Efficacy of infliximab in long-lasting refractory Kawasaki disease

Sirs,

A 2.5 year old boy with high grade spiking fever, skin rash, conjunctivitis, mucositis and cervical lymphadenopathy, was diagnosed as having KD and, on day 5 of fever, treated with IVIG (2 gr/kg) and aspirin. Due to the persistence of fever, he was retreated with Intravenous Immunoglobulin IVIG (day 8). Because of the unremitting disease and evidence of pericardial effusion, three pulses of intravenous Methylprednisolone (IVMP 30 mg/kg/day) were successively administered. He initially became afebrile but malaise and high grade fever recurred (day 21). Echocardiogram showed two aneurysms of the proximal left anterior descending (LAD: 6 mm) and right coronary artery (RCA: 4,5 mm).

On admission to our Unit on day 24, laboratory exams showed ESR 91 mm/hr, CRP 9.6 mg/dl, WBC 21600/mm^3, Hb 8.8 g/dL, PLT 736,000/mm^3 and serum TNF-α 18 ng/l (n.v. 0 - 6). He was retreated with two more IVMP pulses and then started on prednisone (1 mg/kg/day po) Unfortunately, echocardiography showed a new aneurysm at the left circumflex artery (LCA: 8 mm), and warfarin was added to aspirin. After a brief remission he relapsed. Two more IVMP pulses were infused and, on day 49, oral Cyclophosphamide (CPM 2 mg/kg/-day) was started. Nevertheless, he had an episode of acute myocardial ischemia documented by EKG, high serum troponin I levels and myocardial scintiscan. Angiography confirmed the presence of multiple saccular aneurysms of the RCA and LCA, LAD and posterior descending (LPD) coronary arteries (Fig. 1).

On day 71, we administered infliximab (5 mg/kg iv) and the patient's clinical conditions dramatically improved, with no further fever. The inflammatory markers normalized and the immunosuppressive treatment was tapered down and stopped in one month. At the last follow-up visit, eight months after the disease onset, the patient was in good general condition on low dose aspirin and warfarin and the echocardiogram showed a significant reduction of the CAA (RCA 3.5 mm, LCA 3.5 mm, LAD 4.2mm).

This case report underlines the difficulty in controlling the inflammatory process in some KD patients. While the efficacy of IVIG to control the acute phase of the disease and to decrease the incidence of CAA is well proved, 11 - 40% of KD patients fails to respond to the first IVIG treatment (1-6). In this case some studies suggest administering one or more extra doses of IVIG, and this has become the current practice in many centres. Unfortunately, as in our patient, this approach is not effective in 31-49% of the patients (1-6).

As for other vasculitides, alternative treatments such as corticosteroids (CS) (4, 5,7), cyclosporine A (CyA), plasmapheresis and CPM have been tried for the very refractory KD patients (rKD) but the results were not always positive (4, 8).

In our patient, the persistence of active disease after 71 days of illness, two IVIG treatments, seven IVMP pulses, oral Cs and CPM and led us to try infliximab (Remicade®, Schering), a humanized monoclonal antibody against TNF-α, as an ultimate experimental choice. This approach was effective, well tolerated and allowed us to stop the concurrent immunosuppressive drugs and to arrest CAA progression.

The rationale for using this agent in KD is based on the presence of high serum concentrations of TNF-α during the acute and subacute phase of the disease, especially in patients who develop CAA (9). At the time we treated our patient, just one case of infliximab treatment of KD was reported (10). Later on, a series of 17 more cases was reported (11). From the results obtained in these anecdotal cases and our experience, infliximab treatment seems to be very effective even in patients with long lasting disease with an overall 84% response rate. It is reasonable to speculate what the outcome could be if this agent were utilized earlier, as the first choice, in rKD patients.

A multicenter clinical trial, comparing infliximab with IVIG re-treatment, will better define the role of anti-TNF-α therapy in rKD and, probably, confirm the preliminary results obtained in these anecdotal patients.

F. ZULIAN, *MD*
G. ZANON, *MD*
G. MARTINI, *MD, PhD*
G. MESCOLI[1],
O. MILANESI, *MD*

Department of Pediatrics, University of Padua, Italy; [1]Ospedale Maggiore, Bologna, Italy.

Address correspondence and reprint requests to: Francesco Zulian, MD, Dipartimento di Pediatria, Università di Padova, Via Giustiniani 3, 35128 Padova, Italy.
E-mail: zulian@pediatria.unipd.it

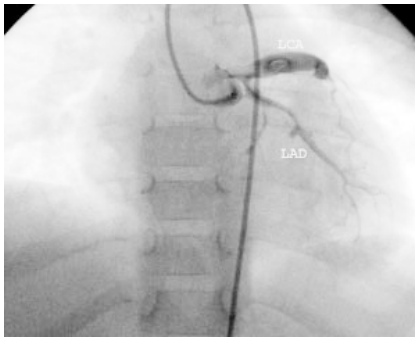

Fig.1 Selective left coronary angiography. A huge fusiform aneurysm of the left circumflex artery (LCA) measuring 8 mm in diameter is evident. The proximal left anterior descending (LAD) artery ia also dilated.

References

1. HAN RK, SILVERMAN ED, NEWMAN A, MC CRINDELE BW: Management and outcome of persistent or recurrent fever after initial intravenous gamma globulin therapy in acute Kawasaki disease. *Arch Pediatr Adolesc Med* 2000;154: 694-9.
2. FALCINI F, CIMAZ R, CALABRI GB *et al.*:Kawasaki disease in northern Italy: a multicenter retrospective study of 250 patients. *Clin Exp Rheumatol* 2002; 20: 421-6
3. BURNS JC, CAPPARELLI EV, BROWN JA, NEWBURGER JW, GLOBE MP: Intravenous gammaglobulin treatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. *Pediatr Infect Dis J* 1998; 17: 1144-8.
4. WALLACE CA, FRENCH JW, KAHN SJ, SHERRY DD: Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics* 2000;105: E78.
5. HASHINO K, ISHII M, IEMURA M, AKAGI T, KATO H: Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *Pediatr Int* 2001; 43: 211-7.
6. DURONGPISITKUL K, SOONGSWANG J, LAOHAPRASITIPORN D, NANA A, PRANCHUABMOBH C, KANGKAGATE C: Immunoglobulin failure and re-treatment in Kawasaki disease. *Pediatr Cardiol* 2003;24:145-8.
7. WRIGHT DA, NEWBURGER JW, BAKER A, SUNDEL RP: Treatment of immunoglobulin resistant Kawasaki disease with pulsed doses of corticosteroids. *J Pediatr* 1996;123:146-9.
8. FREEMAN AF, SHULMAN ST: Refractory Kawasaki disease. *Pediatr Infect Dis J* 2004; 23: 463-4.
9. MATSUBARA T, FURUKAWA S, YABUTA K: Serum levels of tumor necrosis factor, interleukin-2 receptor and interferon-γ in Kawasaki disease involved coronary-artery lesions. *Clin Immunol Immunopathol* 1990; 56: 29-36.
10. WEISS JE, EBERHARD BE, CHOWDHURY D, GOTTLIEB BS: Infliximab as a novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004; 31: 808-10.
11. BURNS JC, MASON WH, HAUGER BS *et al.*: Infliximab treatment for refractory Kawasaki Syndrome. *J Pediatr* 2005 146: 662-7.