Anti-TNF Agent May Be Next Kawasaki Therapy

BY BRUCE JANCIN

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

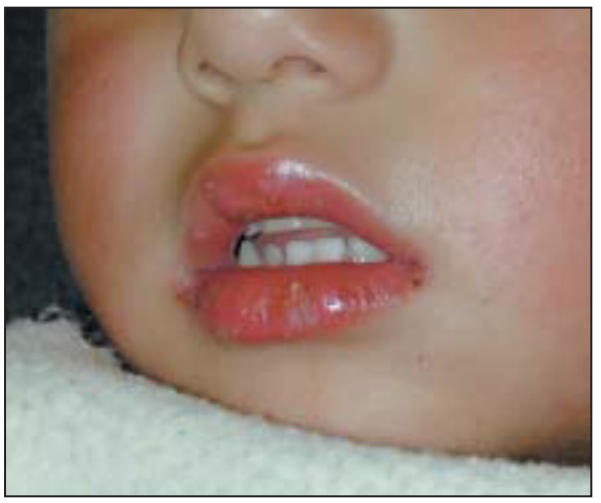
While awaiting the PPD results, the clinician can check off the other prerequisites to infliximab therapy, including a chest x-ray, an assessment of immune status, and a history of possible recent tuberculosis exposures, she explained.

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.

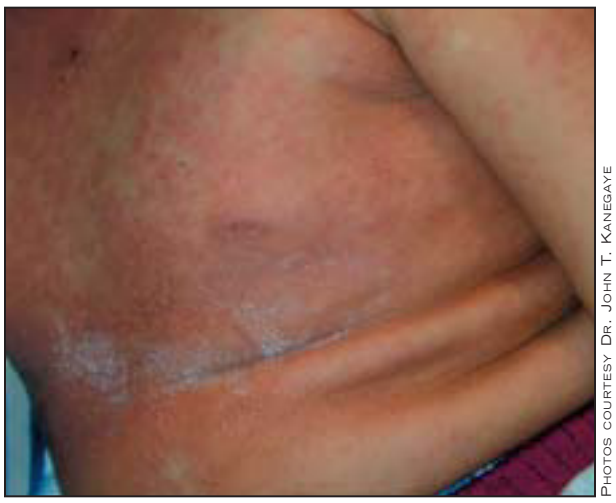
So alternative second-line agents are definitely needed.

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).



This child's lips show the redness and cracking typically seen in children with Kawasaki disease.



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

PHOTOS COURTESY DR. JOHN T. KANEGAYE

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-alpha 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.

Animal models of Kawasaki disease suggested a causal relationship between TNF-alpha 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." ■

Shock May Dominate Presentation of Kawasaki Disease

BY BRUCE JANCIN

VAIL, Colo. — Patients with severe Kawasaki disease can present in shock—and that's something not widely appreciated in emergency departments and ICUs.

This was the thrust of two recent studies of severe Kawasaki disease conducted in Denver and San Diego.

In both studies, patients with Kawasaki disease who were ill enough to be admitted to the ICU were less likely to have an admitting diagnosis of Kawasaki disease than were less severely ill patients admitted to the wards, Dr. Marsha Anderson said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

Severe Kawasaki disease presenting with shock was often mistaken for septic or toxic shock.

As a result, ICU patients with Kawasaki disease were treated with intravenous immunoglobulin (IVIG)—the first-line therapy—a median of 2 days later than were Kawasaki disease patients on the general wards.

"I think we have to consider Kawasaki disease in our differential diagnosis in patients who present in shock," said Dr. Anderson of the University of Colorado, Denver.

In the Denver study, on which she was a coauthor, patients with severe Kawasaki disease as defined by ICU admission constituted 3.3% of a consecutive series of 423 Kawasaki disease patients (Pediatrics 2008;122:e786-90).

Severe Kawasaki often was mistaken for septic or toxic shock, which delayed the correct treatment.

DR. ANDERSON

In San Diego, severe Kawasaki disease was defined as systolic hypotension unresponsive to fluids, with resultant ICU admission of the patients, Dr. Anderson reported.

Severely affected patients accounted for 7% of 187 consecutive Kawasaki disease patients (Pediatrics 2009;123:e783-9).

In both studies, patients with severe disease were significantly more likely to be female, with low platelet counts and high levels of C-reactive protein and band counts, the physician said.

In San Diego, patients with severe Kawasaki disease had significantly lower hemoglobin levels than did less-ill patients; however, in Denver this wasn't the case.

On the other hand, in Denver (but not San Diego) severely affected patients had lower serum albumin levels than did those on the wards, Dr. Anderson said.

In both studies, patients with severe Kawasaki disease were more likely to have IVIG resistance and to require a second dose of IVIG or a second-line therapy.

This was the case for 64% of ICU patients in Denver, compared with 5% on the wards.

Similarly, 46% of severely affected patients in San Diego were IVIG resistant, as were 18% of those on the wards, according to study results.

Coronary artery abnormalities, mitral regurgitation, and left ventricular systolic dysfunction were significantly more common in patients with severe Kawasaki disease than in controls in the San Diego study.

In Denver, there was a strong trend for more coronary artery abnormalities in the ICU patients, but it didn't quite achieve statistical significance, Dr. Anderson reported. ■