Big Changes in Treatment of Systemic JIA

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SNOWMASS, COLO. – Many pediatric rheumatologists are ready to flip the traditional treatment algorithm for systemic juvenile idiopathic arthritis on its head.

"The way we approach this disease is changing very, very rapidly," Dr. Alexei A. Grom observed at the symposium.

Driving this change is the recognition that inflammatory cascades mediated by interleukin-6 (IL-6) and interleukin-1 (IL-1) are pivotal to the pathogenesis of systemic juvenile idiopathic arthritis (SJIA).

"There is quite a bit of enthusiasm in our field for drugs that inhibit these cytokines," said Dr. Grom, a pediatric rheumatologist at Children's Hospital Medical Center, Cincinnati.

SJIA is an autoinflammatory syndrome marked by abnormalities in innate rather than adaptive immunity. It's not a classic autoimmune disease. There are no pathogenic autoantibodies and no autoreactive T cells. That's probably the reason that response rates to anti–tumor necrosis factor-beta (anti-TNF-beta) therapies are substantially lower than in other forms of JIA.

The traditional treatment algorithm for SJIA involves NSAIDs, corticosteroids, and methotrexate or other conventional disease-modifying antirheumatic drugs (DMARDs). When that doesn't bring good results, as is more often than not the case, an anti-TNF biologic is added. And if that doesn't work, there's a switch to a different anti-TNF drug.

"Based on the preliminary results of the clinical trials with the anti-IL-1 and anti-IL-6 biologics, the question is whether in fact we should skip all this and go directly to the IL-1– and IL-6–inhibiting agents," Dr. Grom said. "I think this part of the old algorithm is a waste of time, and the introduction of these new biologics will dramatically change the outcome for these kids."

Time is of the essence in newly diagnosed SJIA because destructive arthritic changes occur relatively early in the course of the disease. It therefore makes little sense to have a patient spend months on methotrexate – a drug that's much less effective in SJIA than in other types of JIA, such as polyarticular JIA (see accompanying story) – before you decide to move on. Similarly, intra-articular steroid injections are substantially less effective and have a shorter duration of response in SJIA than in other types of JIA, he added.

Current practice among pediatric rheumatologists runs the gamut. Some still follow the traditional algorithm. But the more popular position is encompassed in a recently published series of 46 SJIA patients treated at 11 centers around the world. All received the IL-1-blocker anakinra (Kineret) as first-line therapy. Nearly 90% of the patients experienced rapid resolution of their symptoms and prevention of refractory arthritis, prompting the authors to declare that anakinra should be considered first-line therapy in SJIA, rather than a rescue therapy as in the old algorithm (Arthritis Rheum. 2011;63:545-55).

The only biologics approved for the treatment of JIA in the United States at present are etanercept, adalimumab, and abatacept. Anakinra and infliximab see substantial off-label use.

Dr. Grom said that although IL-1 is an extremely attractive target in SJIA, anakinra may not be the best way to approach it. That's because IL-1 receptors are so abundant, being expressed on all cells except red blood cells. These receptors are readily generated on a daily basis, whereas anakinra is rapidly excreted by the kidney, resulting in low blood levels after 24 hours. This might explain recent reports of diminishing clinical effectiveness over time.

An alternative strategy likely to prove more efficient in neutralizing IL-1 involves the use of the IL-1-trap rilonacept (Regeneron), Dr. Grom said. A large, phase III, double-blind, placebo-controlled trial of rilonacept in SJIA is underway. Another phase III, double-blind, placebo-controlled trial in SJIA involves canakinumab (Ilaris), a fully humanized anti-IL–1-beta monoclonal antibody. Results are expected soon.

There is some evidence that IL-6 may be an even more important cytokine than IL-1 in SJIA. A phase II, double-blind, placebo-controlled trial using the anti-IL-6 biologic tocilizumab showed "very promising" results, in Dr. Grom's view, with an ACR-Ped-70 response of 90% by week 48 of the open-label extension phase (Lancet 2008;371:998-1006). A phase III, double-blind, placebo-controlled clinical trial of tocilizumab in SJIA has completed enrollment and is due to report results very soon.

Turning to unconventional therapies for the most severe, refractory cases of SJIA, Dr. Grom said thalidomide is worth considering under these circumstances. The drug has shown benefit in small, uncontrolled series, with only minor side effects. Thalidomide's teratogenicity precludes its use except in children who have failed conventional therapy, he stressed.

He declared having no relevant financial interests. ■