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Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis

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Abstract We evaluated the efficacy and safety of low-dose cyclosporine A (CsA) in patients with refractory lupus nephritis. Nine patients with systemic lupus erythematosus who had lupus nephritis resistant to previous treatment with glucocorticoids and immunosuppressants other than CsA were enrolled in a prospective, open-label study. All patients initially received 2.5 mg/kg per day of CsA; the dosage was adjusted to reach a blood trough level of 80–150 ng/ml. The urinary protein concentration decreased significantly 2 weeks after the initiation of treatment. After 30 weeks of CsA treatment, the mean urinary protein concentration was more than 50% lower than the baseline value, and urinary casts had decreased significantly. There were no significant changes in the levels of serum creatinine, serum anti-double-stranded DNA antibodies, or CH50 during any part of the study. The dose of glucocorticoids was significantly tapered by approximately 50%, without any disease flare. Hypertension developed in one patient, but was controlled with antihypertensive agents. Our results suggest that low-dose CsA therapy is an effective and less toxic alternative to conventional cyclophosphamide therapy for the management of refractory lupus nephritis.

Key words Cyclosporine A · Immunosuppressive drugs · Lupus nephritis · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease characterized by diverse clinical manifestations and the production of a broad spectrum of autoantibodies. Many studies[1–5] have documented that anti-double-stranded DNA (anti-dsDNA) antibodies form immune complexes that are deposited in the kidney and activate complements, inducing glomerulonephritis. Accumulating evidence suggests that T cells play a central role in the pathogenesis of SLE by assisting B cells to produce autoantibodies, leading to the release of cytokines and direct damage to target organs.[6]

Although outcomes of SLE have recently improved in terms of 5- and 10-year survival, a longer survival rate such as 15- and 20-year and the quality of life of patients remain unsatisfactory.[7] Three major factors contribute to poor long-term outcomes: severe organ damage due to disease activity such as lupus nephritis and central nervous system (CNS) lupus, atherosclerotic vascular damage resulting in the cerebral and coronary artery diseases, and infections that may resulted from the compromised immune status, in part by immunosuppressive treatments. Lupus nephritis develops in up to half of all Japanese patients with SLE[8] and is closely related to morbidity and mortality. This situation has created a major therapeutic challenge. For example, approximately one third of patients with lupus nephritis do not respond to the standard corticosteroid therapy and require more aggressive treatments, such as high-dose corticosteroids combined with cyclophosphamide. Monthly treatment with intravenous cyclophosphamide (IVCY) plus high-dose corticosteroids has consistently produced better responses than high-dose corticosteroids alone and is now considered the treatment of choice for severe proliferative lupus nephritis. However, the safety of IVCY has recently become a major concern because of various adverse events, including bone marrow suppression, hemorrhagic cystitis, opportunistic infections, secondary malignancies,[9–11] and gonadal toxicity.[12–14] Indeed, young female patients with severe lupus nephritis or their guardians are likely not to accept treatment with IVCY owing to the risk of irreversible amenorrhea.

Cyclosporine A (CsA) is a cyclic, lipophilic undecapeptide that selectively and reversibly inhibits T-cell-mediated immune response by suppressing the phosphatase activity of calcineurin.[15–17] Cyclosporine A has been successfully

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used since 1978 to prevent graft rejection in patients receiving transplants,[18] who generally receive doses of 10 mg/kg or greater. In animal models of SLE such as MRL-lpr/lpr mice, Cyclosporine A has been shown to prolong survival as compared with IVCY,[19] suggesting that CsA may be useful for the management of lupus nephritis in humans. Sporadic studies[15,16,18] of small series of patients have indicated that CsA is effective for lupus nephritis at a lower dose than that required to prevent graft-versus-host disease (GVHD). To gain a better understanding of the potential benefits of CsA, we prospectively evaluated the efficacy and safety of low-dose CsA in Japanese patients with SLE who had active lupus nephritis refractory to standard treatment with high-dose corticosteroids, with or without immunosuppressive drugs.

