Interleukin-6, -1 Predominate in Systemic JIA

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NEW YORK — The unique inflammatory cytokine profile associated with systemic juvenile idiopathic arthritis may offer therapeutic targets that could ultimately lead to symptom control and prevention of long-term disability in this difficult-to-treat condition.

Systemic juvenile idiopathic arthritis (JIA) turns out to be a very different disease than juvenile polyarthritis, Dr. Daniel J. Lovell said at a rheumatology meeting sponsored by New York University. The disease has a more severe outcome, with up to half of patients continuing to have active arthritis 5-10 years after diagnosis. Most patients have required treatment with methotrexate for their arthritis and corti-

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costeroids for their systemic symptoms such as fever and rash, but the steroid treatment itself can result in significant morbidity, with patients experiencing growth retardation and developing osteoporosis.

It is now known that systemic JIA also differs in pathogenesis. In a cohort that included 82 patients treated with etanercept for a mean of 25 months, response to an anti–TNF-α agent was fair or poor in more than half (J. Rheumatol. 2005;32:935-42). Rather, it appears that interleukin (IL)-6 and IL-1 are the dominant inflammatory cytokines in systemic JIA.

A dose-finding study conducted in Japan found "profound and rapid responses" to treatment with tocilizumab, a humanized monoclonal antibody to the IL-6 receptor, said Dr. Lovell, professor of pediatrics, Cincinnati Children's Hospital Medical Center.

The study included 11 patients whose median age was 9 years and whose median duration of disease was 3 years. The drug was given in doses of 2 mg/kg every 2 weeks for three courses of treatment unless response was inadequate, in which case doses were increased to 4 mg/kg and then 8 mg/kg, depending on effect. Clinical responses were evident 3-4 days after the first treatment, and in some cases, the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) began to fall within hours after the initial infusion, he said.

Within 2 weeks after the third dose, 90.9% of patients had reached an American College of Rheumatology (ACR) pediatric 30 response, the same number also achieved an ACR 50 response, and 63.6% had achieved an ACR 70 (Arthritis Rheum. 2005;52:818-25).

In another study, nine patients whose disease had been resistant to aggressive conventional treatment received anakinra for an average of 6.6 months, and all responded. Complete remission, including resolution of fever and rash, was seen in seven (J. Exp. Med. 2005;201:1479-86). Prior treatments included oral prednisone, intravenous methylprednisolone, and infliximab.

In describing his experience using biologic treatments for juvenile systemic and polyarticular rheumatoid arthritis, Dr. Lovell emphasized that there is a need for better ways of evaluating outcomes. The ACR pediatric 30, typically used as the primary end point in drug trials, is a composite index requiring a 30% improvement in three of six disease components. This end point has been met so commonly in studies evaluating biologics that more stringent criteria are now needed, so Dr. Lovell and a group of international experts recently proposed a new outcome measure termed "inactive disease." To achieve this, all five of the following criteria must be met:

- ► No joints with active arthritis.
- ► No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to systemic JIA.
- ► No active uveitis.
- ► Normal ESR and CRP.
- ► Physician's global assessment indicating no disease activity.

Patients who maintain inactive disease for 6 months are classified as being in clinical remission on medication, those who maintain inactive disease for 12 months while off medications are said to be in clinical remission off medication. ■