Survivors May Risk Neoplasia

Lupus *from page 1*

porosis and osteopenia among children with lupus, which relates both to the inflammation associated with the disease and to the corticosteroid therapy they receive.

Dr. Bargman noted that the increased risk for bone density problems seen in children with lupus raises several questions for long-term management: "What about avascular necrosis and joint replacement? Will a prosthetic hip last into adulthood? Do we want to give bisphosphonates to children and young adults? If we prescribe large amounts of vitamin D and calcium, is extraosseous calcification going to occur?"

The issue of vascular calcification can be considered analogous to what has been reported for children undergoing dialysis, she said. In a study that included 39 young patients with ESRD who underwent electron beam computed tomography to screen for coronary artery calcification, children younger than 20 years had no evidence of calcification (N. Engl. J. Med. 2000;342:1478-83).

"But once they reached age 20, the calcification really started taking off," Dr. Bargman said. One explanation for this is that until about age 20, growth is still occurring and calcium is taken up by growing bone. Once the growth stops, calcium can begin to deposit in extraosseous sites such as blood vessels and soft tissues.

This vascular calcification in turn contributes to these patients' risk for accelerated cardiovascular disease. Some studies have suggested that the incidence of myocardial infarction among young women with lupus is as high as 50 times that of normal controls, and only some of this risk can be attributed to traditional risk factors such as hypertension and dyslipidemia.

Two other factors—chronic inflammation and subclinical renal dysfunction—may also play a role in lupus patients' risk for accelerated cardiovascular disease, she said. Recent data suggest that even a slight degree of renal impairment increases cardiovascular risk. For example, a patient with diffuse proliferative nephritis who has been treated successfully but still has a slight elevation in creatinine level and a small amount of proteinuria is at increased cardiovascular risk, Dr. Bargman said.

Among the 67 patients in Dr. Bargman's cohort, 6 ultimately developed ESRD, and 4 continued to have elevated serum creatinine levels. The remainder had so-called normal serum creatinine, which may not reflect absolutely normal renal function and may not be evident on a random serum creatinine measurement.

The risk begins increasing when the glomerular filtration rate is between 60 and 80 mL/min, she said.

Also, even microalbuminuria resulting from renal scarring has been shown to be statistically associated with increased cardiovascular mortality, she said.

Among the other findings regarding renal outcome in this cohort was the observation that, while patients with class III nephritis tend to continue requiring corticosteroid therapy, those with class IV diffuse proliferative nephritis seemed either to develop renal failure or get better, she said. This raises the question of whether pediatric lupus burns out.

One of her patients suggested that such might be the case. At age 8 years he had nephrotic syndrome and a renal biopsy found diffuse nephritis. "He had a very stormy course, was treated with lots of different alkylating agents, developed CNS psychosis, and even had a stroke during the next 10 years," she said. "But then everything seemed to quiet down and for the last 10 years he has been perfectly well, with no flares, and I wonder if his lupus has burned out."

A patient who presented at age 14 years with renal failure and class IV nephritis had multiple flares and was dependent on dialysis for a while. Each flare left her with a higher creatinine level. "Her father has offered to donate a kidney for her, but we have not been able to get her lupus quiescent enough to be able to go forward with transplantation," she said, noting that cases like this suggest that lupus doesn't burn out.

Another potential long-term concern for young patients with lupus nephritis is the risk for neoplasia. Lessons about later cancer risk for these patients can be drawn from the literature on cancer chemotherapy in children.

One recent study found that pediatric patients treated for cancer who received alkylating agents had a high incidence of subsequent cancers (N. Engl. J. Med. 2006;355:1572-82). ■

Practical Advice for Treating Lupus Nephritis From a Nephrologist's View

On behalf of the nephrology community, Dr. Bargman offered some concluding advice to rheumatologists who treat patients with nephritis:

► One rule is to be patient. It can take weeks or months for an extensive inflammatory infiltrate to resolve and for the serum creatinine level to improve, and sometimes the proteinuria will worsen before it gets better. Don't assume you need to administer more immunotherapy if you don't see improvement in a week. If someone's femur were crushed by a truck, you wouldn't expect him or her to run a marathon the next day. These glomeruli figuratively have been crushed by a truck and need time to heal.

► A second point is that lots of casts and red blood cells are no worse than a few. The number of casts and RBCs obtained during centrifuging depends upon how long you spin the urine, how much of the supernatant you pour off, and how much of a tap you give the centrifuge tube.

