Takayasu Arteritis in Children: Preliminary Experience with Cyclophosphamide Induction and Corticosteroids Followed by Methotrexate

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Objective To review the results of our treatment protocol in the last 7 years.

Study design Six patients (4 girls, 2 boys) with an age range of 12 to 17 years were diagnosed with Takayasu arteritis (TA) during this period. Patients were allocated to receive (1) oral steroids and methotrexate (MTX) (12.5 mg/m^2/week) if they had disease limited to one side of the diaphragm only without pulmonary disease involvement (two patients); and (2) oral steroids and oral cyclophosphamide (CYC) (maximum total dose 150 mg/kg) followed by oral MTX for maintenance as above if the disease was more widespread (four patients).

Results One patient died of pulmonary vasculitis during the first month of therapy. The remaining three patients with involvement of both the thoracic and abdominal aorta and branches received the second protocol for 12 to 18 months. All entered remission. Aortic bypass, aortorenal bypass, balloon dilatation, and unilateral nephrectomy were performed in these patients.

Conclusions The presented single-center experience suggests that CYC induction and corticosteroids followed by MTX is an effective and safe treatment for childhood TA. *(J Pediatr 2007;150:72-6)*

Takayasu arteritis (TA) is a chronic, idiopathic, granulomatous vasculitis of the large arteries. It primarily involves the aorta, its proximal branches, and occasionally the pulmonary arteries, resulting in luminal stenosis, occlusion, or aneurysms. The peak period of onset is during the third decade of life.[1] Clinical manifestations are myalgia, arthralgia, fever, weight loss, and symptoms secondary to ischemia of organs supplied by stenotic vessels. The ischemic symptoms include stroke, visual aberration, angina, and renovascular hypertension. TA can follow a number of courses. The monophasic course is limited to 20% of cases.[1] Progressive or relapsing/remitting cases require medical therapies and/or revascularization interventions. Corticosteroids, methotrexate (MTX), azathioprine, mycophenolate mofetil, and cyclophosphamide (CYC) have all been used in the treatment of TA.[2] A high (50%) relapse rate is observed in adults with corticosteroids.[1,2] Despite the fact that it is the third most common vasculitis in children, there is no consensus on follow-up and no A-level evidence-based data on the treatment of childhood patients.[3]

We reviewed our experience with a combination of prednisolone and CYC for induction, followed by MTX for maintenance treatment in the last 7 years. We report the clinical characteristics, angiographic findings, immunosuppressive therapy, surgical treatment, and outcomes of six pediatric cases.

METHODS

Diagnosis

From 1998 to 2005 we have followed six patients (4 female, 2 male; all Turkish) with TA in our unit. All patients met the criteria of the American College of Rheumatology for TA and the recently introduced pediatric criteria.[4,5] Two were siblings (patients 1 and 5).

APRs	Acute phase reactants	MTX	Methotrexate
CYC	Cyclophosphamide	TA	Takayasu arteritis
MR	Magnetic resonance	TNF	Tumor necrosis factor

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Submitted for publication Mar 14, 2006; last revision received Jun 1, 2006; accepted Oct 12, 2006.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2006.10.059

Features at Pesentation

Clinical features of the patients are summarized in the Table. The mean age at the onset the first symptom(s) was 12 years (10–15 years). Headache was present in two patients; abdominal pain and arthralgia/arthritis was present in two and three patients, respectively.

Patient 2 presented with fatigue, malaise, and thoracic and abdominal pain. She had mild anemia and elevated acute phase reactants (APRs). She was put on mesalazine treatment by a gastroenterologist who diagnosed her as having a mild form of Crohn's disease. She was subsequently diagnosed as having TA by angiography when she later presented with migraine and hypertension. Similarly the third patient was also initially diagnosed as having antral gastritis. Two patients (patients 4 and 5) were initially diagnosed as having familial Mediterranean fever because they had features of serositis and inflammation without hypertension. The former presented at 16.5 years of age, with arthritis, chest, hip, and shoulder pain, hematuria, proteinuria, and elevated APRs; the latter presented at the age 12, with arthralgia and elevated APRs. Their complaints subsided totally with treatment with colchicine. Mutation analysis of MEFV gene revealed no mutation in the former patient, and the latter patient was heterozygous (E148Q/-). This resulted in the delay of the diagnosis of TA for 2 and 4 years, respectively.

