Balking at Biologics in Kids

JIA *from page 1*

symptoms increase and joint damage becomes apparent. But in the last 10 years or so, researchers have begun to ask another question: What would happen if we hit JIA with more effective treatments, earlier on?

For some, the idea has been a hard sell.

"Yes, our most effective medications are expensive, high powered, and with potential side effects, so many physicians are afraid of using them in children," Dr. Wallace said. "But on the other hand, what would be the real value of inactive disease for these kids? What if they could have a very high quality of life – running around and playing soccer – instead of going to the doctor frequently? Getting off medication sooner could mean less overall drug exposure" than that experienced by children who are treated with less-powerful medications but who, after years of treatment, are still on drugs with active or smoldering disease.

Even administrators who guard the bottom line could be happier because of the expected savings, she said. "This way of treating might actually be more cost effective in the long run. With better quality of life and inactive disease, there could be fewer visits to the doctor, less overall utilization of health care resources, fewer joint replacements, fewer parents missing work for a child's illness – there are a lot of pure-ly economic ramifications from having complete disease response."

Bit by bit, the evidence supporting this idea has grown, she said at the meeting. In 2008, a retrospective study of 125 patients with at least 5 years of follow-up found that those who achieved an ACR Pedi 70 (American College of Rheumatology Pediatric 70) score by 6 months after initiation of treatment showed sustained, significantly greater improvement over the long run than did nonresponders. At the end of the study, 55% of the responders had inactive disease, compared with 17% of the nonresponders and 29% of those who responded less favorably to treatment (Ann. Rheum. Dis. 2008;67:370-4).

Imaging studies have shown that joint damage in JIA progresses fastest during the first year of the disease. A 2005 study of 13 children with newly diagnosed polyarticular JIA found progressive joint damage in six children after only 14 months. These children started disease-modifying antirheumatic drugs (DMARDs) at an average of 7.5 months after symptoms appeared. The others – who started DMARDs earlier, at an average of 1.6 months after diagnosis – had no progression (Ann. Rheum. Dis. 2005:64:491-3).

Findings from studies involving adults send a similar message: Treatment timing matters. "The evidence tells us that the disease continues to spread to additional joints, and the burden of disease becomes greater with time," Dr. Wallace said. "The adult and pediatric evidence now tells us that if we treat earlier and get it quieted down early, patients do better in the long run."

The data also confirm that treatment type matters. The most recent evidence comes from a 2010 meta-analysis of 15 randomized, controlled trials comprising 4,200 patients with rheumatoid arthritis of less than 3 years' duration. Treatment regimens in the studies included DMARDs, a combination of tumor necrosis factor (TNF) blockers plus methotrexate, and methotrexate alone. "Both the DMARDs and the combination therapy were superior to methotrexate alone," Dr. Wallace said.

Patients taking the anti-TNF and methotrexate had higher ACR responses, fewer withdrawals for inefficacy or toxicity, lower disability scores, and less erosive damage on imaging. (Rheumatology 2010;49:91-8).

Again, childhood data show similar findings. A study reported at the 2009 ACR annual meeting randomized 60 DMARD-naive JIA patients with just 6 weeks' disease duration to methotrexate, methotrexate plus infliximab, or a combo of methotrexate, sulfasalazine, and hydroxychloroquine. At 6 months, an ACR Pedi 75 response occurred in 100% of the double therapy group, 65% of the triple therapy group, and 10% of the methotrexate-only group.

By 54 weeks, 68% of the double therapy, 40% of the triple therapy, and 25% of the methotrexate groups had inactive disease.

All of these encouraging data lead to the TREAT (Trial of Early Aggressive Therapy) in JIA trial, the results of which Dr. Carol Wallace is eagerly awaiting. The year-long study randomized 85 children with polyarticular or extended oligoarticular JIA to one of two aggressive treatment regimens. Because all of the subjects had a disease duration of less than 12 months, TREAT may provide answers about optimal timing as well as optimal therapy.

'That's actually the beauty of the CARRA network. We can, through our members, make a standard of care based on data. And that's what this study is all about: finding evidence.'

The study is being conducted by CARRA (Childhood Arthritis and Rheumatology Research Alliance). Founded by researchers, CARRA conducts investigator-initiated clinical trials not only for JIA, but also for other childhood rheumatic diseases (www.carragroup.org).

CARRA now comprises 92 pediatric rheumatology centers and more than 300 clinician members all over North America.