► Third, don't flog dead kidneys. If the patient's baseline creatinine level was 4.0 and it increased to 5.7 during a flare, another pulse of Solu-Medrol isn't going to save the kidneys. A baseline creatinine of 4.0 reflects extensive damage, and the patient would be better served by starting to do careful planning for dialysis.

► The most important thing to keep in mind is that there are other causes for elevations in serum creatinine levels besides worsening lupus nephritis, such as vigorous diuresis, especially when in combination with treatment with an ACE inhibitor or an angiotensin receptor blocker. Coadministration of certain other drugs such as cotrimoxazole also can have this effect, as can the presence of acute tubular necrosis.

Predictors of Atherosclerosis Progression Identified in SLE

BY JEFF EVANS
Senior Writer

WASHINGTON — Atherosclerosis is more likely to progress in systemic lupus erythematosus patients when lupus is diagnosed at older ages, when it has existed for a long duration, and when high homocysteine levels are present, according to new research presented at the annual meeting of the American College of Rheumatology.

Other research at the meeting suggested that the risk that women with SLE will develop carotid artery plaque may be determined by the presence of proinflammatory high-density lipoprotein (piHDL) cholesterol.

"We really don't know the rate and determinants of progression of carotid plaque in lupus," said Dr. Mary J. Roman of Cornell University, New York.

She and her colleagues used serial ultrasound scans of the distal carotid artery and clinical assessments to evaluate the progression of atherosclerosis in 159 patients in the Hospital for Special Surgery's SLE registry.

After an average follow-up of 34 months, 28% of the patients had either developed first-time atherosclerotic plaque in the carotid since their baseline assessment or showed an increase in existing plaque since baseline. That is equivalent to progression of atherosclerosis in about 10% of SLE patients per year, Dr. Roman said.

"We may use this observed rate of atherosclerosis progression in assessing the efficacy in future intervention trials," she said.

Compared with patients who had progressive plaque build up, those without plaque progression were significantly younger at baseline (mean age 50 years vs. 36 years) and at diagnosis (mean 36 years vs. 21 years), and had lower serum homocysteine levels at baseline. Patients without progression of atherosclerosis also tended to have more aggressive treatment of disease than those who experienced progression.

For each 10-year increase in either age at diagnosis or disease duration, patients were about three times more likely to have plaque progression than no plaque or stable plaque. Progression of atherosclerosis occurred in 56% of patients in the highest tertile of baseline serum homocysteine levels (7.9 mcmol/L or greater).

For each 10-year increase in either age at diagnosis or disease duration, patients were about three times more likely to have plaque progression.

"Other than older age, traditional risk factors were not associated with progression of atherosclerosis," Dr. Roman noted.

In a separate presentation, Dr. Maureen McMahon of the department of rheumatology at the University of California at Los Angeles reported preliminary results from an ongoing study that suggest the development of carotid artery plaque in women with SLE is associated with the presence of piHDL.

After conducting B-mode ultrasound screening of the carotid artery and taking blood samples of women with SLE and healthy control women, Dr. McMahon and her colleagues found that 42 of 95 (44%) women with SLE had piHDL, compared with 3 of 52 (6%) age-matched control women. Significantly more SLE patients with carotid plaque had piHDL than did SLE patients without plaque (93% vs. 38%). But there was no significant difference in the presence of piHDL between control patients with and without plaque.

Oxidized low-density lipoprotein (LDL cholesterol) directly and indirectly promotes the production of inflammatory cytokines, the migration of monocytes into the subepithelial space of vessels, and the formation of macrophages that take up the oxidized LDL cholesterol and form foam cells that build an atherosclerotic plaque. Normal HDL cholesterol helps to reduce the effect of oxidized LDL cholesterol by promoting cholesterol efflux from cells and by inhibiting the oxidization of LDL cholesterol. During periods of acute inflammation, HDL cholesterol may become proinflammatory and unable to perform its usual protective function, Dr. McMahon explained.

SLE patients with piHDL were 25 times more likely than control patients to have plaque after controlling for the traditional cardiovascular risk factors of hypertension, elevated LDL cholesterol, age, body mass index, diabetes, and high-sensitivity C-reactive protein.

"Measurement of piHDL may be one tool to identify [SLE] patients at risk for the development of atherosclerosis," Dr. McMahon concluded.

The SLE patients had a mean age of about 43 years and were not selected for a history of cardiovascular disease. None of the patients was allowed to take statins within 6 months of entry into the study. ■

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