Combined cyclosporine and prednisolone therapy in adult patients with the first relapse of minimal-change nephrotic syndrome

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Abstract

Background. Although minimal-change nephrotic syndrome (MCNS) is highly steroid-responsive, some patients show frequent relapses, necessitating administration of repeated courses of prednisolone (PSL) at high doses. The adverse effects of long-term PSL treatment include osteoporosis, infection, diabetes, cataract, etc., most of which are serious. It is therefore necessary to establish useful strategies to reduce the PSL dose.

Methods. Patients with the first relapse of MCNS were randomly assigned to two groups, namely, the CyA (AUC 1700–2000 ng/ml) + PSL (0.8 mg/kg/day) group (n = 26) and the PSL alone (PSL) (1.0 mg/kg/day) group (n = 26), and the clinical characteristics were compared between the two groups. All patients used C2 for CyA monitoring.

Results. A significant decrease of the urinary protein excretion (P = 0.02) and serum total cholesterol (P = 0.003) was observed at 2 weeks from the first relapse in the CyA + PSL group. The increase in the serum total protein (P = 0.03) and serum albumin (P = 0.007) as compared with that in the PSL group was also observed in the CyA + PSL group at this time-point. The time to remission in the CyA + PSL group was shorter than that in the PSL group (P = 0.006).

Conclusion. It was possible to obtain early remission and reduce the PSL dose with combined CyA and PSL therapy in patients with MCNS.

Keywords: cyclosporine; minimal-change nephrotic syndrome; relapse
Introduction

Minimal-change nephrotic syndrome (MCNS) is the most common cause of idiopathic nephrotic syndrome (INS) in children, accounting for ~75% of all paediatric cases [1]; conversely, among adults, this condition accounts for only 20% of all cases of INS [2,3]. MCNS is mainly characterized by the nephrotic syndrome, which may be persistent or remit and recur spontaneously [4]. The risk of ESRD in patients with MCNS is extremely low. Although the pathogenesis of MCNS remains largely unknown, immunologic disturbances have been implicated [5]. Steroid therapy is the first-line treatment for MCNS. Adults with MCNS generally receive low doses of prednisolone (PSL) per kilogram body weight (1.0 mg/kg/day), which may explain the remission rate of 80% [6,7]. A prolonged course of steroid therapy, however, entails an increased risk of steroid toxicity. The optimal dose and duration of steroid therapy, as well as the optimum administration schedule to avoid steroid toxicity, have yet to be established in patients with nephrotic syndrome. Administration of immunosuppressive drugs such as cyclosporine might play a role in reducing the frequency and severity of steroid toxicity. Cyclosporine, an immunosuppressive agent belonging to the class of calcineurin inhibitors, has beneficial effects in adult patients with steroid-resistant and frequently relapsing nephrotic syndrome [8]. However, several reports indicate that prolonged use of cyclosporine may be associated with chronic renal injury, even in patients with normal renal function [9,10]. In addition, hypertension and malignant tumours sometimes develop in patients with idiopathic nephrosis treated with cyclosporine [11]. There is a lack of coherent guidelines to guide clinicians on the optimal use of this drug.

To examine the clinical benefits of cyclosporine, we conducted a randomized controlled study of the drug in 52 Japanese adult patients with MCNS.

Methods

Study design

The study was a prospective randomized parallel-group open-label trial. Eligible patients consisting of MCNS patients on first relapse were randomly assigned by the trial nephrologists to treatment with cyclosporine + prednisolone (CyA + PSL group), or prednisolone alone (PSL group). Randomization was performed employing a simple randomization method. The randomization sequence was kept concealed by the secretary until the end of the trial. The study was conducted with the approval of the Institute’s Ethics Committee, after obtaining the patients’ written informed consent.

