Clinical Trials Unlikely

sJIA *from page 1*

ciates at the University of Alabama, Birmingham, wrote that rheumatologists are "generally hesitant to combine biologics" because of studies published in the mid-2000s, which found that treatment with a combination of anti-cytokine biologics did not result in improvements but increased the infection risk in adults with rheumatoid arthritis.

But because of the literature on the effectiveness of anakinra (Kineret) and abatacept (Orencia) separately in patients with systemic JIA, they have used these two agents as polytherapy "in selected patients," they said in the letter. Abatacept was added to the treatment regimens of the four female steroid-dependent patients, aged 6-12 years, with refractory systemic JIA, whose symptoms started at age 8 months to 10 years. The addition of abatacept appeared to be beneficial in all four patients, "allowing dose reduction of both anakinra and corticosteroids while improving arthritis joint count, as well as controlling systemic features of disease," Dr. Cron and his associates reported.

While pediatric rheumatologists do not routinely combine biologics, they may in refractory cases of sJIA.

DR. LEHMAN

For example, the joint count went from 25 to 8 affected joints after abatacept was started to address destructive arthritis in one patient, an 8-year-old with sJIA since age 2 who had responded well to corticosteroids, anakinra, and methotrexate. And after the first abatacept infusion, her erythrocyte sedimentation rate started to normalize after being elevated for 6 years.

Over 8-17 months after starting treatment with abatacept, none of the patients had any infusion reactions, significant infections, "or other notable adverse effects," they wrote, adding, "although the evidence is anecdotal at present, a controlled clinical trial to assess the efficacy and safety of this combination therapy in children with refractory sJIA is warranted." they wrote.

"Other than our small case series, there are no [published] data that I am aware of on mixing biologics to treat JIA," Dr. Cron said in an interview. He noted that this approach is controversial, partly because of some data in adults with RA, which found that combining interleukin-1 blockers with TNF blockers did not improve disease control but did result in an increase in infections – and because of the underlying concern over the increased risk of cancer with increased immunosuppression.

While blocking two different cytokines "may not be prudent, there may be a role for anti-cytokine plus costimulation blockade as in our case series," said Dr. Cron, professor of pediatrics and medicine and director of the division of pediatric rheumatology at Children's Hospital of Alabama and the University of Alabama. These four children were treated with anakinra, an interleukin-1 receptor antagonist, and abatacept, a selective costimulation modulator, because they had responded to anakinra "but needed more therapy to lower their corticosteroid burden, their degree of arthritis, and their risk of ongoing macrophage activation syndrome," he said, adding, "these children with systemic JIA are rather sick so the risk was calculated."

Since chronic steroid use is also associated with an increased risk of infections, the risk of infection may actually be lower with combined biologics compared with one biologic and corticosteroids. While biologics are expensive, steroid-associated side effects, including potential hospitalizations, "are not cheap," he noted.

Dr. Cron said that a controlled clinical trial of this approach is highly unlikely, though, because very few patients would meet eligibility and the potential risk of adverse events – and new drugs such as the interleukin-6 receptor inhibitor tocilizumab (Actemra) are expected to become available, which "may supplant the need for this particular combination."

Dr. Daniel J. Lovell, the Joseph E. Levinson Professor of Pediatrics at Children's Hospital Medical Center, Cincinnati, said in an interview that with the expanding number of biologics that have been tested in children, "there are other options to use besides combining more than one biologic … so the norm is still to use one biologic at a time." For example, abatacept has been found to be effective in about 30% of children who have previously failed treatment with a biologic. Among his concerns about the use of more than one biologic is that targeting the immune process in two different directions may contribute to additional risks.

But finding a treatment that is effective for the small number of patients with sJIA who are resistant to current therapies, including biologics, remains a challenge. "In those instances, you're forced to find something that works,' he said, adding, "fortunately, that's a very small percentage of the overall JIA patient" population.

Dr. Lovell agreed that it was unlikely that combination biologics would be studied in clinical trials "because the treatments we have are effective for the vast majority of children, and as more biologics are developed that work by different mechanisms, then we will have an increased number of ways to address the disease and, hopefully, find one that works for an individual child."