Materials and methods

Patients

Patients were eligible if they met all of the following criteria: (1) a diagnosis of SLE according to the 1997 revised classification criteria for SLE proposed by American College of Rheumatology;[20] (2) active renal disease, including persistent proteinuria (more than 0.5 g/day or 50 mg/dl); (3) an unsatisfactory clinical response or recurrent exacerbations of disease despite 12 weeks of previous therapy. We excluded patients if they had (1) a serum creatinine level of greater than 1.2 mg/dl; (2) hypertension refractory to antihypertensive drugs (systolic pressure greater than 160 mmHg or diastolic pressure greater than 100 mmHg); (3) current or a history of malignant disease; (4) uncontrolled infections; (5) previously received CsA; or (6) poor compliance with previous treatment regimens. We also excluded women who were pregnant or nursing. Informed consent was obtained from all patients before enrollment.

Study protocol

Cyclosporine A (Neoral; Novartis Pharmaceuticals, Tokyo, Japan) was given orally at an initial dose of 2.5 mg/kg per day in two divided doses (100, 125, or 150 mg/day). The dose was adjusted to maintain a blood trough level of 80–150 ng/ml and was reduced by 25 mg/day if either the serum creatinine level or blood pressure was elevated by 30% or more as compared with the respective baseline values. Before study entry, patients were observed for 12 weeks; the dose of corticosteroids was unchanged for at least the last 2 weeks.

Clinical assessments

All patients underwent clinical, laboratory, and immunological evaluations every 4 weeks. Examinations included assessment of blood pressure, complete blood counts, liver function (transaminases and bilirubin), serum creatinine, blood urea nitrogen, total serum protein, serum albumin, electrolytes, blood sugar, complement hemolytic activity (CH50), anti-ds-DNA titer, urinary protein concentration and daily amount, and urine sediments. Urine samples were collected at each visit. Patients were interviewed at every visit to monitor adverse events. The clinical response of lupus nephritis to treatment was evaluated according to the criteria proposed by National Institutes of Health,[21] with slight modification (Table 1).

Table 1. Criteria for evaluating response of lupus nephritis to therapy

A.	Complete remission: absence of cellular casts, hematuria and urinary protein excretion less than 0.5 g/day (or equivalent concentration) and stable >30% serum creatinine level
B.	Partial remission: stable serum creatinine level and (1) >50% reduction in concentration of protein excretion or (2) stable (no increase by >50% or more) concentration of protein excretion and >50% reduction in RBC/hpf
C.	Aggravation: 100% increase in serum creatinine level or >50% increase in concentration of protein excretion
D.	No change: Not meeting any of the above criteria

Statistical analysis

Descriptive statistics include means and standard deviations. Wilcoxon's matched-pairs test was used to calculate levels of statistical significance.

Results

Patients' characteristics

Between 1998 and 2000, we enrolled nine Japanese patients (eight women and one man) who had a diagnosis of SLE with lupus nephritis resistant to treatment with glucocorticoids, immunosuppressants, or both (Table 2). The mean ± standard deviation (SD) of age was 37.0 ± 12.0 years (range: 17–57 years). The duration of renal disease (from the date of diagnosing lupus nephritis until the start of CsA treatment) was 90.1 ± 107.4 months (range: 7–254 months). Seven of the nine patients failed to respond to previous treatment with conventional immunosuppressive drugs. Two patients had previously received cyclophosphamide (one patient orally, and another intravenously), three had received azathioprine, and three had received mizoribine. In seven patients, nephrotic syndrome had developed within 3 months before treatment with CsA. At the start of CsA treatment, five patients had nephrotic syndrome (patients 2, 3, 4, 6, and 7). One patient had a history of CNS involvement (patient 8), three had malar rashes (patients 1, 2, and 4), two had serositis (patient 2 and 3), five had arthritis

Table 2. Patients' characteristics

No.	Age (years)/Sex	Duration of renal disease (months)	Urinary protein excretion (mg/dl)	Previous therapy	Response
1	17/F	24	84	High GC, AZ, MZB	Poor
2	33/F	156	185	High GC, AZ	Poor
3	57/M	8	600	High GC, IVCY	Poor/interrupted because of nausea
4	45/F	8	167	High GC	Poor
5	46/F	21	200	High GC, POCY	Poor
6	40/F	199	141	High GC, MZB	Poor
7	34/F	50	114	High GC, AZ	Poor
8	24/F	7	134	High GC	Poor
9	37/F	240	116	High GC, MZB	Poor

