Earlier Biologics Use in JIA Allows Less Steroids

More remissions are not the new rule with aggressive therapy, but other markers show improvement.

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VALENCIA, SPAIN – Over the past 18 years, remission rates in juvenile idiopathic arthritis may have increased, steroid therapy has decreased, and treatment has been started earlier for children with the disorder, findings from two retrospective database studies suggest.

The studies examined the changing roles of medication and differences in clinical response among a total of 1,346 patients. Both studies showed that medical therapy has undergone a dramatic change.

Dr. Ricardo Russo said he did not find any evidence of improved remission rates in his cohort of 80 patients, followed from 1992 to 2009.

However, other disease markers showed improvement, he said. Specifically, "patients with disease onset [between 1992 and 2009] were exposed to more intensive, earlier immunomodulotherapy, including the new biologics, resulting in reduced corticosteroid usage, less joint damage, and possibly lower rates of disability," said Dr. Russo of the Hospital de Pediatria "Prof. Dr. Juan P. Garrahan," Buenos Aires.

Data from the German Juvenile Idiopathic Arthritis Etanercept Registry showed even better outcomes, according to Dr. Ivan Foeldvari of the Hamburg (Germany) Rheumatology Center for Children and Young People.

For 1,266 children who took etanercept from 2000 to 2008, the results "indicate that patients starting etanercept in recent years were treated earlier, received less pretreatment, [and] less concomitant corticosteroids."

With earlier, aggressive treatment, more children have achieved a pediatric ACR 70 and are in remission after 1 year of treatment, Dr. Foeldvari said.

During the first few years of the analysis, the average disease duration at the time of beginning etanercept was 6 years; by 2008, that had decreased to 3 years. The percentage of patients who began taking the drug within the first 2 years of active disease increased from 17% in 2000 to 40% in 2008.

The german regsitry's data from 2000, which marks the beginning of the study period, showed that it was common for children to receive pretreatment with numerous antirheumatic agents, including cytotoxic agents. Children received an average of three such agents during that era of juvenile idiopathic arthritis (JIA) treatment; some children got as many as nine such agents.

However, once the biologics era was resolutely underway in 2008, children were receiving a mean of one pretreatment disease-modifying antirheumatic drug (DMARD), Dr. Foeldvari said.

In 2000, most patients took corticosteroids (95% of children in the registry), methotrexate (83% of children in the registry), and other DMARDs (45% of children in the registry) before starting etanercept.

By 2007, 31% of children in the registry used concomitant corticosteroids, 61% received methotrexate, and 14% received other DMARDs.

Clinical outcomes showed significant improvement over the years, he said. The number of patients reaching a pediatric ACR 70 response increased from 57% to 74%. The rate of inactive disease within 1 year was 24% in 2000, compared with 54% in 2008, according to Dr. Foeldvari.

Over the course of his investigation, Dr. Russo found similar trends in children's therapy, which compared treatment and clinical results in 80 patients [34 treated from 1992 to 1998 and 46 from 2000 to 2009]. The median follow-up period was 55 months.

During the 1990s, methotrexate was used by a total of 91% of children in the registry during their first year of treatment and by 87% during their second year.

In contrast, during the 2000s, 62% of children in the registry used methotrexate during their first year of treatment and 65% during their second year. Corticosteroid use followed a similar decline, he said.

The study also pointed up the ever-more-important role being played by biologic medications in JIA therapy, with these drugs used in a mean of 50% of patients in the 2000s era, and in no patient during the 1990s.

The most widely used biologic agents were the tumor necrosis factor antagonists (23 of 46 children treated between 2000 and 2009, 50%), followed by abatacept (2 children, 4%), and anakinra (2 children, 4%).

In addition, Dr. Russo said he found evidence of patients being treated at an earlier stage of their disease and more effectively, because those who started treatment in the 1990s showed a significantly lower rate of joint damage over a 5-year period than did those who started therapy during the 2000s.

However, Dr. Russo said he did not see any significant differences in clinical measures of disease activity, including inactive disease or remission, on or off medication.

"It was difficult to compare disability rates because in the two eras, we used different measures of disability," he added.

