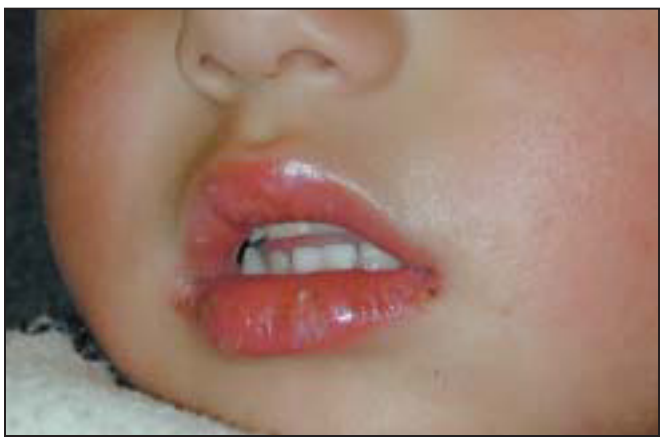
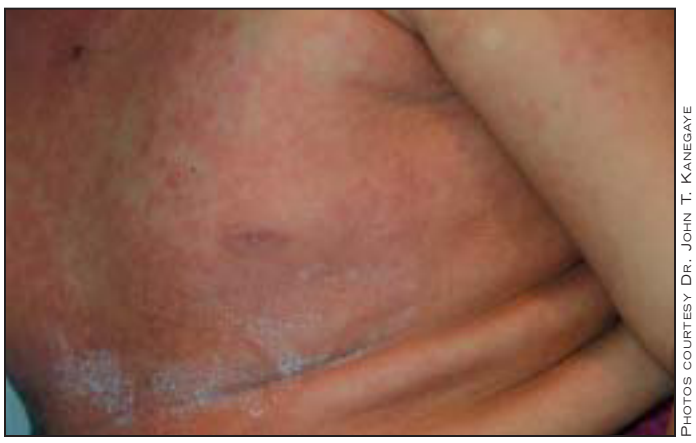
Anti-TNF Agent May Be Next Kawasaki Therapy

BY BRUCE JANCIN



This child's lips show the redness and cracking that are typical changes seen in children with Kawasaki disease.



This patient's rash on the trunk shows multiple small pustules overlaying a diffuse erythematous eruption.

PHOTOS COURTESY DR. JOHN T. KANEGAYE

VAIL, COLO. — The next frontier in Kawasaki disease therapy will involve determining the role of anti–tumor necrosis factor therapy.

There are sound theoretical reasons why an anti-TNF agent such as infliximab should be beneficial in patients with Kawasaki disease. Anecdotal reports have suggested that this is indeed the case when infliximab is given to patients with persistent fever after a first dose of intravenous immunoglobulin (IVIG).

Moreover, results of the first major randomized trial of infliximab vs. a second dose of IVIG in patients with persistent or recrudescent fever after an initial dose of IVIG showed infliximab to be safe, well tolerated, and effective.

However, the trend for better outcomes with infliximab fell far short of significance in the 24-patient trial, which was powered as a safety study, Dr. Marsha Anderson said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

"We'll need another study to say definitively if one treatment is better than the other," noted Dr. Anderson of the University of Colorado at Denver.

In the meantime, infliximab is gaining traction as an off-label alternative to a second dose of IVIG at centers of expertise in managing Kawasaki disease.

At the Children's Hospital, Denver, for example, a purified protein derivative (PPD) skin test or tuberculin skin test is now routinely started as soon as a child with possible Kawasaki disease comes through the door.

That's because a negative PPD is one of the prerequisites for infliximab. Because the PPD takes a couple of days to produce results, starting the test as soon as possible means that the results should come in around the time it will be apparent if a first infusion of IVIG at 2 g/kg isn't working, making it possible to give infliximab without delay.

While awaiting the PPD results, the clinician can check off the other prerequisites to infliximab therapy, including a chest x-ray, an assessment of immune status, and a history of possible recent tuberculosis exposures, she explained.

More than a decade ago, a multicenter U.S. study showed that 13% of patients with Kawasaki disease fail to respond to a single infusion of IVIG, and half of these nonresponders are resistant to a second dose. So alternative second-line agents are definitely needed.

In the first-ever randomized trial, 24 Kawasaki disease patients with persistent or recrudescent fever 2-7 days after initial treatment with IVIG at 2 g/kg, plus aspirin, were assigned to second-line therapy with either a second dose of IVIG or infliximab at 5 mg/kg given intravenously over 2 hours at six participating U.S. centers.

