Stop MTX After Remission in Most JIA Patients

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PHILADELPHIA — Extending methotrexate for more than 6 months after induction of remission had no added benefit for preventing long-term flares in a randomized study of more than 300 patients with juvenile idiopathic arthritis.

The findings also showed that measuring serum levels of the inflammatory marker myeloid-related protein (MRP)8/14 predicted which patients in remission would experience flares off treatment and which would not.

Based on these results, MRP8/14 now is routinely used at the University of Muenster (Germany) to guide withdrawal of methotrexate from JIA patients in remission, Dr. Dirk Foell said at the annual meeting of the American College of Rheumatology.

"This is the first controlled trial analyzing the necessary time of treatment continuation once remission is achieved in a rheumatic disease," said Dr. Foell, a pediatric rheumatologist at the university. Continuing methotrexate longer than 6 months after achieving clinical remission "does not influence the risk of JIA relapses and cannot be recommended in general," he said. However, some patients may reach an unstable remission on medication, giving them a status of clinical but not immunologic remission. "MRP8/14, a marker of phagocyte activity, indicates subclinical inflammation and identified patients with an increased risk of relapse in whom therapy may not be safely stopped," said Dr. Foell.

The researchers proposed a MRP8/14 cutoff of 690 ng/dL—the level now used in Muenster to guide methotrexate withdrawal—because it combined the best level of specificity and sensitivity for predicting relapse. But they recognize that the statistical cutoff is not ideal for all cases. Dr. Foell and his colleagues continue to look for more intelligent markers of inflammation to detect at-risk patients, he added.

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A multicenter collaboration of PRINTO (Paediatric Rheumatology International Trials Organization) randomized 364 JIA patients with clinical remission on methotrexate. The average age of the patients was 11 years, about two-thirds were girls, nearly 90% were white, and their median disease duration at enrollment was 3 years. The researchers took patients off methotrexate after either 6 or 12 months of remission. They took serum specimens from 188 patients (52%) just before cessation of methotrexate therapy to measure MRP8/14, which is very stable in the serum.

In an intent-to-treat analysis, the rates of relapse flares during years 1 and 2 of follow-up were not significantly different in the two treatment arms. In contrast, an analysis of patients based on their MRP8/14 levels showed a dramatic difference in flare rates. Those with a level of less than 690 ng/dL just before cessation of methotrexate had a flare rate of 26 per 1,000 patient-months in the first year of follow-up, and 20 per 1,000 patient-months through 2 years of follow-up.

Patients with a MRP8/14 level of 690 ng/dL or more had rates of 57 flares per 1,000 patient-months and 48 flares per 1,000 patient-months, respectively, a statistically significant difference between the two arms.

The relapse rates of patients with low or high MRP8/14 levels began to diverge after the first 2 months off methotrexate, and continued to steadily diverge after that.

This investigator-initiated study received no major industry support, said Dr. Foell; it did receive some funding from Wyeth Pharmaceuticals, the German Rheumatology League, and PRINTO. Dr. Foell disclosed that he has been a scientific adviser to Wyeth, Regeneron Pharmaceuticals Inc., and Cis-Bio International. ■