TREAT was conducted at 15 CARRA sites. Both weekly treatment arms included subcutaneous methotrexate at 0.5 mg/kg. Group A also received placebo etanercept, folate, NSAIDs as necessary, and a placebo prednisone taper. Group B received, in addition to methotrexate, weekly subcutaneous injections of etanercept at 0.8 mg/kg; folate; NSAIDs as needed; and a 4-month prednisone taper that started at 0.5 mg/kg.

The study's primary end point is the rate of inactive disease at 6 months. Secondary end points include the rate of ACR Pedi 70 by 4 months; clinical remission on medication by 12 months; safety of the treatment, and MRI of the knee to show potential biologic changes associated with active and inactive disease.

The children's mean age was 11 years and their mean disease duration was just over 4 months. They had a mean of 22 active joints and a mean erythrocyte sedimentation rate of 37. Their mean Physician Global Assessment score was nearly 7. Most of the children (69%) were positive for antinuclear antibodies; 36% were rheumatoid factor positive.

The last subject visits have just occurred, and so full data analysis has not been completed. Dr. Wallace said that 77 patients finished out the pivotal first 6 months of the trial.

At that point, those children who achieved a state of inactive disease continued on their assigned treatment arm until the end of the trial, or until they had a flare.

Those who still had active disease at 6 months could opt for up to 6 months of open-label etanercept plus methotrexate and a prednisone taper, or up to two intra-articular injections while continuing on their blinded treatment. If they then experienced a flare, they discontinued the trial.

By the end of October, 67 patients (77%) had completed 12 months of the trial. Dr. Wallace and her coinvestigators expect to release the results in the first quarter of 2011.

Despite its relatively small size, she said, TREAT could be practice transforming. "Whatever the result, we plan to deploy this treatment as quickly as we can in clinical practice.

"That's actually the beauty of the CARRA network. We can, through our members, make a standard of care based on data. And that's what this study is all about: finding evidence.

"We must continue to look for evidence that supports the best way to treat JIA."

Although Amgen supplied the etanercept for TREAT, the study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health. Dr. Wallace has no financial disclosures with regard to the study. ■

Biologics May Pose Low Cancer Risk to Children With JIA

BY RICHARD HYER

EXPERT ANALYSIS FROM A CLINICAL SYMPOSIUM SPONSORED BY THE ACR

CHICAGO – The risk for cancer in children taking a biologic agent for management of juvenile idiopathic arthritis appears to be small, Dr. Daniel J. Lovell said.

Parents ask: "Is this therapy going to increase my child's risk for cancer?" said Dr. Lovell, a pediatric rheumatologist at the Cincinnati Children's Hospital Medical Center. To answer that question, one must determine:

1. the risk for cancer in the healthy pediatric population;
2. whether the cancer risk is increased in those who develop JIA;
3. whether the risk is increased by nonbiologic therapies for JIA; and
4. whether exposure to biologic therapy raises the risk.

We have an accurate answer to No. 1, but the accurate answer to No. 4 requires that we also have answers to Nos. 2 and 3, which we do not at this time, Dr. Lovell said.

The arthritis in children with persistent oligoarticular JIA can often be successfully treated only with intra-articular corticosteroids. However, the risk for uveitis is highest in this subtype of JIA. The uveitis of JIA is a chronic, nongranulomatous inflammation of the anterior uveal tract of the eye, and is asymptomatic in up to 80% of children. In 70% of the cases, both eyes will be involved within 1 year.

Although the proper initial treatment of JIA-associated uveitis is topical corticosteroid eye drops, Dr. Lovell suggested that if the need for ongoing topical therapy persists beyond 3 months, then there may need to be systemic anti-inflammatory treatment for the uveitis, even though this might alarm an ophthalmologist. Complications of topical or local corticosteroid therapy in the eyes include cataract, glaucoma, and band keratopathy.

With systemic JIA, which is thought by many to be an autoinflammatory disease rather than an autoimmune disease, the logical therapeutic choices are biologics that specifically block either interleukin (IL)-1 or IL-6, because they are the cytokines most directly involved in the disease's pathophysiology.

Some children with systemic JIA demonstrate a rapid and dramatic response to treatment with the IL-1 receptor antagonist anakinra, but some do not respond, and in some the benefit wanes with ongoing treatment (Ann. Rheum. Dis. 2008;67:302-8).

Results of treatment of systemic JIA with the IL-6 inhibitor tocilizumab have been very promising. Patients treated with this biologic often start to show

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Earlier Biologics Use in JIA Allows Less Steroids

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

BY MICHELE G. SULLIVAN

FROM THE CONGRESS OF THE EUROPEAN PEDIATRIC RHEUMATOLOGY SOCIETY

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." ■

VITALS

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. ■