Eleven of 12 infliximab-treated patients became afebrile, as did 8 of 12 IVIG-treated patients. Per protocol, patients with persistent fever after a second dose of IVIG were given infliximab, resulting in two of the four becoming afebrile; the two nonresponders to third-line infliximab were placed on corticosteroids and became afebrile (J. Pediatr. 2008;153:833-8).

All told, only 3 of 16 patients (19%) who received infliximab as second- or third-line therapy after not responding to first-line IVIG required additional therapy, compared with 4 of 13 (31%) who received IVIG as second- or third-line therapy.

Even before this clinical trial, anti-TNF therapy was generating interest among Kawasaki disease researchers because serum levels of the inflammatory cytokine are known to be elevated in the setting of acute Kawasaki disease, and they are highest in patients who develop coronary artery defects.

Findings from research on animal models of Kawasaki disease suggested a causal relationship between TNF and coronary pathology.

The initial randomized trial was kept small because of safety concerns. Infliximab is known to increase the risk of serious infections, including tuberculosis and opportunistic infections. It also has adverse effects in patients with moderate to severe heart failure.

But infliximab proved safe and well tolerated in the randomized trial, which excluded patients with immunosuppressive conditions, fungal infections, or recent exposure to or a history of tuberculosis.

Until more definitive data on infliximab as second-line therapy become available, Dr. Anderson recommended the following approach in patients with continued fever 36 hours after a first dose of IVIG: First, rethink the diagnosis, carefully revisiting the history and physical exam.

Then consider a rheumatology consultation to rule out juvenile rheumatoid arthritis and other rheumatologic diseases.

Finally, recommend that the patient be seen at a medical center with extensive Kawasaki disease experience, because at present, she said, the optimal treatment after a first unsuccessful dose of IVIG is "uncharted territory." ■

Link Found Between Bowel Disease and Etanercept in JIA

BY MITCHEL L. ZOLER

COPENHAGEN — Children with juvenile idiopathic arthritis who received etanercept had a surprisingly high rate of inflammatory bowel disease in a review of 1,515 patients.

The incidence of inflammatory bowel disease (IBD) in these patients, drawn from five European registries, was roughly 500 IBD cases per 100,000 patient-years of follow-up, 100-fold higher than in the general pediatric population, Dr. Nico M. Wulffraat said at the annual European Congress of Rheumatology.

"The incidence seems very high. We need more data to confirm this early finding," said Dr. Wulffraat of the University Medical Center Utrecht (the Netherlands).

It's possible that IBD is an adverse effect of etanercept (Enbrel) treatment, or perhaps IBD is an intestinal complication of juvenile idiopathic arthritis (JIA), Dr. Wulffraat said.

A third possibility is that JIA is an extraintestinal manifestation of IBD. He said this explanation was unlikely because JIA preceded the appearance of IBD by several years; in one case, the interval between diagnosis of JIA and onset of IBD was 12 years.

'We need more data to confirm this early finding.' The pathology leaves little doubt that this was IBD, and not a transient effect on the colonic mucosa.

The study used data on JIA patients that were collected by registries in Denmark, Finland, Germany, Italy, and the Netherlands from 1999 through 2007.

The 1,515 JIA patients listed with the registries as being treated with etanercept were followed for 2,900 patient-years, during which time 18 patients developed IBD.

Of these 18 patients, 16 had their diagnosis confirmed by colonoscopy and pathology studies. Clinical information was available for 12 of these patients.

The review excluded JIA patients who were diagnosed with IBD before they began receiving etanercept.

"The pathology leaves little doubt that this was IBD, and not a transient effect on the colonic mucosa," Dr. Wulffraat said.

When IBD was diagnosed, patients switched from etanercept to a different tumor necrosis factor inhibitor, such as adalimumab (Humira) or infliximab (Remicade), or to a different type of drug such as sulfasalazine. Adalimumab and etanercept both have Food and Drug Administration–approved indications for treating JIA; infliximab does not.

The high incidence rate contrasts with results from a study published in 2001 that found a population-based IBD incidence of 5.2 per 100,000 person-years in children younger than 16 years from the United Kingdom and the Republic of Ireland who were studied prospectively in 1998-1999 (Lancet 2001;357:1093-4).

Analysis of the 12 patients who had clinical data showed no single, unique presentation of IBD, although all patients had abdominal pain and diarrhea. They were also all negative for HLA-B27, and none had a family history of IBD.

All three IBD types appeared: In all, 75% had Crohn's disease, with the rest developing either ulcerative colitis or indeterminate colitis.

The average time between JIA onset and the diagnosis of IBD was nearly 8 years. The time between the start of etanercept treatment and IBD appearance ranged from 9 days to 5 years.

Dr. Wulffraat said that he and his associates had no financial disclosures. ■