Clarithromycin reduces prednisolone requirements for treatment of intractable Takayasu arteritis

Sirs,

Takayasu arteritis is a chronic inflammatory arteritis with infiltration of lymphocytes and occasional giant cells in three vessel layers that lead to wall thickening and fibrosis with destruction of elastic tissue in the large vessels (1). Steroids, the mainstay of treatment, are primarily used for the arteritis but approximately half of patients so treated are responsive. While cytotoxic agents such as azathioprine, methotrexate and cyclophosphamide are used for unresponsive patients or in combination with steroids for intractable patients, difficulty persists in inducing remission and 25% of patients with active disease remain unresponsive. In this report, we discuss clarithromycin as a novel strategy for the treatment of Takayasu arteritis.

A 32-year-old woman had been suffering from fever of unknown origin since 1992. Complaints of middle-upper thoracic and back pain, high-grade fever up to 38ºC with leucocytosis, and increasing C-reactive protein were observed when the disease was active. She was diagnosed with adult Still's disease by the first physician seen and had been treated with prednisolone at an initial dose of 30 mg/day since 1997. The physician tried reducing the prednisolone, but could not reduce it below 17.5 mg/day and the disease recurred several times. Although finally diagnosed as having Takayasu's arteritis, the fever did not resolve and the patient came to our hospital in April 2002. Her general status was one of wasting disease with weight loss (BMI 16.5 kg/ cm^2). Continuous bruit was audible bilaterally at the neck and differences in systolic blood pressure between the arms presented on physical examination.

Laboratory studies showed leucocytosis and C-reactive protein 146 mg/l. The results of other blood tests for autoimmune disease (antinuclear antibodies (Ab), anti-DNAAb, anti-RNPAb, anti-Sm Ab, anti-cardiolipin-beta 2 glucoprotein 1 complex Ab, anti-cardiolipin Ab (IgG) and anti-neutrophil cytoplasmic Ab) were all negative. A renal/liver function test and a clotting screen including thrombomodulin were within normal limits. MRA examination showed inflammatory lesions of the arteries located at branches from the aortic arch, including the bilateral carotid and subclavian arteries and the aortic arch proper (Fig.1A). The thoracic descending aorta and abdominal aorta appeared to be intact, suggesting that the angiographic and clinical classification was Type I and Group I, respectively (2, 3).

We chose full-dose prednisolone (45 mg/day) therapy principally because the disease had progressed to intractable inflammation due to insufficient treatment (Fig. 1B). After one month we began reducing the dose. Beneficial effects were observed down to a dose of 25 mg/day, but additional reductions caused, as before, recurrence of the disease. Meanwhile immunosuppressive therapies (azathioprine 50 mg per day or methotrexate 7.5 mg per week) were tried for the purpose of converging the activities and reducing the daily dose of prednisolone, but abandoned due to the appearance of increased C-reactive protein levels and skin rash. Ultimately, we managed to reduce the maintenance prednisolone dose to < 10 mg/day by combining it with clarithromycin.

Takayasu's arteritis is considered to be an autoimmune disease, while viral and bacterial infections have also been considered to play a role in the pathogenesis of large-vessel arteritis (4-6). We suspected that our case might have been mediated by microparasites including *Chlamydia pneumoniae*, due to the long course of the disease, the ineffectiveness of low-dose prednisolone and the lack of response to immunosuppressive agents. Given the possibility of infection, we added clarithromycin which has antibacterial, anti-inflammatory and immunosuppressive effects (7). Leucocytosis and the elevated C-reactive protein improved about 3 days after beginning clarithromycin (400 mg/day) and we succeeded in reducing the prednisolone to < 10 mg/day. Decreased thickening of the left carotid artery wall was confirmed by computed tomography (Fig. 1C and 1D), and obvious improvement of the patient's general condition was observed based not only on objective tests but also on the increasing body weight, reappearance of menstruation and an improved quality of life. The anti-inflammatory and immunosuppressive activities of macrolide antibiotics have been reported and the usefulness of clarithromycin has been confirmed in the treatment of rheumatoid arthritis (8,9). Additionally, the macrolide tacrolimus is an immunosuppressant agent used in transplantation. Although it is uncertain whether the effects were directly or indirectly dependent on its antibacterial activities, beneficial effects of clarithromycin as a steroid-sparing drug were observed in the current intractable case.