As for the four patients in the case series, Dr. Cron said that three remain on abatacept. The patient whose joint count decreased from 25 to 8 continues to do well on the combination of anakinra, steroids, methotrexate, and abatacept, which she has been taking for 2 years. If she misses a dose of abatacept, she does worse. Another patient is doing "relatively well" on anakinra, steroids, and abatacept, which she also has been taking for about 2 years, "and is also dependent on getting abatacept in a timely manner to feel well."

A third patient who was on anakinra, steroids, and abatacept is doing well on abatacept alone and may soon be tapered off abatacept, which is now being administered every 6 weeks, as opposed to every 4 weeks, as reported in the letter. Another patient continued to do well on steroids, methotrexate, abatacept, and anakinra, but developed an allergic reaction to abatacept, and is currently on a combination of steroids, methotrexate, anakinra, and rituximab, "but is not as well controlled," Dr. Cron said.

Dr. Lovell and Dr. Cron are both authors of the 2011 ACR JIA treatment guidelines.

Dr. Lehman is on the speakers bureaus for Abbott, Amgen, and Pfizer, and is a consultant to Biomarin, Cephalon, Genzyme, and Novartis. Dr. Cron served as a consultant to Genentech on the use of tocilizumab for sJIA. Dr. Lovell directs a research network that conducts clinical trials of new biologics. ■

Canakinumab Injections Lessened Systemic JIA Symptoms

BY JENNIE SMITH

FROM THE 18TH EUROPEAN PEDIATRIC RHEUMATOLOGY SOCIETY CONGRESS

BRUGES, BELGIUM – Canakinumab, an investigational interleukin-1b antibody also known as ACZ885, has been shown to lessen symptoms of systemic juvenile idiopathic arthritis more than placebo.

The medication, which has yet to be licensed in any country, is administered once a month by subcutaneous injection, instead of intravenous infusion.

The end point of the study was a reduction in disease activity by 30% according to American College of Rheumatology Pediatric criteria (ACR Pedi 30), which were modified for the study to include absence of fever, according to Dr. Nicolino Ruperto of the Pediatric Rheumatology International Trials Organization (PRINTO) and Istituto G Gaslini in Genoa, Italy.

Results from a phase III, manufacturer-sponsored, randomized controlled trial (n = 84) of canakinumab showed that a single injection of 4 mg/kg lessened symptoms by 30% or more in 83.7% of patients in the treatment arm (n = 43), compared with 9.8% in the placebo arm (n = 41), at 15 days (Pediatr. Rheum. 2011;9[Suppl 1]:O21).

Patients enrolled in the study were between 2 and 19 years old, with active disease but no macrophage activation syndrome.

For the study group as a whole, the mean disease duration was 3.4 years; mean CRP was 200.6 mg/L; mean number of active joints was 14.1; and mean prednisone equivalent therapy was 0.3 mg/kg per day.

Dr. Ruperto told the conference that the study participants had spiking intermittent fever at enrollment lasting at least 3 days, and they were allowed to continue on methotrexate or corticosteroids during the trial, but no biological agents besides the study medication.

A majority of patients in the treatment arm (67.4%) achieved ACR Pedi 50 improvement, compared with 4.9% for placebo, and about a third (32.6%) in the study arm saw improvement of ACR Pedi 100, compared with none for placebo. Both ACR Pedi 30 and ACR Pedi 50 responses with canakinumab remained significantly higher than with placebo at day 29.

Adverse events occurred in 55.8% of canakinumab and 39% of placebo patients. Dr. Ruperto said that the most frequently reported adverse events in the study group were upper respiratory problems and gastrointestinal complaints.

No patients discontinued the trial because of side effects; however, 6 patients in the treatment arm and 37 in the placebo arm discontinued because for lack of therapeutic effect.

Two deaths occurred in the study group after the completion of the trial, during the long-term follow-up period, Dr. Ruperto told the congress. Both deaths were due to macrophage activation syndrome; one complicated with sepsis and the other with pulmonary hypertension. ■

VITALS

Major Finding: Of 41 children given active treatment, 83.7% achieved at least an ACR Pedi 30 response, compared to 9.8% of 41 given placebo.

Data Source: A 15-day follow-up of 84 children with JIA who received either a single dose of canakinumab or placebo.

Disclosures: The study was funded by Novartis. Dr. Ruperto reported having no financial conflicts of interest. Two of his coinvestigators are Novartis shareholders and one is a Novartis employee.