Patients

We enrolled Japanese adults (older than 18 years old) with biopsy-proven minimal-change disease. All patients were initially treated with oral PSL (1.0 mg/kg/day) at the time of the first episode. The duration of the initial daily corticosteroid therapy varied, largely depending on the pattern of response, and varied from 4 to 6 weeks. Thereafter, the daily dose was reduced by 10 mg every 4 weeks. The dose reduction by 10 mg every 4 weeks was continued until a daily dose of 10 mg was reached, which was then maintained for 12 months. All patients who developed the first relapse between January 2000 and April 2008 were admitted to our nephrology department and enrolled in this study. Patients with systemic illness, malignancy, diabetes, hepatitis B surface antigen positivity or renal vein thrombosis and those who had received immunosuppressive drugs for ≤2 months were excluded from the study.
A total of 20 patients (76.9%) in the PSL group and 25 patients (96.2%) in the CyA + PSL group achieved complete remission at 4 weeks. In the PSL group, complete remission was 92.3% at 3 months and 76.9% at 6 months. In the CyA and PSL group, complete remission was 92.3% at 3 months and 80.8% at 6 months. There were no significant differences in the percentage of patients in complete remission at 4 weeks, 3 and 6 months between the CY A + PSL group and the PSL group. Six patients (23.1%) in the PSL group and five patients (19.2%) in the CyA + PSL group developed relapse during the 6-month observation period.

The CyA + PSL group received a significantly lower dose of oral PSL (46.1 ± 11.3 mg/day) than the PSL group (56.0 ± 11.9 mg/day: P = 0.004). All 26 patients in the CyA + PSL group were administered cyclosporine at the dose of 600–800 ng/ml of C2. We found a correlation between the AUC0–4 and C2 (P < 0.0001, R^2 = 0.8) (Figure 1). The mean dosage of CyA was 1.8 ± 0.4 mg/kg/day. There were no major adverse events, such as elevation of the S-Cre level or hypertension during the observation period.

The proteinuria profile during the study period is presented in Table 2. In the CyA + PSL group, the urinary protein excretion decreased from 6.4 ± 3.4 g/day at baseline to 0.5±1.6 g/day at 2 weeks (P < 0.0001), 0.01 ± 0.06 g/day at 4 weeks (P < 0.0001), 0.2 ± 0.9 g/day at 3 months (P < 0.0001) and 0.6 ± 1.2 g/day at 6 months (P < 0.0001). Similarly, there was also a significant change in the urinary protein excretion in the PSL group, from 6.9 ± 2.4 g/day at baseline to 1.8 ± 2.3 g/day at 2 weeks (P < 0.0001), 0.4 ± 1.3 g/day at 4 weeks (P < 0.0001), 0.2 ± 0.7 g/day at 3 months (P < 0.0001) and 0.5 ± 1.2 g/day at 6 months (P < 0.0001). Comparison of the two groups revealed that the urinary protein excretion at 2 weeks was significantly lower in the CyA + PSL group than in the PSL group (P = 0.02). There were no significant differences in the urinary protein excretion at 4 weeks, 3 months or 6 months between the two groups.

The TP and Alb were significantly higher in the CyA + PSL group compared to the PSL group (20.5 ± 11.1) (Figure 2).

The renal function and blood pressure remained unchanged, with no significant differences between the two groups throughout the observation period.

### Table 1. Baseline clinical characteristics of patients with minimal-change nephrotic syndrome

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PSL + CyA</th>
<th>PSL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female: male)</td>
<td>26:26</td>
<td>14:12</td>
<td>12:14</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.0 ± 9.3</td>
<td>34.0 ± 7.4</td>
<td>33.0 ± 11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119.2 ± 12.5</td>
<td>119.8 ± 10.1</td>
<td>118.6 ± 13.7</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.3 ± 8.6</td>
<td>72.0 ± 7.5</td>
<td>73.4 ± 12.1</td>
<td>NS</td>
</tr>
<tr>
<td>UP (g/day)</td>
<td>6.7 ± 2.9</td>
<td>6.4 ± 3.4</td>
<td>6.9 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>4.4 ± 0.9</td>
<td>4.5 ± 0.9</td>
<td>4.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.2 ± 0.7</td>
<td>2.3 ± 0.6</td>
<td>2.1 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>402.4 ± 111.0</td>
<td>381.3 ± 112.0</td>
<td>424.4 ± 107.7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration until first relapse (days)</td>
<td>766.9 ± 700.8</td>
<td>690.0 ± 631.6</td>
<td>816.4 ± 760.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
BP, blood pressure; UP, proteinuria; eGFR, estimated glomerular filtration rate; NS: not significant.
P-value: significantly different between CyA + PSL and PSL groups.