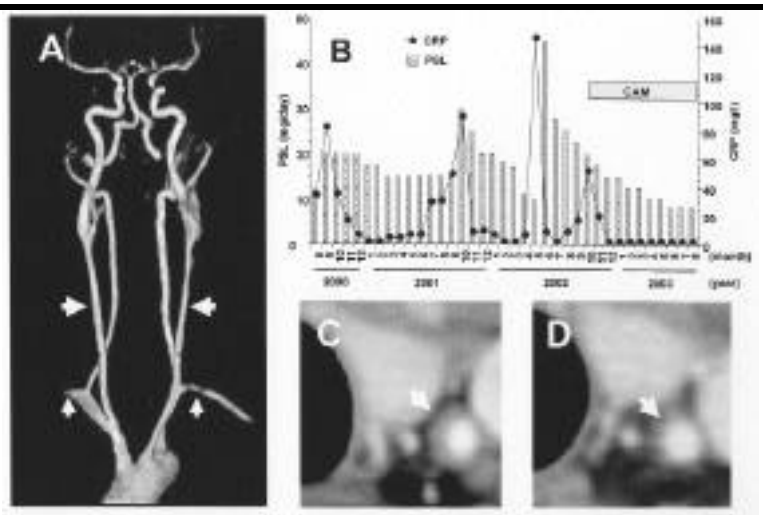

Fig. 1. (**A**) Magnetic resonance angiography (MRA) showing an arteritis lesion of the bilateral carotid (**large arrow**) and subclavian (**small arrow**) arteries. (**B**) Clinical time course (CRP: C-reactive protein; PSL: predonisolone; CAM: clarithromycin). Improvement in wall thickening of the left carotid artery can be seen by comparing the appearance before (**C**) and after (**D**) clarithromycin therapy.

K. YAMAGUCHI[1], *MD* A. MURASHIMA[1], *MD*
Y. YAMAMOTO[2], *PhD*

[1]Dept. of Perinatology, National Center for Child Health and Development, Tokyo, Japan.
[2]Department of Basic Laboratory Sciences, Graduate School of Medical Sciences, Osaka University, Osaka, Japan
Address correspondence to: Koushi Yamaguchi, MD, PhD, Division of Maternal Medicine, Department of Perinatology, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.

References

1. JOHNSTON SL, LOCK RJ, GOMPLES MM: Takayasu arteritis (review). *J Clin Pathol* 2002; 55: 481-6.
2. MORIWAKI R, NODAM, YAJIMAM, SHARMABK, NUMANO F: Clinical manifestations of Takayasu arteritis in India and Japan-new classification of angiographic findings. *Angiology* 1997; 48: 369-79.
3. ISHIKAWAK : Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). *Circulation* 1978; 57: 27-35.
4. DALCANTO AJ, VIRGIN HW 4th: Animal models of infection-mediated vasculitis: implications for human disease. *Int J Cardiol* 2000; 75 (Suppl. 1): S37-45; discussion S47-52.
5. LEINONEN M, SAIKKU P: Evidence for infectious agents in cardiovascular disease and atherosclerosis. *Lancet Infect Dis* 2002; 2: 11-7.
6. KALAYOGLU MV, LIBBY P, BYRNE GI: *Chlamydia pneumoniae* as an emerging risk factor in cardiovascular disease. *JAMA* 2002; 288: 2724-31.
7. IANARO A, IALENTI A, MAFFIA P *et al*.: Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther* 2000; 292: 156-63.
8. SAVIOLAG, ABDI AL, ROSSINI P *et al*.: Clarithromycin in rheumatoid arthritis patients not responsive to disease-modifying antirheumatic drugs: an open, uncontrolled pilot study. *Clin Exp Rheumatol* 2002; 20: 373-8.
9. ZALEWSKA-KASZUBSKA J, GORSKA D: Anti-inflammatory capabilities of macrolides. *Pharmacol Res* 2001; 44: 451-4.