Low-Dose Cyclosporine Treatment in Chinese Nephrotic Patients With Idiopathic Membranous Nephropathy: An Uncontrolled Study With Prospective Follow-up

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Abstract: *Introduction:* The optimal dose of cyclosporine A (CsA) in treatment of nephrotic proteinuria in idiopathic membranous nephropathy (IMN) remains inconclusive. We evaluated the efficacy and safety of low-dose CsA combined with low-dose prednisone as induction therapy for Chinese nephrotic patients with IMN. *Methods:* We conducted a prospective observational cohort study in 18 patients with IMN and nephrotic proteinuria. Twelve patients were refractory to other immunosuppressive therapies. The initial dose of CsA was 1 to 1.5 mg/kg/d combined with 0.15 to 0.50 mg/kg/d prednisone. The dose of CsA was adjusted monthly by 20% to 30% according to efficacy and the 12-hour trough blood concentration (C_0) of CsA around 100 ng/mL for 6 months; when proteinuria was <1 g/d, CsA was tapered gradually to a dose of 0.6 to 1 mg/kg/d. *Results:* Two patients discontinued CsA because of refractory hypertension. The remaining 16 patients had been followed up for 44 ± 15 weeks. Remission was observed in 11 patients (68.8%: complete remission, 6 and partial remission, 5). The effective dose of CsA for remission was 2.1 ± 0.4 (1.5–2.5) mg/kg/d, and the mean C_0 of CsA was 92.5 ± 23.5 (58–124) ng/mL. All the 16 patients experienced well-controlled adverse effects, including hypertension (n = 12), hyperuricemia (n = 12), increase of serum creatinine (n = 2), etc. *Conclusions:* Low-dose CsA combined with low-dose prednisone was effective and safe as induction therapy in majority of Chinese nephrotic patients with IMN, including those refractory to other immunosuppressive regimens.

Key Indexing Terms: Cyclosporine; Idiopathic membranous nephropathy; Nephrotic syndrome. **[Am J Med Sci 2010;339(6):532–536.]**

Idiopathic membranous nephropathy (IMN) is one of the most common glomerular diseases in adult patients with nephrotic syndrome. Persistence of nephrotic proteinuria portends a poor prognosis, whereas its remission, partial or complete, usually indicates a good outcome regarding to renal survival.[1,2]

Administration of a combination of alkylating agents and high-dose corticosteroids can induce remission of nephrotic proteinuria in approximately 66% to 92% of patients with IMN, but relapse rate and associated adverse effects are high.[3,4] Although several small clinical trials have shown induction regimen of low-dose cyclosporine A (CsA, 2–3 mg/kg/d) to be efficient for patients with IMN, international workshop recommendations still suggested 3 to 4 mg/kg/d as the appropriate initial dose.[5,6] However, the optimal dose for Chinese patients remains to be elucidated. In this study, we evaluated the efficacy and safety of low-dose CsA combined with low-dose prednisone as induction therapy for Chinese nephrotic patients with IMN.

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PATIENTS AND METHODS

Patients

Eighteen adult patients with histologically proven membranous nephropathy, diagnosed in the Peking University First Hospital between 2005 and 2007, were recruited. All the patients had nephrotic proteinuria (≥3.5 g/d) and serum creatinine <133 μmol/L. Secondary causes of membranous nephropathy, including malignancy, hepatitis B virus infection, lupus, putative drugs, and toxins, were actively excluded.

The average age of the 18 patients was 44 ± 14 (18–57) years; male-to-female ratio was 11/7. Their median proteinuria was 5.1 (range, 3.5–20.3) g/d, serum albumin was 31.4 ± 6.0 g/L, and serum creatinine was 72.9 ± 10.2 μmol/L. Pathologic stages were classified as 9 patients with stage I, 8 patients with stage II, and 1 patient with stage III, according to the classification of Ehrenreich and Churg.[7]

Before this present study, 12 patients had received immunosuppressive therapies; 9 of the 12 had 0.8 to 1.0 mg/kg/d oral prednisone combined with 1.5 mg/kg/d oral cyclophosphamide for 3 months and then had their prednisone tapered by 5 to 10 mg/d monthly, 5 of the 9 had a transient partial remission (PR) but relapsed, the other 4 had no response (NR); 2 of the 12 had 0.8 to 1.0 mg/kg/d oral prednisone combined with 1.5 to 2.0 g/d mycophenolate mofetil for 6 and 8 months, respectively, 1 of them had a PR but relapsed, and the other had NR; and the last 1 of the 12 patients who had oral tripterygium glycosides had a transient PR and relapsed. The interval between previous immunosuppressive therapy and the start of CsA therapy was >6 months, except for 2 patients who started CsA therapy just 1 month after previous immunosuppressive therapy, because the nephrotic status of both patients exacerbated, and 1 of the 2 patients experienced an episode of pulmonary thromboembolism. The remaining 6 patients had not been treated with any immunosuppressive therapy before, and nephrotic proteinuria sustained or even increased after >6 months of angiotensin-converting enzyme inhibitor or angiotensin II subtype 1 receptor blocker treatment.

Informed consent was obtained from each patient. The research was in compliance with the Declaration of Helsinki.