High GC, high-dose glucocorticoids (equivalent to more than 0.5 mg/kg/day of prednisolone); AZ, azathioprine; MZB, mizoribine; POCY, oral cyclophosphamide; IVCY, intravenous cyclophosphamide

(patients 2, 3, 6, 8, and 9), and three had leukopenia or thrombocytopenia (patients 1, 3, and 4). Prior to the study, renal biopsy was performed in two patients (patients 6 and 7). Both patients revealed World Health Organization (WHO) type V (membranous) lupus nephritis. At the start of treatment with CsA, however, the kidney was the only major organ involved, and no patient had active CNS lupus or serositis. All patients tested positive, or had a history of testing positive, for anti-ds-DNA antibodies. Three tested positive for anti-Sm antibodies, eight for anti-SS-A antibodies, five for anti-U1-RNP antibodies, and four for antiphospholipid antibodies.

Six patients had received statins (patients 2, 3, 5, 6, 8, and 9). One patient had received angiotensin-converting enzyme inhibitor (patient 9) and one had received angiotensin-receptor antagonists (patient 6).

Proteinuria and renal function

The significant decrease in the urinary protein during treatment with CsA was impressive (Fig. 1). After only 2 weeks of treatment with CsA, a significant reduction of the urinary protein concentration significantly fell to about 50% (97.0 ± 15.0 mg/dl) of the baseline value. After 30 weeks, the urinary protein concentration (63.2 ± 9.9 mg/dl) was 67% lower ($P < 0.01$) than the baseline value (193.4 ± 52.3 mg/dl), with six of the nine patients showing a reduction of greater than 50%. At the initiation of CsA treatment, three patients had persistent hematuria (patients 3, 4, 5). Microscopic hematuria resolved after 4 weeks in all three patients. Moreover, microscopic hematuria was not detected during the study in all but one patient, who only had marginal hematuria. Urinary casts were observed in five patients (patients 1, 2, 4, 6, 8) at the start of CsA treatment, but disappeared within 30 weeks in all patients.

Immunological data

There was no significant change in the serum anti-ds-DNA antibody titer or the CH50 level after the start of CsA treatment. However, the serum anti-ds-DNA antibody titer showed a trend toward a decrease during CsA treatment (Fig. 2). The levels of IgG remained unchanged.

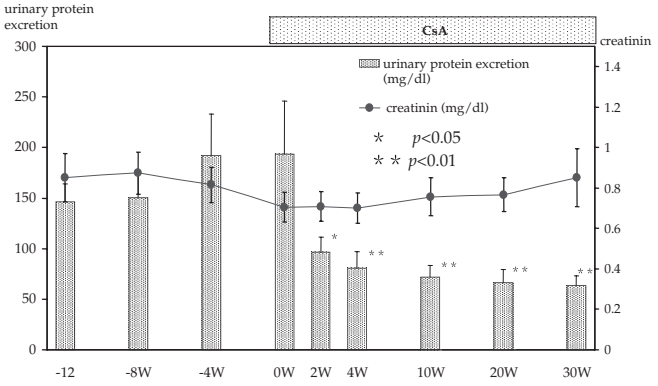

Fig. 1. Time courses of mean urinary protein excretion (mg/dl) and serum creatinine level (mg/dl) during cyclosporine A (*CsA*) therapy in nine patients with systemic lupus erythematosus. Asterisks indicate significant differences ($P < 0.05$ or $P < 0.01$) as compared with value at 0 weeks (*W*)

Steroid-sparing effect

Before treatment with CsA, the mean prednisolone (PSL) dose was 20.1 ± 2.4 mg/day, similar to the dose 12 weeks before the start of CsA treatment (21.1 ± 5.9 mg/day; Fig. 3). After 30 weeks of CsA treatment, the dose of prednisolone (11.6 ± 0.7 mg/day) was significantly lower than the baseline dose, without any disease flare. This represented an approximately 50% reduction in the dose of prednisolone.

Side effects

Overall, low-dose CsA treatment (2–3 mg/kg per day) was well tolerated. Hypertension developed in one patient. No patient had nephrotoxicity, gingival hyperplasia, hirsutism, liver dysfunction, neurological symptoms, or nausea.

