Heart Disease in Lupus: 'Startlingly' Worrisome

BY NANCY WALSH
New York Bureau

LONDON — The incidence of coronary heart disease among young women with systemic lupus erythematosus is "startlingly" worrisome, Ian Bruce, M.D., said at the Sixth European Lupus Meeting.

Studies have shown that the annual incidence of ischemic heart disease in lupus patients is 1.3%-1.5%. In comparison, the incidence among those with newly diagnosed type 2 diabetes and among those who have had a first myocardial infarction is 2%-2.2% per annum. "This latter number may be higher, but you have to remember that these are men in their mid- to late 50s, while the lupus patients in these studies are women whose average age is 35-37," said Dr. Bruce, of the University of Manchester (England).

The prevalence of myocardial infarction or angina in lupus cohorts ranges from 7% to 10%, depending on patient age and duration of follow-up, he said.

Moreover, as survival improves, the prevalence of the disease increases, as does the proportion of lupus patients who are older and at even greater risk for cardiovascular disease, he said.

Some epidemiologic work has suggested that the peak age of onset also is increasing and now occurs between the fifth and seventh decades. Damage accrues more quickly among patients who are older at onset, he added.

Atherosclerosis also occurs much earlier in women with lupus than in healthy women. "In women younger than 45 in the general population, you virtually do not see plaque, whereas women with lupus are beginning to acquire plaque at that early age," Dr. Bruce said.

Classic risk factors clearly are implicated in the premature atherosclerosis and coronary heart disease seen in lupus. There is a much higher prevalence of hypertension, diabetes, and renal impairment, and lupus patients typically have other risk factors such as higher levels of LDL cholesterol and triglycerides (Arthritis Rheum. 2003;48:3159-67).

And these risk factors do have an impact. "In a cohort study, we stratified patients according to their total cholesterol levels and found that among those with persistently elevated cholesterol, 24% developed a cardiac event during 12 years of follow-up, compared with 3% whose cholesterol level was normal or varied only slightly with disease flares," Dr. Bruce said at the meeting, sponsored by the British Society for Rheumatology.

But classic risk factors do not tell the whole story. (See box.) In the general population, risk for a cardiac event increases as risk factors accumulate. "Lupus patients, however, seem to be set at an intrinsically higher baseline, and the accumulation of risk factors has an even more devastating effect," he said.

A great need exists for properly conducted clinical trials of potential interventions for these patients. "We need to see if what we think will work actually does work and what the magnitude of risk reduction is with a particular intervention," he said.

Statins are an example. "Everywhere they have been used so far, they have been associated with a reduction in risk of coronary disease events by about 30%. You could assume that also might be the case in lupus, but that could be a dangerous assumption, because these drugs might not be as well tolerated by lupus patients," Dr. Bruce said. ■

Mediators and Markers: Look for Clues

As the severity of atherosclerosis and heart disease in systemic lupus erythematosus (SLE) becomes clearer, so do possible mediators and markers. A series of posters presented at the meeting by researchers from the Karolinska Institute, Stockholm, explored potential contributing factors:

► **LDL cholesterol.** Increased LDL-cholesterol oxidation contributes to lupus-related cardiovascular disease, reported Anna Cederholm, M.D. She presented data on 26 women with lupus plus cardiovascular disease, 26 women with lupus but no clinical manifestations of cardiovascular disease, and 26 normal controls.

Circulating levels of oxidized LDL cholesterol were increased in both lupus groups, as was platelet-activating factor acetylhydrolase (PAF-AH). Levels of oxidized LDL cholesterol and PAF-AH also were significantly higher in the lupus patients with cardiovascular disease than in those with lupus and no heart disease. Because PAF-AH binds to LDL cholesterol, it also may contribute to atherogenesis, Dr. Cederholm said.

► **Anti–HDL-cholesterol antibodies.** SLE-related dyslipidemia showed a surprising pattern in a study of women with a history of cardiovascular disease, reported J. Su, M.D. Large, rather than small, LDL- and HDL-cholesterol particles characterized the dyslipidemia profile. This was not an expected atherogenic lipid profile.

Antibodies against apolipoprotein A_1 in HDL cholesterol also were elevated and were associated with the presence of tumor necrosis factor. Whether these anti–apo A_1 antibodies play a pathogenic role—for example, by inhibiting the anti-inflammatory properties of HDL—is under investigation, Dr. Su said.

► **Homocysteine.** Hyperhomocysteinemia in patients with lupus correlates with markers of inflammatory activity and is a risk factor for cardiovascular disease, said Elisabet Svenungsson, M.D. In fasting blood samples obtained from a cohort of 208 patients, homocysteine levels were associated with acute phase reactants including C-reactive protein, serum amyloid A protein, fibrinogen, and complement.

Hyperhomocysteinemia also correlated with the presence of arterial disease and nephritis. "It may cause endothelial activation and damage and thus adds to the inflammatory burden that we believe renders SLE patients highly susceptible to cardiovascular disease," she said.

In Lupus, Antioxidants Are More Influential

BY ANNE SCHECK
Contributing Writer

LONG BEACH, CALIF. — Antioxidants have been taking a back seat to fatty acids in research on the dietary factors that may influence systemic lupus erythematosus, but an overview of the literature suggests that vitamins may affect disease progression more than lipids.

That is the tentative conclusion of Glinda Cooper, Ph.D., who presented the results of a review of the potential dietary influences on systemic lupus erythematosus (SLE) at the annual meeting of the American College of Nutrition.

"What is it that affects the expression of these self-antigens" associated with disease? Dr. Cooper asked. Because fatty acids have been shown to influence inflammation, they have been studied much more extensively than any other dietary component, she noted.

Over the past decade, one hypothesis has been that omega-3 fatty acids protect against inflammatory responses in lupus. Fatty acids are precursors to prostaglandins, which either inhibit or promote inflammation, she explained. However, a review of the literature shows "we're just not seeing much" in terms of a demonstrated effect from their intake, said Dr. Cooper, principal investigator of the Carolina Lupus Study at the National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

Neither the Nurses' Health Study nor an observational study of 200 patients with SLE showed an association with fatty acid ingestion. In the latter, however, there was a link between decreased disease activity and increases in vitamins C, E, and A, she said. Some investigations are showing that vitamin C, along with other antioxidants, may help curb expression of symptoms.

A study done by researchers at Johns Hopkins University, Baltimore, found lower blood levels of β-carotene, α-tocopherol, and retinol in blood donors who developed SLE 2-15 years later, compared with donors matched for race, age, and sex. This was a small study, but the results bear more investigation, she said.

Studies in mice have associated the course of disease and the level of fatty acids in the diet, Dr. Cooper said. But in human studies, "there is a disconnect." It may be that other factors enhance the influence of fatty acids, or that the dietary source from which they originate has some kind of effect on how well they are used by the body. ■