Consider Misdiagnosis in Refractory Kawasaki

BY AMY ROTHMAN SCHONFELD

NEW YORK — Although the majority of children with Kawasaki disease responds well to intravenous immunoglobulin therapy, 10%-15% of these patients are refractory to the first course of IVIG, and 50% of those continue to manifest fever after the second IVIG dose.

At a meeting sponsored by New York University, Dr. Philip J. Kahn described current treatment options for the child with refractory Kawasaki disease.

"Kawasaki disease is the No. 1 cause of acquired heart disease in children in developed countries. In 2000, over 4,000 hospitalizations in the United States were attributed to Kawasaki disease," said Dr. Kahn, a pediatric rheumatologist at the NYU Langone Medical Center. "In the United States, all patients diagnosed with Kawasaki disease are treated, primarily because the children appear very ill, and they face a 20% risk of aneurysm if left untreated."

Fortunately, IVIG reduces the risk of aneurysm to less than 5%, according to Dr. Kahn.

He recommended 2 g/kg over 8-12 hours, although the dose may be divided over 2 days.

Clinicians may also follow a protocol of 400 mg/kg per day for 4 days, especially when myocarditis is present.

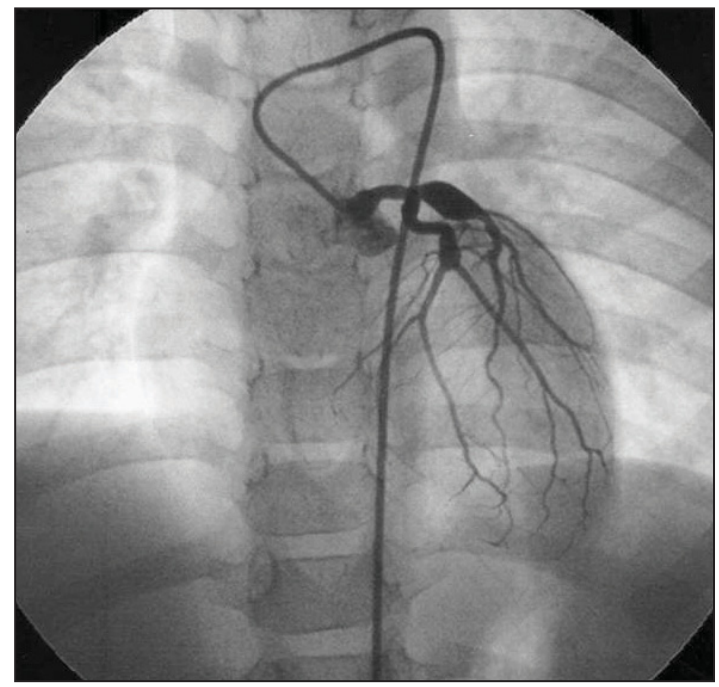
Aspirin does not appear to lower the risk of aneurysm, said Dr. Kahn.

Because of the risk of aneurysm, failure to respond to IVIG is a serious concern. Patients who continue to have recrudescent or persistent fever 48 hours after the first IVIG dose should receive a second IVIG dose, according to Dr. Kahn.

If fever persists after the second dose, rethink your diagnosis, said Dr. Kahn.

Consideration should be given to other possible etiologies, such as infection (for example, streptococcus, staphylococcus, Epstein-Barr virus, adenovirus, measles, Rocky Mountain spotted fever, or leptospirosis), drug reaction (for example, to antibiotics, anticonvulsants, or antifungals), autoimmune disease (such as systemic juvenile idiopathic arthritis or polyarteritis nodosa), or acrodynia (for example, a mercury hypersensitivity reaction).

If the child is still thought to have Kawasaki disease, other treatment options are available. Steroids can shorten the duration of fever and hospital stays.



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Giant fusiform aneurysms of the left coronary artery and left anterior descending artery are visible in a child with Kawasaki.

A recent report found fewer coronary lesions in high-risk Kawasaki disease patients who were given pulse methylprednisolone with IVIG than in those given IVIG alone (Eur. J. Pediatr. 2009;168:181-5.)

Because tumor necrosis factor–alpha is elevated during the acute phase of Kawasaki disease and high levels are found in patients who develop aneurysms, studies have investigated the use of infliximab, an anti-TNF-alpha agent.

Indeed, fever ceased within 24 hours in 11 of 12 Kawasaki disease patients who were refractory to IVIG and were treated with infliximab (5 mg/kg), and the treatment was found to be safe and well tolerated (J. Pediatr. 2008;153:833-8.)

Other medications that have been used to treat IVIG-refractory Kawasaki disease include the protease inhibitor ulinastatin (combined with aspirin), the platelet GPIIb/IIIa inhibitor abciximab, and pentoxifylline, which acts by inhibiting the synthesis of TNF.