Outcome

The outcome of treatment, evaluated according to the criteria in Table 1, was complete remission in two patients, partial remission in four, and no change in three.

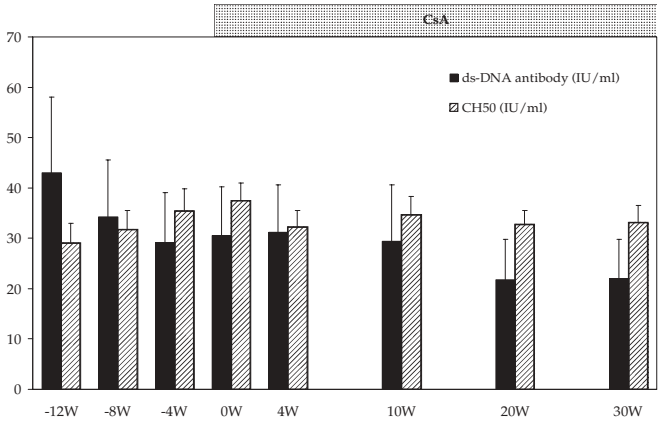

Fig. 2. Time courses of anti-double-stranded DNA (*ds-DNA*) antibody (*black bars*) and CH50 (*hatched bars*) titers during CsA therapy. The levels of anti-dsDNA antibody and CH50 did not change significantly during CsA treatment

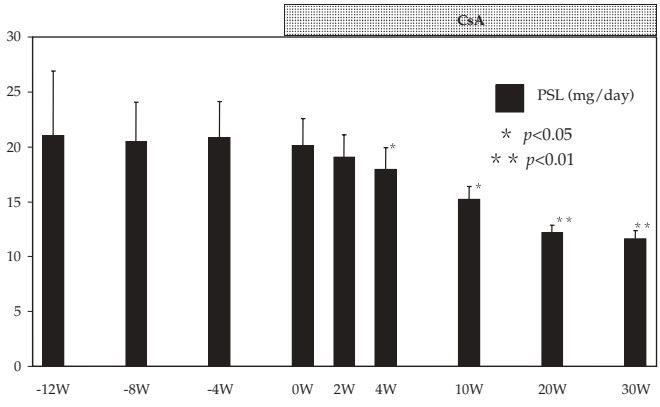

Fig. 3. Time courses of prednisolone (*PSL*) dose during treatment with cyclosporine A. Asterisks indicate significant differences ($P < 0.05$ and $P < 0.01$) as compared with the value at 0 weeks (*W*)

Discussion

This prospective, open-labeled study demonstrated that 30 weeks of low-dose CsA therapy was effective and well tolerated in Japanese patients with lupus nephritis. Most of our patients (seven of nine) had nephrotic syndrome. A good response (complete or partial remission) to low-dose CsA was obtained in 70% of the patients, and all but one continued to receive CsA for more than 12 months. During the study period, the mean dose of prednisolone was decreased from 20.1 mg/day to 11.6 mg/day, suggesting that low-dose CsA therapy had a clinically significant steroid-sparing effect. There were no major side effects.

Intravenous cyclophosphamide is usually given to patients with active lupus nephritis that fails to response to oral or intravenous high-dose pulse therapy with steroids. The addition of three IVCY to initial treatment with monthly pulses for 6 months reduces the frequency of relapse from 50% to about 10% at 5 years.[22] More recently, IVCY combined with monthly pulses of methylprednisolone has been shown to have a higher remission rate (85%) than either therapy alone (methylprednisolone, 29% and IVCY, 65%).[21] However, the substantial benefits of IVCY regimens are not achieved without the risk of severe side effects. IVCY often causes amenorrhea and premature ovarian failure.[12–14] This is one of the main reasons why many premenopausal females with lupus nephritis refuse to receive IVCY regimens. Another major concern with IVCY regimens is an increased risk of malignancies such as lymphoma, leukemia, and transitional cell carcinoma of the uroepithelium. These potential problems have increased the need for alternative immunosuppressive agents that are both effective and safe.