### Table 2. Changes in proteinuria in the CyA + PSL and PSL groups

<table>
<thead>
<tr>
<th>Week (W)</th>
<th>CyA + PSL</th>
<th>P-value</th>
<th>PSL</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month (M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 W</td>
<td>6.4 ± 3.4</td>
<td>&lt;0.0001</td>
<td>1.8 ± 2.3</td>
<td>&lt;0.0001</td>
<td>0.6</td>
</tr>
<tr>
<td>4 W</td>
<td>0.01 ± 0.06</td>
<td>&lt;0.0001</td>
<td>0.4 ± 1.3</td>
<td>&lt;0.0001</td>
<td>0.1</td>
</tr>
<tr>
<td>3 M</td>
<td>0.2 ± 0.4</td>
<td>&lt;0.0001</td>
<td>0.2 ± 0.7</td>
<td>&lt;0.0001</td>
<td>0.9</td>
</tr>
<tr>
<td>6 M</td>
<td>0.6 ± 1.2</td>
<td>&lt;0.0001</td>
<td>0.5 ± 1.2</td>
<td>&lt;0.0001</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
NS: not significant.
P-value: significantly different from baseline.
P-value: significantly different between CyA + PSL and PSL groups.

Fig. 1. Correlation between AUC0–4 and C2 (y = 1.7x + 602, R^2 = 0.8, P < 0.0001).
Table 3. Changes in clinical parameters in the CyA + PSL and PSL groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CyA + PSL</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>3 months</th>
<th>6 months</th>
<th>PSL</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119.8 ± 11.5</td>
<td>118.5 ± 11.4</td>
<td>117.5 ± 11.5</td>
<td>120.1 ± 10.4</td>
<td>120.6 ± 11.4</td>
<td>118.6 ± 11.7</td>
<td>120.7 ± 12.0</td>
<td>120.1 ± 11.7</td>
<td>120.6 ± 13.8</td>
<td>118.4 ± 13.7</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.9 ± 10.1</td>
<td>69.9 ± 10.1</td>
<td>71.6 ± 10.1</td>
<td>68.2 ± 10.4</td>
<td>71.3 ± 10.4</td>
<td>71.7 ± 6.8</td>
<td>70.9 ± 11.4</td>
<td>69.9 ± 11.4</td>
<td>70.4 ± 13.8</td>
<td>68.9 ± 13.4</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>4.5 ± 0.9</td>
<td>5.2 ± 0.8</td>
<td>5.6 ± 0.5</td>
<td>6.3 ± 0.6</td>
<td>6.4 ± 0.6</td>
<td>4.3 ± 0.3</td>
<td>4.7 ± 0.7</td>
<td>5.4 ± 0.5</td>
<td>6.4 ± 0.7</td>
<td>6.5 ± 0.4</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.3 ± 0.6</td>
<td>3.1 ± 0.6</td>
<td>3.5 ± 0.5</td>
<td>4.1 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>2.1 ± 0.7</td>
<td>2.5 ± 0.6</td>
<td>3.2 ± 0.5</td>
<td>4.2 ± 0.5</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Total-cholesterol (mg/dl)</td>
<td>381.3 ± 112.0</td>
<td>317.2 ± 80.9</td>
<td>281.3 ± 77.2</td>
<td>238.2 ± 50.4</td>
<td>242.0 ± 58.9</td>
<td>424.4 ± 107.7</td>
<td>411.5 ± 128.9</td>
<td>298.6 ± 130.1</td>
<td>224.7 ± 36.7</td>
<td>226.0 ± 46.8</td>
</tr>
<tr>
<td>Complete remission</td>
<td>-</td>
<td>0/26 (0%)</td>
<td>0/26 (0%)</td>
<td>0/26 (0%)</td>
<td>0/26 (0%)</td>
<td>-</td>
<td>0/26 (0%)</td>
<td>0/26 (0%)</td>
<td>0/26 (0%)</td>
<td>0/26 (0%)</td>
</tr>
</tbody>
</table>

**P** value: significantly different from PSL group.

Values are expressed as mean ± SD.

