Effective Treatment with Cyclosporine A of a Child with Systemic Lupus Erythematosus Resistant to Cyclophosphamide Pulse Therapy

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Suzuki, K., Tanaka, H., Tsugawa, K. and Ito, E. Effective Treatment with Cyclosporine A of a Child with Systemic Lupus Erythematosus Resistant to Cyclophosphamide Pulse Therapy. Tohoku J. Exp. Med., 2006, 208 (4), 355-359 — Intermittent intravenous cyclophosphamide pulse therapy (IVCY) has been reported to be effective for the treatment of refractory systemic lupus erythematosus (SLE). However, there is a proportion of patients with SLE, who are IVCY-resistant and need a long-term therapy to sustain the remission. We report here a case of a 6-year-old Japanese girl with SLE refractory to IVCY. She suffered from persistent hypocomplementemia and recurrent flares despite receiving methylprednisolone pulse, mizoribine pulse and IVCY therapy. Administration of cyclosporine A (CsA) was, therefore, initiated. Within 2 months of the start of CsA administration, the serum levels of C3, C4 and complement hemolytic activity began to increase rapidly, and finally returned to the normal levels. The serum anti-dsDNA antibody titer was decreased significantly after the initiation of this treatment. The prednisolone dose could be successfully tapered without precipitation of any flares. No adverse effects of CsA were observed. Based on these clinical observations, we suggest that CsA might be an effective treatment option for selected cases of refractory SLE.

Systemic lupus erythematosus (SLE) is a life-threatening illness associated with a multitude of long-term complications. Aggressive immunosuppressive therapy, such as methylprednisolone pulse therapy (MPT) (Tanaka et al. 2001), intermittent intravenous cyclophosphamide pulse therapy (IVCY) (Boumpas et al. 1992; Gourley et al. 1996; Lebman and Onel 2000) and oral mizoribine (MZR) pulse therapy (Tanaka et al. 2003), have been used effectively for the control of disease activity in patients with SLE. Recently, cyclosporine A (CsA) has been reported as another treatment option for cases of refractory SLE, resistant to aggressive immunosuppressive therapy (Coccavo et al. 1997; Sakano et al. 2004). However, clinical reports of the use of the drug in such cases remain few.

Here, we report on the case of a Japanese girl...
with IVCY-resistant SLE, in whom aggressive immunosuppressive therapy consisting of MPT followed by oral prednisolone (PSL) combined with IVCY and MZR proved to be ineffective, and successful clinical remission and reduction in the frequency of flares were achieved following treatment with CsA.

**CASE REPORT**

A 6-year-old Japanese girl was brought to a regional hospital, with a 2-week history of fatigue, productive cough and high fever. Her previous clinical history was unremarkable. Laboratory investigation revealed pancytopenia (total leukocyte count, 3,170/μl; hemoglobin, 8.6 g/100 ml; platelet count, 35,000/μl), low levels of serum C3 (21 mg/100 ml; normal range, 60-110 mg/100 ml), C4 (3.6 mg/100 ml; normal range, 15-40 mg/100 ml), serum complement hemolytic activity (CH50) (< 12 U/ml; normal range, 20-40 U/ml), and a positive test for anti-nuclear antibody (ANA) (= 1 : 640; normal range, < = 1 : 40) with increased serum anti-dsDNA antibody titers (more than 400 IU/ml; normal range, < 12 IU/ml). Echocardiographic examination revealed moderate pericardial effusion, with no signs of pericardial tamponade, suggestive of acute pericarditis. A diagnosis of SLE was made, and treatment was started with PSL at the dose of 40 mg (1.5 mg/kg) daily. Rapid improvement of her clinical symptoms was observed, and she was later referred to our hospital for further examinations in April 2005.