"But it was my clinical impression that there was a tendency toward a lower percentage of disabled patients in the 2000s."

Dr. Russo also did not look specifically at osteoporosis in the groups, but said "I have the feeling that we now see fewer patients with short stature than we did in the past." ■

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Major Finding: Treatment for idiopathic juvenile arthritis has changed dramatically since 1992, with a decrease in corticosteroids and an increase in biologic therapy, and possibly with improved clinical outcomes.

Data Source: Two retrospective studies of 1,346 children found significant changes in medication regimens and less joint damage, and pointed to improved remission rates.

Disclosures: The German Etanercept Registry is sponsored by Wyeth Biopharma. Dr. Foeldvari has been on advisory boards for Abbott, Bristol-Myers Squibb, Essex Pharma GmbH, Roche, and Wyeth. Dr. Russo did not present any disclosure information.

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improvement in systemic features within hours, and their arthritis was also greatly improved (Lancet 2008; 371:998-1006).

On the subject of medications, including biologics, used to treat children with JIA, it is critical to calculate the dose on the basis of milligrams per kilogram or body surface area. "That really causes you to think about your medical math," said Dr. Lovell. He gave the example of a 6-year-old child, height 4 feet 11 inches, weight 55 lb, whose dosages for common JIA treatments according to the published pediatric recommendations, which are based on weight or surface area, were very similar to adult doses. It is a common problem for adult rheumatologists who treat JIA patients to use the right drugs but in amounts below the efficacious dose because of concern about giving a child adult-sized dosages.

"My advice to you is look at the dosage based on milligrams per kilogram or milligrams per meter squared, do your math, gird your loins, and write the prescription. If you're going to use the agent, you have to do it in the proper dose in the kids to get the proper effect."

The observed frequency of cancer in children with JIA treated with etanercept based on FDA data is six cases in 9,200 patients or one case per 1,533 children.

In the polyarticular forms of JIA, where more than five joints are involved, the most common treatment approach is methotrexate.

"Methotrexate is our most studied agent ever in terms of kids with arthritis," said Dr. Lovell. However, many children with polyarticular forms of JIA do not respond to or tolerate methotrexate. It is in these children that the anti–tumor necrosis factor (anti-TNF) biologics have shown dramatic benefit.

The question of whether biologics increase a child's risk for cancer is actually several linked questions, said Dr. Lovell. These include the child's background risk, independent of arthritis; the risk from just having JIA (which is unknown); the risk from prior treatments for JIA such as methotrexate and steroids; and the potential risk from taking biologics.

Dr. Lovell has developed his own unofficial estimate of risk, limited to etanercept, because that's where the best JIA-related data are found. The observed frequency of cancer in children with JIA treated with etanercept based on FDA data is six cases in 9,200 patients or one case per 1,533 children. Epidemiologic data for the overall incidence of cancer in American children under the age of 15 years are one case per 7,252 children. Accordingly, the relative risk compared with the healthy pediatric population is 4.7 – with many caveats, he says.

"Fortunately, this still means that cancer in children with JIA treated with etanercept is very uncommon – about one case of cancer in every 1,500 children with JIA treated with etanercept." In other words, relatively modest.

Dominick Co of Children's Hospital of Wisconsin, Milwaukee, said, "We have a number of very difficult poly-JIA patients who seem to have an initial response to some of the biologics and then after several months will not respond, and we'll switch them. Have you had a similar experience with cycling through biologics?"

Dr. Lovell responded that he saw poly-JIA patients treated with biologics "where there was an initial excellent response and then a secondary loss of response. We went back to the families and the patients and discussed the situation with them. In about half of the patients (usually adolescents), that loss of response was due to the patient developing poor compliance with taking the biologic since they felt so well. In other cases the loss of response was more difficult to understand, but it certainly occurs and we have dealt with it by either increasing the dose of the biologic or changing to another biologic."

Dr. Lovell disclosed consulting fees or other remuneration from Centocor, Amgen, Abbott, Pfizer, Regeneron, Hoffman-La Roche, Novartis, UBC, Xoma, and Wyeth. ■