Therapy Design

The initial dose of CsA was 1 to 1.5 mg/kg/d in 2 divided equal doses at a 12-hour interval combined with 0.15 to 0.50 mg/kg/d prednisone (median, 0.25 mg/kg/d, tapered after 3 months). The dose of CsA was adjusted monthly by 20% to 30% according to efficacy and the 12-hour trough blood con-

TABLE 1. Baseline characteristics of patients with or without remission

	Patients With Remission (n = 11)		
	Without Previous Immunosuppressive Therapy (n = 4)	With Previous Immunosuppressive Therapy (n = 7)	Patients Without Remission (n = 5)
Male/female	3/1	4/3	4/1
Age (yr)	46 ± 11	36 ± 15	57 ± 11
Proteinuria (g/24 hr)	6.93 ± 2.57	6.30 ± 2.70	7.7 ± 6.9
Serum albumin (g/L)	29.2 ± 4.5	33.6 ± 5.2	30.0 ± 7.7
Serum creatinine (μmol/L)	76.0 ± 14.0	71.3 ± 9.4	74.9 ± 10.9
eGFR (mL/min/1.73 m^2)[15]	103.6 ± 19.9	114.4 ± 23.7	106.6 ± 23.1
Pathologic stage	I (1) II (2) III (1)	I (3) II (4)	I (3) II (2)

eGFR = $175 \times Scr^{-1.234} \times age^{-0.179} \times (0.79$ if female$)$.[15]

centration (C_0) of CsA with a target around 100 ng/mL for at least 6 months. The highest dose of CsA was 2.5 mg/kg/d; when proteinuria was reduced to <1 g/d, the dose of CsA was tapered monthly by 10% to 20% to a maintenance dose of 0.6 to 1 mg/kg/d. When serum creatinine increased >30% above the baseline, the dose of CsA was reduced or the CsA was discontinued if the increased serum creatinine could not back to baseline. Angiotensin-converting enzyme inhibitors or angiotensin II subtype 1 receptor blockers were given to all the patients and remained unchanged during the study. If patients had blood pressure >130/80 mm Hg, calcium channel blockers such as retard-releasing nifedipine or amlodipine were added as appropriate.

Follow-up

During follow-up, all the 18 patients were monitored at the end of week 2 for the first time after start of CsA therapy and monthly thereafter. Serum creatinine, serum albumin, complete blood count, and 24-hour urinary protein were examined periodically. Symptoms and blood pressure of the patients were recorded at every visit. All patients were followed up for >26 weeks.

Outcome Measures

The outcome judgments were adapted from literature with some modification.[8] In brief, complete remission (CR) was defined as reduction of proteinuria to <0.3 g/d and serum albumin >35 g/L; PR was defined as a 50% reduction of proteinuria and in the range of 0.3 to 3.4 g/d and serum albumin >35 g/L; NR was defined as reduction of proteinuria <50% or proteinuria >3.5 g/d, or serum albumin <35 g/L. Relapse was defined as recurrence of nephrotic range proteinuria again after remission. CsA-associated hypertension was considered when patients had new-onset hypertension or systolic/diastolic blood pressure increase >20 mm Hg of initial level in patients with hypertension. CsA-associated hyperuricemia was defined as serum uric acid increase >100 μmol/L of initial level and >420 μmol/L.

Statistic Analysis

Mean ± SD was used for continuous variables. Median (range) was used for nonnormal distribution data. Wilcoxon signed-rank test was used to compare the mean values of clinical data, parameters of treatment, and different outcome between patients with remission and without remission. A P value <0.05 was considered significant. All analyses were performed using SPSS for windows version 10.0.

RESULTS

Efficacy of the Low-Dose CsA Regimen

Two patients withdrew because of severe headache or chest pain, both of them had refractory hypertension (>180/100 mm Hg). The remaining 16 patients kept on the therapy and had been followed up for 44 ± 15 weeks. Their baseline characteristics were shown in Table 1. Remission was observed in 11 of the 16 patients (68.8%: CR, 6 and PR, 5) with proteinuria decreasing from 6.4 ± 2.6 g/d to 0.7 ± 0.6 g/d and serum albumin increasing from 31.7 ± 5.3 g/L to 42.3 ± 2.4 g/L. The effective dose of CsA for remission was 2.1 ± 0.4 (1.5–2.5) mg/kg/d, and the mean 12-hour trough concentration of CsA was 92.5 ± 23.5 (58–124) ng/mL. Interestingly, the effective 12-hour trough concentration of CsA <100 ng/mL was observed in 5 patients who had received a CsA dose of 1.8 ± 0.4 (1.5–2.4) mg/kg/d and had a mean 12-hour trough CsA concentration of 75.5 ± 13.6 (58.1–96.1) ng/mL. However, after clinical remission of the 11 patients, the mean estimated glomerular filtration rate (eGFR) significantly decreased from 106.68 ± 23.11 to 93.16 ± 21.41 mL/min/1.73 m^2 ($P < 0.05$). The remaining 5 patients (31.2%) were not responsive. Their detailed clinical parameters before and after treatment are shown in Table 2. Association between clinical parameters (serum albumin and 24-hour urinary protein) and the dose and C_0 of CsA is shown in Figure 1.

CR or PR was observed in 80% (4 of 5 cases) of patients without previous immunosuppressive therapy and 63% (7 of 11 cases) of patients who had been treated before. The mean interval between starting treatment and achieving PR was 14 ± 9 weeks, and the cumulative dose of prednisone was 25.3 (22.7–31.6) mg/kg. The mean interval between starting treatment and achieving CR was 28 ± 12 weeks, and the cumulative dose of prednisone was 50.2 (25.7–60.1) mg/kg.

Comparison of Clinical and Treatment-Related Parameters Between Patients With and Without Clinical Remission

Table 3 shows a comparison of treatment-related parameters between patients with and without remission; patients with remission had a much longer treatment duration than those without remission ($P = 0.002$). Table 4 shows a comparison of treatment-related parameters between patients with and without previous immunosuppressive therapy, no significant difference was observed.