On admission, her body temperature was 37.2°C and blood pressure was 124/70 mmHg. There was no history of facial erythema, oral ulcers, or joints swelling. Laboratory examination revealed the following values: total leukocyte count, 12,440/μl with normohemogram; hemoglobin, 11.6 g/100 ml; platelet count, 255,000/μl; erythrocyte sedimentation rate, 6 mm in the first hour; serum total protein, 6.8 g/100 ml; albumin, 4.2 g/100 ml; blood urea nitrogen, 12 mg/100 ml; serum creatinine, 0.3 mg/100 ml; serum total cholesterol, 263 mg/100 ml; serum C-reactive protein (CRP), < 0.1 mg/100 ml; serum sodium, 138 mEq/liter; serum potassium, 4.4 mEq/liter; serum chloride, 104 mEq/liter, and serum calcium, 8.9 mg/100 ml. Immunological tests on the serum revealed the following values: ANA, = 1 : 2,560; anti-dsDNA antibody, 96 IU/ml; IgG, 1,250 mg/100 ml; IgA, 136 mg/100 ml; IgM, 144 mg/100 ml; C3, 67 mg/100 ml; C4, 6 mg/100 ml, and CH50, 16 U/ml. Although urinalysis showed no proteinuria and hematuria, a percutaneous renal biopsy revealed mild mesangial hypercellularity with an increase of endothelial cell and infiltration of granulocytes in the capillary by light microscopy of periodic acid-Schiff-stained sections. Immunofluorescence revealed 2 + of IgG and IgA, 1 + of IgM, C3 and C1q deposits in a granular pattern with mesangial and capillary distribution. Electron microscopy showed numerous deposits of varying size within mesangial area. The overall pathology was lupus nephritis of class III (A). Chest x-ray and echocardiography revealed no evidence of pericardial effusion.

Despite a 6-week course of PSL (40 mg daily for 2 weeks, followed by 30 mg daily for 4 weeks), the serum hypocomplementemia and elevated anti-dsDNA antibody titers persisted. MPT was administered followed by oral PSL at the dose of 25 mg daily combined with MZR, which was partially effective. Because of the appearance of steroid toxicity, such as severe obesity, osteoporosis and glucosuria, the PSL dose had to be decreased to 15 mg daily, which induced severe depression of the serum complement levels with elevation of the serum anti-dsDNA antibody titers. She developed fever, with the body temperature increasing to 40°C, and acute dyspnea. The serum levels of CRP and ferritin increased to 8.9 mg/100 ml and 346 ng/ml, respectively. Echocardiography revealed moderate pericardial effusion. No pathogenic microorganism was isolated from the sputum and blood cultures. Emergency MPT was administrated based on the diagnosis of SLE flare, which resulted in the rapid disappearance of fever and dyspnea along with a significant decrease in the serum levels of CRP and ferritin. The pericardial effusion resolved completely. Thereafter, the patient was started on monthly IVCY (500-1,000 mg), followed by PSL at the dose of 15 mg daily combined with MZR.
pulse therapy. However, the hypocomplementemia and elevated serum anti-dsDNA antibody titers persisted during the next 5 months, and the patient developed recurrent pericarditis, with increased serum levels of CRP and ferritin in August and October 2005.

Therefore, CsA administration was initiated at 75 mg (1.8 mg/kg) daily, administered as a single-dose (Nakahata et al. 2005), with PSL at the dose of 15 mg daily, in place of IVCY. The trough blood level of CsA remained between 25 and 32 ng/ml, and the peak blood level was 959 ng/ml. The 0-4h area under the time-concentration curve (AUC) was 2,007 ng · h/ml. The serum levels of C3, C4 and CH50 began to increase rapidly, and finally returned to the normal levels (112 mg/100 ml, 18 mg/100 ml and 29.2 U/ml, respectively) within a month following the start of CsA therapy. The serum anti-dsDNA antibody titer also decreased significantly after the initiation of this treatment. At present, three months after the initiation of CsA, the patient is free from cardiac manifestations and has shown no adverse effects of CsA. The PSL dose has been tapered to 12.5 mg daily, without any exacerbations (Fig. 1).

**DISCUSSION**

Aggressive immunosuppressive therapy, such as MPT, IVCY and MZR pulse therapy, has been reported to be effective for the treatment of SLE (Boumpas et al. 1992; Gourley et al. 1996; Lebman and Onel 2000; Tanaka et al. 2001, 2003), and of the available options, IVCY has been reported to be the most effective for the initial treatment of active SLE (Balow and Austin 2004). Boletis et al. (1999) reported that approximately 80% of patients with active lupus nephritis showed satisfactory response to 6 monthly IVCY, with a reduction in the number of unexpected severe exacerbations. In our patient, however, hypocomplementemia with elevated serum anti-dsDNA antibody titers persisted, with recurrent pericarditis, despite IVCY treatment.

