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 18 ng/l (n.v. 0 - 6). He was retreated with two more IVMP pulses and then started on prednisone (1 mg/kg/day). 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 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 4.2 mm).

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 fail 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.

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References

Letters to the Editor

Fig.1 Selective left coronary angiography. A huge fusiform aneurysm of the left circumflex artery (LCA) measuring 3.5 mm in diameter is evident. The proximal left anterior descending (LAD) artery is also dilated.