Immunosuppressants have sometimes been used to treat the vasculitis that is associated with Kawasaki disease, and in Japan some patients have undergone plasmapheresis.

Interestingly, the incidence of Kawasaki disease in children who are aged younger than 5 years is much higher in Japan (112 per 100,000) than in the United States, where it is higher in children of Asian descent (32.5 per 100,000) than in children of non-Asian descent (9.1 per 100,000), according to Dr. Kahn. Unlike the United States, where all children diagnosed with Kawasaki disease receive treatment, in Japan the clinicians utilize scoring systems to identify patients who are at high risk for aneurysm development, and they treat only those selected patients.

Some medications discussed in this review are not approved for use in Kawasaki disease. ■

Disclosures: *Dr. Kahn had no financial disclosures to report.*

Drug Combo Offers Long-Term Benefit in Pediatric SLE

BY AMY ROTHMAN SCHONFELD

NEW YORK — A combination of rituximab and cyclophosphamide offers significant long-term benefits to children with systemic lupus erythematosus, according to Dr. Thomas J.A. Lehman, who presented the results at a meeting sponsored by New York University.

"This combination is extremely effective, much more than either drug alone," in the treatment of systemic lupus erythematosus (SLE), said Dr. Lehman, chief of the division of pediatric rheumatology at the Hospital for Special Surgery and professor of clinical pediatrics at Cornell University, both in New York.

'This combination is extremely effective, much more than either drug alone' in the treatment of pediatric SLE.

DR. LEHMAN

SLE Disease Activity Index (SLEDAI) scores dropped from a mean of 9.79 before treatment to 1.43 after 12 months of treatment ($P = .0009$) for the group of 14 patients. C3 complement levels significantly increased ($P = .0023$), whereas the sedimentation rate fell ($P = .0134$). No changes were seen in hemoglobin levels or white blood cell levels.

Another marker of success was that patients were able to reduce their need for daily prednisone therapy. The mean daily dose fell by about two-thirds, from 33.3 mg/day to 11.96 mg/day after 12 months ($P = .0004$).

The protocol consists of a doublet of rituximab (750 mg/m^2) on day 0, followed by cyclophosphamide (750 mg/m^2) on day 1.

The doublet is repeated on days 14 and 15, and then the 2-week schedule is repeated at 6 and 18 months. These drugs have not been approved for the treatment of SLE in children.

Patients receive high-dose intravenous corticosteroids and intravenous diphenhydramine prior to rituximab infusion. Over the course of 3 years, most patients received at least three courses of therapy.

The group consisted of 11 females and 3 males who were about 12 years old when they were diagnosed with SLE.

Treatment with this protocol generally began 2 years after diagnosis, when the children were more than 14 years old. Five children were Asian, four children were Hispanic, three were white, and two were black. Six of the children had received prior cyclophosphamide monotherapy.

No serious adverse events were reported. Four patients had adverse events, including one each of urinary tract infection, herpes zoster, cellulitis, and lymphadenitis. All events resolved with treatment.

Four children were followed for at least 18 months after being diagnosed with biopsy-confirmed diffuse proliferative glomerular nephritis.

After undergoing the rituximab/cyclophosphamide treatment, all had normal complement levels and no indication of hematuria, proteinuria, or other urinary abnormalities and two of the four had negative antinuclear antibody (ANA) testing more than 1 year after treatment. "All these patients believe that they are cured," says Dr. Lehman.

Dr. Lehman said that he is generally reluctant to discontinue prednisone, so all patients continue to receive approximately 10 mg/day of the drug. He reported that none of the children on prednisone showed signs of steroid toxicity such as depression, hirsutism, or Cushing's syndrome.

This protocol may not be appropriate for all children with SLE, according to Dr. Lehman. Not all children with SLE require aggressive therapy.

Data from studies done in the 1970s demonstrate that 30% of children with SLE do well with long-term, low-dose prednisone, whereas 30% develop steroid complications and 40% die or require dialysis, he said.

Aggressive therapy should be considered for children with persistent anemia (hemoglobin less than 10 g), persistent diastolic hypertension, pulmonary hypertension, or persistent hematuria (greater than 20 RBC/high-power field), or who have had recurrent emergency admissions for any reason.

The prevalence of SLE among children is estimated to be between 5 and 10 cases per 100,000 children. An estimated 8% of cases develop before children are 14 years of age, and about 15% develop before age 16. ■

Disclosures: *The study received no commercial funding. Dr. Lehman is on the speakers bureau of Abbott Laboratories, Amgen Inc., and Pfizer Inc.*