Five patients had involvement of both the thoracic and abdominal aorta. Renal arteries were involved in five patients (bilateral in four patients); pulmonary arteries were involved only in one patient.

Treatment Potocol

Patients were allocated to receive (1) oral steroids and MTX (12.5mg/m^2/week) if they had disease limited to one side of the diaphragm only, and without pulmonary disease; and (2) oral steroids and oral CYC (1.5–1.7 mg/kg/day) for a total of 12 weeks (maximum total dose 150 mg/kg) followed by oral MTX as above if the disease was more widespread (four patients). Pulse methylprednisolone (bolus) was given for 3 consecutive days in the presence of life-threatening disease as judged by the primary physician. Oral prednisone was started at 1 mg/kg/day for 4 weeks to be tapered to a maintenance dosage of 5 to 10 mg/day by 12 weeks if the APRs were normal. All patients are still on low-dose alternate-day corticosteroids.

RESULTS

Four patients were eligible for treatment with the second approach (prednisolone, CYC, and MTX). One patient (patient 2) died of pulmonary vasculitis during the first month of therapy. The remaining three (patients 1, 3, and 4), with involvement of both the thoracic and abdominal aorta and branches, received steroids with oral CYC for 12 weeks followed by weekly MTX for 12 to 18 months. Two patients (patients 5 and 6) had vasculitis of the abdominal aorta and renal artery, and they received steroid plus MTX. All entered remission.

Angiographic control: at follow-up, all patients underwent magnetic resonance (MR) angiography on a yearly basis and when they had clinical symptoms or increased APRs. Relapse was defined as new stenotic lesions or thickening of the vessel wall on MR angiography.

Aortic bypasses were performed in two patients, whereas aortorenal bypass was performed in two other patients (three renal units). In one patient the contralateral renal artery stenosis was managed by a balloon dilatation, and unilateral nephrectomy had to be performed in another patient.[6] One patient (patient 3) had a relapse at 1 year with re-stenosis of the graft.

There were no serious side effects, and all patients were symptom-free at their last visits. No patient suffered from cystitis during CYC therapy, or from bone marrow depression or hepatotoxicity secondary to MTX. In one patient (patient 2) MTX had to be switched to mycophenolic acid because of mild hair loss and malaise.

DISCUSSION

TA is one of the interesting vasculitides, with its age at onset, distribution of vascular involvement, and the type of vessel destruction it displays. It is not a self-limited vasculitis such as Henoch Schönlein purpura or Kawasaki disease; thus, it requires prolonged treatment. The high relapse rate also necessitates extended treatment. Serial angiographic studies have shown that new lesions can be found in 61% of patients even when the disease is thought to be in remission.[1]

The delay in diagnosis in our patients ranged from 1 month to 5.5 years; it was 4 and 5.5 years in two cases. Vanoli et al have suggested that age at onset less than 15 years was associated with a higher probability of a delay in diagnosis.[7] This fact suggests that pediatricians need to be better aware of this disease.

Long duration of immunosuppression is a problem in children. Corticosteroids have been the main treatment, however 60% of patients experience toxicity from these drugs.[8] Thus, we need to find corticosteroid-sparing agents, and to taper corticosteroids, transitioning to agents of low toxicity for maintenance.

CYC has been a frequently chosen immunosuppressive drug in other vasculitides. Most authors recommend using CYC only for patients with severe TA refractory to other immunosuppressive drugs because of concerns about toxicity.[1,2] However, when data from large studies were complied, a cumulative dose of up to 200 to 250 mg/kg was considered safe for most children in terms of gonadal toxicity.[9] Thus, we decided to employ this drug at the start at a dose of up to 150 mg/kg maximum total dose if the patient had widespread disease and high APRs. We suggest that the results of this small group favor the short use of this drug. Larger controlled studies with long follow-up will clarify whether these patients were overtreated.

Wegener granulomatosis is another chronic vasculitis with very high relapse rates. Studies have shown that although CYC is required for severe patients, patients without renal