* **P** < 0.05.

Discussion

While MCNS is known to be highly steroid-responsive, some patients show frequent relapses. The reported relapse rates in cases of adult-onset MCNS have varied from 30% to 80% [2, 3, 6, 7, 13–15], and our previous data suggested a relapse rate of 67.1% [16]. The frequency of relapses in cases of adult-onset MCNS might also be related to repeated courses of treatment with high doses of PSL. In our previous study, some patients show frequent relapses. The reported relapse rates in cases of adult-onset MCNS have varied from 30% to 80% [2, 3, 6, 7, 13–15], and our previous data suggested a relapse rate of 67.1% [16]. The frequency of relapses in cases of adult-onset MCNS might also be related to repeated courses of treatment with high doses of PSL. In our previous study, some patients show frequent relapses. The reported relapse rates in cases of adult-onset MCNS have varied from 30% to 80% [2, 3, 6, 7, 13–15], and our previous data suggested a relapse rate of 67.1% [16]. The frequency of relapses in cases of adult-onset MCNS might also be related to repeated courses of treatment with high doses of PSL. In our previous study, some patients show frequent relapses. The reported relapse rates in cases of adult-onset MCNS have varied from 30% to 80% [2, 3, 6, 7, 13–15], and our previous data suggested a relapse rate of 67.1% [16].
therapy was added to the cyclosporine therapy. There were no significant changes in the creatinine clearance or blood pressure during the study period. A recent study compared the effect of low-dose cyclosporine (2–3 mg/kg/day) following intravenous pulse methylprednisolone therapy and PSL alone on time to complete remission. The time to remission was significantly lower in the cyclosporine following intravenous methylprednisolone therapy (11.0 ± 5.6 days) than in the PSL alone (21.5 ± 15.8 days) [22]. This result was similar to that of our study. However, there have been no randomized controlled trials. We report the first randomized controlled trial of cyclosporine in adults with MCNS. We used cyclosporine microemulsion (104 ± 25 mg/day: 1.8 ± 0.4 mg/kg/day) and maintained the C2 concentration at 600–800 ng/ml. Dose adjustments based on the absorption profile are likely useful due to the poor oral absorption of the drug and low oral bioavailability in patients with nephrotic syndrome. Several reports indicate that the protracted use of cyclosporine may be associated with chronic renal injury, even in patients with normal renal function [9,10]. Hypertension develops in 14% of patients with idiopathic nephrosis treated with cyclosporine, and its incidence has been reported to be similar in adults and children [11]. Malignant tumours have been reported in patients with INS [11]. Therefore, attention must be paid to the adverse effects of the drug and the clinical response. Safer and more effective treatments are urgently needed. Ittel et al. previously evaluated the efficacy and safety of long-term cyclosporine treatment in idiopathic nephritic syndrome. They suggested that long-term maintenance treatment of MCNS with cyclosporine was efficacious and safe at least for a period of up to 43 months. Cyclosporine was started at 3–5 mg/kg/day given orally in two divided doses, and the dose was titrated to maintain through whole blood concentrations between 50 and 150 ng/ml. Initially, the cyclosporine treatment was combined with PSL (1.0 mg/kg/day) and PSL was tapered off within six weeks. Proteinuria declined from 11.3 ± 2.1 g/day to 2.1 ± 1.4 g/day within 2 months, and after 6 months the mean proteinuria was 0.7 ± 0.4 g/day. Complete remission was achieved in 9 of 15 patients [23]. We used preprandially low-dose cyclosporine for our adult patients with MCNS. The present study might show the efficacy of preprandial administration of cyclosporine. There were no major adverse events, such as renal injury or hypertension during the observation period. Combined therapy can induce early remission and facilitate reduction of the steroid dose. Combined cyclosporine and PSL therapy could be reduced PSL of total dose 2.5 g in comparison with only PSL. Therefore, combined low-dose cyclosporine and PSL therapy might avoid steroid toxicity in multi-relapse MCNS. After the 6-month observation period, the follow-up duration ranged from 6 months to 8 years (average 26 months). The frequency of relapse was not related to the repeated high-dose PSL or the duration of tapering steroids. After a treatment period of 6 months to 1 year, 8 patients attempted to withdraw of cyclosporine therapy for the purpose of preventing cyclosporine toxicity. Studies with a longer follow-up and large numbers are required in order to evaluate whether or not the frequency of relapse in multi-relapse MCNS may be reduced by combined cyclosporine and PSL therapy.

