Kids With cSLE Live Longer, Face More Challenges

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NEW YORK – The good news in the management of childhood-onset systemic lupus erythematosus is that children who are diagnosed with the disease have a better prognosis and are living longer.

The bad news is that over the course of a lifetime, affected children develop more morbidities and experience more medication-induced toxicities, which create additional management challenges, according to Dr. Phillip Kahn, who spoke at the meeting.

About 15%-20% of lupus cases present in childhood. Children younger than age 5 years rarely have the disease, but up to 40% of patients with childhood-onset SLE (cSLE) present prior to puberty, said Dr. Kahn of New York University.

The presenting symptoms of cSLE may be as vague as diffuse lymphadenopathy, fever, and malaise. Cutaneous symptoms such as mucocutaneous lesions may help make the diagnosis.

The incidence of cSLE is estimated to be 10-20 cases per 100,000 individuals, but the incidence is higher in blacks, at 200 cases per 100,000 individuals (Lupus 2007;16:546-9; 2005;14:83-8).

Often the diagnosis is delayed in children, as their clinical features do not fall within those defined by the 1997 American College of Rheumatology's SLE criteria, which have not been validated in children.

For example, Dr. Kahn described the case of a 13-year-old girl who presented with "constitutional symptoms" such as diffuse lymphadenopathy, malaise, weight loss, and fever – none of which are included in the 1997 criteria.

Mucocutaneous lesions are common in children, with up to 70% presenting with malar rash, 30% with alopecia, 66% with oral ulcers, and 10% with nasal ulcers.

"Although nasal ulcers are less common in children than adults, they still may result in perforation of the septum," he said. Other common manifestations include painful polyarthritis, hepatosplenomegaly, headache, photosensitivity, and Raynaud's phenomenon.

Up to 40% of cSLE patients have neuropsychiatric symptoms, significantly more than do adults (Lupus 2008;17:314-22).

An important diagnostic tool for cSLE is a positive ANA (antinuclear antibody) finding, which is present in essentially all children with cSLE. In contrast, up to 10% of adults with SLE do not have a positive ANA, said Dr. Kahn.

Childhood-onset lupus may predict mortality in adults (Arthritis Care Res. [Hoboken] 2010;62:1152-9) and thus physicians must be vigilant about detecting, preventing, and aggressively treating some of its more dangerous manifestations.

To prevent recurrent infection, Dr. Kahn recommends keeping a child up to date with immunizations, treating infections promptly when they occur, and considering PCP (pneumocystis carinii pneumonia) prophylaxis in the appropriate patient. Children with cSLE are also at increased risk for premature atherosclerosis, with dyslipidemia seen in 60%-85% of affected children (Nat. Clin. Pract. Rheumatol. 2008;4:258-65). Statin therapy may be appropriate in these children, especially to prevent long-term adverse events such as early MI. For example, adults – especially women – who had cSLE have increased incidence of MI when they reach their 30s (Arthritis Rheum. 2009;61:13-20). The ongoing APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) trial is investigating, in greater detail, cardiovascular risk and the use of statins in cSLE (Lupus 2010;19:1315-25).

Because nephropathy is the main cause of mortality and morbidity in cSLE, it is important to monitor urinary markers of renal function. Nephropathy may take a greater toll on a pediatric patient, compared with adults; data show that children are more likely to have renal involvement, need hemodialysis and kidney transplantation, and require hospitalization and emergency department visits (Lupus 2008;17:314-22; Arthritis Rheum. 2009;61:13-20).

To avoid end-stage renal disease, Dr. Kahn urges tight blood pressure control, as well as antihypertensive medication as necessary.

"We know that 90% of the patients who ultimately develop renal disease will do so within the first 2 years of disease, so if you follow a patient for [more than 2] years and they do not develop the disease, the good news is they are much less likely to develop nephropathy," said Dr. Kahn.

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Major Finding: Childhood-onset SLE may be difficult to diagnose because its symptoms differ from that of adult-onset SLE. But cSLE is a predictor of mortality, and steps should be taken to control morbidities such as infection, premature atherosclerosis, and nephropathy. Prednisone remains a cornerstone of pharmacotherapy but has serious side effects, including osteoporosis and impaired growth. Additional nontargeted and targeted options are available.

Data Source: A clinical update presentation based on published reports and clinical experience.

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In the 1950s, the 5-year survival rate for SLE in adults and children ranged from 18% to 70%; 30 years later, 5-year survival rose to 60%-93%, in large part because of the introduction of prednisone.

Currently, prednisone is almost universally given to those with cSLE, and the proportion of children who are treated with prednisone is significantly higher than the proportion of adults with SLE (97% vs. 70%; *P* less than .0001) (Arthritis Rheum. 2008;58:556-62). The result is greater risk of osteoporosis, diabetes, and growth failure.

Among the barriers to effective treatment are physicians' failure to detect subtle changes in early disease and a lack of awareness of neuropsychaitric manifestations of the disease.

In fact, up to 40% of cSLE patients have growth failure or short stature, in part because of chronic steroids.

That is why Dr. Kahn posed the question, "Can we move beyond steroids?"

Until recently, the only Food and Drug Administration–approved medications for SLE were prednisone, hydroxychloroquine, and aspirin.

Steroid-sparing immunomodulatory therapy is sometimes used off label when major organ (such as brain or kidney) involvement develops, but most evidence regarding the efficacy of these medications pertains to renal proliferative disease in adults.

Cyclophosphamide is often used for induction of nephritis, but 30% of patients may still develop end-stage renal disease despite treatment, said Dr. Kahn. Mycophenolate mofetil has been shown to have equal efficacy to cyclophosphamide in induction of remission of nephritis, but sufficient pediatric data are lacking. Azathioprine is effective for maintenance therapy of nephritis after the induction phase.

Other options that are sometimes used include intravenous immunoglobulin, methotrexate, calcineurin inhibitors (such as tacrolimus), plasmapheresis, and autologous stem cell transplantation/immunoablative therapy.

More recently, the focus has been on target-specific therapy for SLE with potentially fewer side effects.

Rituximab, which targets B cells that have the CD20 surface antigen, is sometimes used to treat resistant patients, but there is no strong clinical evidence to demonstrate its effectiveness in cSLE (Arthritis Rheum. 2009;61:482-7; Clin. J. Am. Soc. Nephrol. 2009;4:579-87).

Abatacept, which targets T cells by binding to B7 peripheral membrane protein, has shown some clinical benefit in a phase IIB randomized clinical trial, and is undergoing clinical testing as an add-on induction therapy with cyclophosphamide (Arthritis Rheum. 2010;62:3077-87).

Belimumab, a monoclonal antibody that targets BLyS (B-lymphocyte stimulator)/BAFF (B-cell activating factor), is the first FDA-approved medication for SLE in more than 50 years, based on recent clinical trials that demonstrate increased efficacy and fewer flares of disease, compared with placebo (Arthritis Rheum. 2009;61:1168-78; Lancet 2011;377:721-31).

Although recent data regarding belimumab provide some hope, it "may be naive to think that a target-specific therapy exists in this complex, polygenic, heterogeneous disease," commented Dr. Kahn.

In concluding his talk, Dr. Kahn spoke about some barriers to the effective treatment of cSLE.

These include physicians' failure to detect the subtle changes of early disease, a lack of awareness regarding the neuropsychiatric manifestations of the disease, and physicians' fear of being overly aggressive with treatment.

He also warned about overt or covert adolescent noncompliance, and the danger of adolescents' dropping out of the health care system once they need to transition to adult care. ■