There have been several reports on the efficacy of CsA in cases of refractory SLE (Caccavo

![Fig. 1. Clinical course of the patient.](image)

CsA, cyclosporine A (50 mg and 75 mg daily, respectively); MPT, methylprednisolone pulse therapy; PSL, prednisolone (40 mg, 30 mg, 25 mg, 20 mg, 15 mg and 12.5 mg daily, respectively); MZR, mizoribine; IVCY, intermittent intravenous cyclophosphamide pulse therapy; P.E., pericardial effusion; ds-DNA, anti-dsDNA antibody (normal range < 12 IU/ml); C3, normal range 60-110 mg/100 ml; C4, normal range 15-40 mg/100 ml; CH50, complement hemolytic activity (normal range 20-40 U/ml).
et al. 1997; Sakano et al. 2004). Caccavo et al. (1997) reported on the efficacy of CsA in 30 patients with refractory SLE, including 11 IVCY-resistant patients. They reported a significant decrease of the mean disease activity score following the initiation of CsA administration in these cases, which allowed a significant reduction of the PSL dose. Sakano et al. (2004) recently reported on the successful use of CsA in a case of steroid-resistant SLE. They suggested that CsA might reverse steroid resistance, because an extremely low dose of CsA was effective for their patient. Indeed, CsA has been reported to be a potent inhibitor of P-glycoprotein, which has been shown to be related to multidrug resistance to chemotherapies in leukemia and to disease-modifying anti-rheumatic drugs in rheumatoid arthritis (Griffiths and Emery 2001). Interestingly, Lee et al. (2004) reported that a proportion of patients with SLE have a silent mutation in codon 766 of the glucocorticoid receptor (GR) gene. Although further studies are needed, a possible mutation in the GR gene may also attribute to variability in steroid responsiveness of SLE (Lee et al. 2004). Considering the reports in the literature and our own patient’s clinical course, we suggest that treatment with CsA might be beneficial in selected patients with refractory SLE resistant to conventional immunosuppressive agents. Indeed, we speculate from the present case that the indication of CsA might be in cases with frequent flares associated with elevated serum levels of ferritin and CRP, because these parameters elevation suggest that the patient has inflammatory hypercytokinemia.

We have previously demonstrated that administration of CsA as a single daily, even if low, dose is optimal for obtaining maximum efficacy and minimum toxicity in patients with steroid-dependent nephrotic syndrome (Nakahata et al. 2005). Therefore, in our present case with SLE, we administered CsA at the initial dose of 1.8 mg/kg daily as a single dose, since the optimal dose of the drug for the treatment of SLE still remains to be clarified. The treatment at this dosing schedule yielded a sufficient AUC 0-4, considering the results in stable renal transplant patients receiving the drug in the maintenance phase (Uchida et al. 2004), without any adverse effects of CsA. Because estimation of AUC has been suggested as a means for standardizing CsA administration (Uchida et al. 2004), we believe that further studies are needed to clarify the precise AUC in patients with SLE.

It has been reported that the major adverse effect of CsA is nephrotoxicity (Griffiths and Emery 2001). However, Ferrario et al. (1999) reported on the efficacy of CsA in patients with lupus nephritis without significant adverse events. Although the long-term efficacy and safety of CsA, including the potential long-term nephrotoxicity, in patients with SLE, still remain unclear, our experience suggests that CsA, even at low-dose, may be an effective treatment option for selected cases of SLE refractory to conventional immunosuppressive therapy. Further studies on a larger number of cases, however, are needed to confirm the results.

References


Lee, Y.M., Fujiwara, J., Munakata, Y., Ishii, T., Sugawara, A., Kaku, M., Kokubun, S., Sasaki, T. & Funato, T. (2004) A mutation of the glucocorticoid receptor gene in patients with steroid-dependent nephrotic syndrome (Nakahata et al. 2005). Considering the results in stable renal transplant patients receiving the drug in the maintenance phase (Uchida et al. 2004), without any adverse effects of CsA. Because estimation of AUC has been suggested as a means for standardizing CsA administration (Uchida et al. 2004), we believe that further studies are needed to clarify the precise AUC in patients with SLE.