In conclusion, we found that combined low-dose cyclosporine and PSL therapy in adult patients with MCNS significantly reduced the time to remission and allowed the PSL dose to be reduced as compared to therapy with PSL alone. These results suggest that this treatment is rational and should be considered as an important option in the management of patients with MCNS.

Conflict of interest statement. None declared.

References
Early versus late start of immunosuppressive therapy in idiopathic membranous nephropathy: a randomized controlled trial

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Abstract

Background. Immunosuppressive therapy in idiopathic membranous nephropathy (iMN) is debated. Accurate identification of patients at high risk for end-stage renal disease (ESRD) allows early start of therapy in these patients. It is unknown if early start of therapy is more effective and/or less toxic than late start (i.e. when GFR deteriorates).

Methods. We conducted a randomized open-label study in patients with iMN, a normal renal function and a high risk for ESRD (urinary β2m >0.5 μg/min, UIgG >125 mg/day). Patients started with immunosuppressive therapy (cyclophosphamide for 12 months, and steroids) either immediately after randomization or when renal function deteriorated (ΔsCr ≥+25% and sCr >135 μmol/l or ΔsCr ≥+50%). End points were remission rates, duration of the nephrotic syndrome (NS), renal function and complications.

Results. The study included 26 patients (24 M/2 F), age 48 ± 12 years; sCr 96 μmol/l (range 68–126) and median proteinuria 10.0 g/10 mmol Cr. Early treatment resulted in a more rapid onset of remission (P = 0.003) and a shorter duration of the NS (P = 0.009). However, at the end of the follow-up (72 ± 22 m), there were no differences in overall remission rate, sCr (93 versus 105 μmol/l), proteinuria, relapse rate and adverse events.

Conclusions. In high-risk patients with iMN, immunosuppressive treatment is effective in inducing a remission. Early treatment shortens the duration of the nephrotic phase, but does not result in better preservation of renal function. Our study indicates that treatment decisions must be based on risk and benefit assessment in the individual patient.

Keywords: cyclophosphamide; immunosuppressive treatment; membranous nephropathy; randomized controlled trial; renal outcome

Introduction

Idiopathic membranous nephropathy (iMN) is one of the most common causes of the nephrotic syndrome in adults. The natural course of the disease is highly variable; 14–56% of patients develop a spontaneous remission, whereas 34–62% of patients develop renal insufficiency [1]. The role of immunosuppressive therapy in iMN is heavily debated, and very recent reviews have doubted the efficacy of immunosuppressive therapy [2–4].

Until recently, only one randomized controlled trial supported the efficacy of immunosuppressive therapy on hard end-points [5]. This study favoured treatment of all patients with iMN and a nephrotic syndrome with chlorambucil and prednisone. Implementation of this treatment strategy in daily clinical practice has the potential to cause harm, since ~50% of patients will be exposed unnecessarily to immunosuppressive therapy. Therefore, most authors advocate to restrict immunosuppressive therapy to patients with established renal insufficiency, the best predictor of end-stage renal disease (ESRD) [6–8]. When compared with historical controls, patients with renal failure benefited from immunosuppressive therapy [9]. Unfortunately, patients with renal insufficiency are more prone to develop treatment-related complications [1,10].