

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 diag-

nosed 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.

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 cardiovascu-

lar 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 A₁ in HDL cholesterol also were elevated and were associated with the presence of tumor necrosis factor. Whether these anti-apo A₁ 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.

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. ■

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. ■

VYTORIN® (ezetimibe/simvastatin)

VYTORIN: There are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See Ezetimibe and Simvastatin below.)

Ezetimibe: The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin: Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

ADVERSE REACTIONS

VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN has generally well tolerated.

Table 1 summarizes the frequency of clinical adverse experiences reported in $\geq 2\%$ of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 5 similarly designed, placebo-controlled trials.

Table 1*
Clinical Adverse Events Occurring in $\geq 2\%$ of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class	Placebo (%)	Ezetimibe 10 mg (%)	Simvastatin** (%)	VYTORIN** (%)
Adverse Event	n=311	n=502	n=1234	n=1236
Body as a whole - general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and connective tissue disorders				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.

** All doses.

Post-marketing Experience: The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

Ezetimibe: Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole - general disorders:* fatigue; *Gastrointestinal system disorders:* abdominal pain, diarrhea; *Infection and infestations:* infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders:* arthralgia, back pain; *Respiratory system disorders:* coughing.

Post-marketing Experience: The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema and rash; elevated creatine phosphokinase; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely, myopathy/rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole - general disorders:* asthenia; *Eye disorders:* cataract; *Gastrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders:* eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy. *Musculoskeletal system disorders:* muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgia.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

Ear and labyrinth disorders: vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting.

Hepatobiliary disorders: hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

Metabolism and nutrition disorders: anorexia.

Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction.

Eye disorders: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ -glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

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