 23,504 patients during June 2002-May 2006 at 1,380 sites in 46 countries. This study randomized rheumatoid arthritis (RA) patients to treatment with 90 mg etoricoxib once a day or 75 mg diclofenac twice a day. Osteoarthritis (OA) patients were randomized to receive either 75 mg diclofenac twice daily or one of two dosages of etoricoxib, 90 mg or 60 mg.

The other two studies in the analysis were the Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) trial, in which 7,111 patients received 90 mg etoricoxib once daily or 50 mg diclofenac three times daily, and EDGE II, in which 4,086 patients were treated with 90 mg etoricoxib once daily or 75 mg diclofenac twice daily.

In all three studies, patients were followed out to 3 years, with an average follow-up of 18 months. Patients had a broad range of cardiovascular risk. Use of aspirin and proton pump inhibitors was allowed in appropriate patients.

'The similar risk of thrombotic events between etoricoxib and diclofenac can be explained by the profound inhibition of COX-2 shared by the two agents.'

In the pooled analysis of the three studies, the primary end point was the first occurrence of any fatal or nonfatal venous or arterial thrombotic event, including MI, unstable angina, intracardiac thrombus, thrombotic stroke, and transient ischemic attack. The rates were 1.24 events/100 patient-years in the etoricoxib group and 1.30 events/100 person-years in the diclofenac group, a nonsignificant difference, reported Dr. Cannon, a cardiologist at Brigham and Women's Hospital, Boston.

Secondary end points were a subset of arterial thrombotic events only and the Antiplatelet Trialists' Collaboration (APTC) end point of MI, stroke, and vascular death. There were no significant differences in these end points.

The MEDAL program provides "more information that is very valuable, but it doesn't clarify the entire issue" of the thrombotic safety of COX-2 selective and nonselective NSAIDs, Dr. Roy Altman, professor of medicine at the University of California, Los Angeles, said in an interview.

The MEDAL program was the largest-ever trial in arthritis patients, and the first to demonstrate a significant reduction of GI events with a cyclooxygenase-2 (COX-2) inhibitor, compared with traditional NSAIDs. Rates of upper GI events clinical events were lower with etoricoxib than with diclofenac (0.67 and 0.97/100 patient-years, respectively). But there was no difference between groups in complicated upper GI events, such as perforated ulcers.

The nonsignificant difference in complicated upper GI events "is probably the most bothersome thing about the study," because etoricoxib is supposed to be GI-protective and has even more COX-2 selectivity than some other COX-2 selective NSAIDs, such as rofecoxib, Dr. Altman said.

Whether these results can be applied to other traditional NSAIDs is questionable, however, because observational studies have shown diclofenac to have the highest relative risk for myocardial infarction, Dr. Luis Alberto Garcia Rodriguez and Dr. Paola Patrignani of the Spanish Centre for Pharmacoepidemiologic Research, Madrid, wrote in an editorial accompanying the published report (Lancet 2006; DOI:10.1016/S0140-6736[06]69667-0). "The similar risk of thrombotic events between etoricoxib and diclofenac can be explained by the profound inhibition of COX-2 shared by the two agents."

"The hypothesis that diclofenac is partially COX-2 selective I think is not supported" because only one article has ever said that diclofenac has some COX-2 selectivity, Dr. Altman said (N. Engl. J. Med. 2001;345:433-42).

But naproxen "clearly is the one that would have been more helpful to compare" with etoricoxib, he said, because naproxen was compared against rofecoxib in Merck's VIGOR (Vioxx Gastrointestinal Outcomes Research) trial and naproxen is more widely used (over-the-counter and prescription) in the United States than diclofenac.

Dr. Cannon told reporters that although observational studies have shown differences among COX-2 inhibitors in cardiovascular risks, randomized trial data have shown no such difference, with the exception of naproxen, which carries a lesser risk that may be explained by an antiplatelet effect at high doses.

"Our results today address one question: In these patients with arthritis, a selective agent didn't increase risk compared with other agents," said Dr. Cannon. The message to clinicians and patients is that there are options to treat arthritis. "We are moving to an era where we do have choices, and we should be choosing different treatments for different patients."

Dr. Cannon receives research grant support from Merck, which sponsored and monitored the study, and did the statistical analysis. The results were published simultaneously with the presentation in the Lancet 2006;(DOI:10.1016/S0140-6736[06]69666-9).

Etoricoxib is approved for use in more than 60 countries but not yet in the United States.

Several days before the presentation, Merck resubmitted its new drug application to the FDA for the approval of etoricoxib for the symptomatic treatment of only osteoarthritis, instead of indications also in rheumatoid arthritis and other conditions. In the MEDAL program, RA and OA patients had similar risk for cardiovascular thrombotic events with both drugs, but only 28% of the patients had RA. RA patients also usually require higher doses of NSAIDs, which would emphasize any cardiovascular thrombotic risk. These considerations may have had led Merck to not seek etoricoxib as an indication for RA, Dr. Altman suggested. ■

Senior writer Jeff Evans contributed to this report.