Cyclosporine A is a selective inhibitor of T lymphocytes that is often used to prevent GVHD in allograft recipients. An early pilot study evaluating the efficacy and safety of CsA in patients with lupus nephritis found that 10 mg/kg per day was nephrotoxic.[23,24] The nephrotoxicity of CsA is related to high blood trough levels or increased areas under the curve.[25] Low-dose CsA therapy (up to 5 mg/kg per day) with a target blood trough level of less than 200 ng/ml has thus been studied by several groups.[26–28]

An early study of 10 patients with moderately active SLE demonstrated that low-dose CsA was well tolerated.[29] A subsequent study reported marked clinical and serological improvements in 5 of 10 patients with lupus nephritis. Low-dose CsA therapy decreased proteinuria from 4.7 ± 2.6 to 1.5 ± 1.1 g/24 h in a study done by Manger et al.,[30] and from 9.11 ± 4.20 to 1.45 ± 1.12 g/24 h in another study, reported by Dostal et al.[31] A favorable response to low-dose CsA was also obtained in patients with biopsy-proven diffuse proliferative lupus nephritis, which reverted to mesangial lupus nephritis in all 17 patients at 12 months,[32] as well as in patients with membranous lupus nephritis.[33] The clinical response to low-dose CsA in children with severe lupus nephritis has been shown to be comparable to that of oral cyclophosphamide.[27] In addition to decreasing disease activity, CsA also allows the corticosteroid dose to be reduced.

One important question is how CsA reduces proteinuria within only 2 weeks. It is tempting to speculate that CsA inhibits the functions of activated T lymphocytes, which produce excessive amounts of cytokines, express increased levels of adhesion molecules, and provide help B cells to produce autoantibody.[15–17] Other nonimmunological mechanisms include decreased local glomerular blood flow or alteration of the glomerular barrier to protein infiltration. Our data do not support the involvement of hemodynamic changes due to intrarenal vasoconstriction, thereby decreasing the glomerular filtration rate (GFR), since both the daily amount of urinary protein excretion and the urinary protein concentration were dramatically reduced, whereas the serum creatinine level remained unchanged. Because we demonstrated the decrease in urinary protein concentration instead of daily urinary protein excretion, the response to CsA was unlikely to be considerably affected by the decrease in GFR due to the nephrotoxicity of CsA. In addition, CsA treatment decreased urinary sediments, suggesting the effect on inflammatory process, in part through altering T-cell function. However, our patients showed no signifi-

cant improvement in immunological variables such as the anti-dsDNA titer and CH50, which contrasts with the findings of several prior studies.[26,29,33] Discrepancies in immunologic effects may have resulted from differences in clinical characteristics, such as immunologic status, disease duration, renal histopathology, or previous treatments. These results imply that CsA affects both the functions of activated T lymphocytes, independently of its effects on anti-dsDNA antibody production by B cells and alteration of the glomerular barrier to protein infiltration. Only two patients had renal biopsy before CsA treatment and we expected that various types of lupus nephritis (WHO type II, III, IV and V) in other patients from clinical points of view. Thus, further studies are needed to elucidate the correlation between renal histological patterns and the therapeutic outcome of CsA.

Adverse events of CsA were mild and less frequent in our patients than in previous studies.[26,28,29,32,33] We attribute the low incidence of mild adverse events, at least in part, to monitoring the trough level and adjusting the dose of CsA to maintain a target level of 80 to 150 ng/ml.

Currently, the use of CsA during pregnancy is not recommended. Nevertheless, its lack of teratogenic potential[27] and several case reports documenting uneventful pregnancies and deliveries in women with SLE who received CsA[35,36] suggest that it may be the treatment of choice for pregnant women with active SLE poorly controlled by corticosteroids alone.

In summary, low-dose CsA was effective in six of nine Japanese patients with active lupus nephritis refractory to treatment with corticosteroids and other immunosuppressive agents. Cyclosporine A promptly reduced the urinary protein excretion, without causing serious side effects. Experimentally, early treatment with CsA has been shown to inhibit the development of lupus nephritis in two different murine models,[37,38] suggesting that a combination of CsA and glucocorticoids as initial therapy for lupus nephritis might be effective and safe, and allow the dose of steroids to be reduced. A prospective study evaluating examining this combination as initial treatment in patients with recent-onset SLE appears warranted.

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