Systemic Vascular Damage Seen in Pediatric SLE

BY NANCY WALSH
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For the first time, systemic arterial stiffening has been linked with left ventricular hypertrophy and dysfunction in patients with pediatric-onset lupus, according to Dr. Pak-Cheong Chow and colleagues from the department of paediatrics and adolescent medicine of the University of Hong Kong.

An increase in carotid arterial stiffness was previously observed among patients with adult-onset systemic lupus erythematosus (SLE), but these older patients typically also have premature atherosclerosis, hypertension, dyslipidemia, and other potentially confounding factors.

Systemic arterial stiffness has been documented in children with other vasculitic diseases, such as polyarteritis nodosa, but arterial function in young SLE patients has not been studied, the investigators said.

In order to investigate this aspect of pediatric-onset lupus, they studied 32 patients and 15 controls, performing pulsed-wave Doppler and standard M-mode echocardiography, tissue Doppler imaging, and imaging of the right and left common carotid arteries.

Mean age at diagnosis was 11.7 years, mean disease duration was 6.3 years, and mean systemic lupus erythematosus disease activity index (SLEDAI) was 4. A total of 21 patients had nephritis, 11 had antiphospholipid antibodies, and two had antiphospholipid syndrome. At the time of the study, 28 patients were receiving prednisone, with a mean daily dose of 5.4 mg.

The study also found that arterial stiffness correlated with the disease activity score and was an independent determinant of LV mass and function.

Echocardiographic findings among the lupus group included thicker interventricular septum, thicker left ventricular (LV) posterior wall, greater indexed LV mass, and lower LV fractional shortening and ejection fraction compared with controls.

They also showed reductions in LV free wall systolic strain and strain rate, as well as a lower mitral annular systolic velocity, findings that are indicative of LV systolic dysfunction. Patients also had significantly lower E wave velocity, E deceleration time, E/A ratio, and diastolic strain rates, suggesting LV diastolic dysfunction relating to impaired relaxation.

In addition, the average carotid arterial stiffness index was significantly greater among the lupus patients, and on univariate analysis, this index correlated significantly with SLEDAI, albeit not with age, body mass, diastolic blood pressure, damage index, daily prednisone dosage, or duration of disease. On multiple linear regression analysis, SLEDAI and systolic blood pressure remained significantly correlated with carotid stiffness index after adjustment for these variables.

With regard to the relation between arterial stiffness and LV structure and function, the average carotid arterial stiffness index correlated positively with LV posterior wall thickness, interventricular septal thickness, indexed LV mass, and myocardial performance index. Negative correlations were seen with E wave velocity, e_m velocity, or strain rates.

Multiple regression analysis determined carotid arterial stiffness was a significant determinant of indexed LV mass, e_m velocity, and left ventricular strain rate after adjustment for age, sex, body mass index, and blood pressure.

"Our study provides the first evidence that systemic arterial stiffening is associated with LV hypertrophy and dysfunction in a young cohort of patients with pediatric-onset SLE," wrote the authors (J. Rheumatol. 2007;34 [Epub ahead of print]).

The study also found that arterial stiffness correlated with the disease activity score and was an independent determinant of LV mass and function.

The authors noted arterial stiffening in SLE likely links to immune complex–induced complement activation and inflammatory cell infiltration in the arterial wall. Longitudinal studies are needed to see if reducing stiffness and improving ventricular function reduce the risk of early cardiovascular disease in these patients. ■

Rituximab Appears Safe for SLE, But Protocols Are Needed

BY PATRICE WENDLING
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MIAMI BEACH — Rituximab treatment appears safe and efficacious for refractory systemic lupus erythematosus in children, Dr. Obioma Nwobi and colleagues reported in a poster at the annual Masters of Pediatrics conference sponsored by the University of Miami.

Average SLE Disease Activity Index scores improved from 43 at baseline to 28 at 6 months post treatment in 16 children. Rituximab was well tolerated in 15 patients, but one died 20 days after starting rituximab of acute bacterial endocarditis.

Rituximab (Rituxan) has come under scrutiny after two patients treated with rituximab for SLE developed progressive multifocal leukoencephalopathy (PML), a viral infection of the central nervous system.

SLE is not an approved indication for rituximab, which selectively depletes CD20+ B cells. It is approved only for the treatment of non-Hodgkin's lymphoma and refractory rheumatoid arthritis.

The death in the current study was likely "related to the severe immune suppression imposed by the use of Cytoxan prior to the rituximab," senior author Dr. Carolyn Abitbol said in an interview.

"Although Cytoxan has long been considered the 'standard of care' in treating SLE nephritis because of its efficacy, the primary cause of death in lupus patients is infection," she said.

The safety and efficacy of rituximab has been established in at least three adult SLE trials, numerous rheumatoid arthritis trials, and in more than 300,000 patients treated for lymphomas, said Dr. Abitbol, professor of pediatrics and clinical director of pediatric dialysis, University of Miami.

Dr. Abitbol agreed with a recent statement that the reported deaths were the results of extreme immunosuppression, and were not attributable to rituximab (the statement can be located online at www.hopkins-arthritis.som.jhmi.edu/news-archive/2007/genentech-PML.html). The children in the study were treated from February 2003 through January 2007 and had long-standing SLE for an average of 3 years post diagnosis. Three children were on maintenance hemodialysis for over 6 months. All had received immunosuppressant protocols including Solu-Medrol (16), Cytoxan (16), azathioprine (5), and MMF (13) without adequate control of extrarenal symptoms.

Rituximab infusions were administered weekly at an initial dose of 188 mg/m^2, followed by a dose of 375 mg/m^2 for a total of two to four doses. The mean age of the children was 16 years. There were 15 girls, 11 African Americans, 4 Hispanics, and 1 white child.

Six months after treatment, significant decreases were observed from baseline in average urine albumin:creatinine ratio (3,756 mg/g vs. 361 mg/g), urine protein:creatinine ratio in patients not on dialysis (4.2 mg/dL vs. 0.7 mg/dL), and serum creatinine (1.2 mg/dL vs. 0.6 mg/dL).

Significant increases were seen in serum albumin levels (2.6 mg/dL vs. 3.5 mg/dL) and CD4 T cells (344 vs. 556). An insignificant increase in CD8 T cells also was observed (332 vs. 590). CD 20+ B cells decreased significantly at 6 months from baseline (243 vs. 74). B-cell depletion, measured serially over 6-18 months, lasted an average of 6-8 months.

The authors said collaborative controlled trials are needed in children to develop protocols for rituximab as a component of induction and/or maintenance therapy for SLE. ■