Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome

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Abstract

Background. Treatment of adults with steroid-dependent minimal change nephrotic syndrome (SD-MCNS) can be a significant challenge. Cyclophosphamide (CYC) and cyclosporin (CYA) are often effective steroid-sparing agents. Tacrolimus (TAC) may be another treatment option.

Methods. This open, prospective cohort study enrolled Chinese adults with SD-MCNS. At the start of the study, we administered TAC or intravenous CYC together with prednisone (0.5 mg/kg/day), the dose of which was tapered off throughout the study. The TAC cohort received oral TAC (target trough blood level of 4–8 ng/ml) for 24 weeks and the CYC cohort received intravenous CYC (750 mg/m² body surface) once every 4 weeks for 24 weeks.

Results. Twenty-six patients met the criteria for enrollment (14 patients in the CYC group and 12 patients in the TAC group). One patient from each group discontinued treatment because of a drug-related side effect. Complete remission (CR) after the 24-week therapeutic period was 76.9% (10/13) in the CYC group and 90.9% (10/11) in the TAC group. The mean time required for CR in the TAC group was significantly less than in the CYC group (P = 0.031). Eight of 13 (61.5%) patients in the CYC group and 8 of 11 (72.7%) patients in the TAC group successfully stopped steroids and changed their status from steroid dependence. Sixty percent (6/10) of the CYC patients and 50% (5/10) of the TAC patients who achieved CR maintained remission during the follow-up period of 23.0 ± 10.1 months. Four (40%) CYC patients and five (50%) TAC patients experienced relapses, and two CYC patients experienced frequent relapses.

Conclusion. A 24-week course of TAC is a favorable steroid-sparing agent for treatment of Chinese adults with SD-MCNS. Therapy with TAC accompanied by a tapering dose of prednisolone appears to yield quicker remission than treatment with CYC together with prednisone.

Keywords: adults; intravenous cyclophosphamide; minimal change nephrotic syndrome; steroid dependence; tacrolimus

Introduction

Steroid dependence is a major complication that may result from the standard steroid treatment of minimal change nephrotic syndrome (MCNS). Repeated and prolonged steroid therapy places patients at risk of cushingoid obesity, hypertension, infections, psychological disturbances, osteoporosis and cardiovascular morbidity later in life. Various steroid-sparing immunosuppressive agents, such as cyclosporin (CYA), cyclophosphamide (CYC) and mycophenolate mofetil (MMF), are used to induce remission and reduce negative effects of steroids in patients with steroid-dependent nephrotic syndrome (SDNS) [1–4]. Of these agents, CYC and CYA seem to be most effective and are widely used in pediatric and adult patients with steroid-dependent minimal change nephrotic syndrome (SD-MCNS) [1–3,5,6]. However, CYA, CYC and MMF are also associated with numerous toxic effects. The use of CYC is associated with bone marrow depression, infections, haemorrhagic cystitis, alopecia, bone marrow depression, gonadal failure and malignancy [6,7]. The major problems of CYA treatment are the risks of renal toxicity after long-term therapy and frequent relapse after withdrawal [1,3,8].

Tacrolimus (TAC) is an immunosuppressive macrolide of the calcineurin inhibitor (CNI) group that is widely used following organ transplantation [9,10]. Compared with CYA, TAC is more potent in cytokine suppression and seems to cause less renal toxicity [10,11]. CYA, also a CNI, is effective in treating SDNS, suggesting that other immunosuppressants that target the calcineurin pathway may be effective in treatment of these patients [1,3,6]. TAC has already been shown to be effective in maintaining remission in paediatric patients with SDNS [12]. However, data on the use of TAC in treatment of SDNS are still limited and the efficacy of TAC treatment in these patients is unknown.
There are no data from controlled experiments on the use of TAC in adults with SD-MCNS.

The purpose of this study is to evaluate the efficacy and safety of TAC in treatment of adults with SD-MCNS, and to compare TAC with intravenous CYC.

**Patients and methods**

**Study design**

We conducted an open, prospective, cohort study at a single medical center, the Kidney Disease Center of the First Affiliated Hospital, College of Medicine, Zhejiang University, People’s Republic of China. The scientific and ethics committee of our hospital approved the study protocol and we obtained informed consent from all patients before the study. We informed patients of the potential risks associated with TAC and CYC, and allowed each patient the option of treatment with oral TAC or intravenous CYC.

**Patients**

We enrolled Chinese adults (older than 18 years) with biopsy-proven minimal change disease, nephrotic syndrome (defined by the presence of nephrotic-range proteinuria > 3.5 g/24 h with serum albumin < 30 g/l), steroid dependence and serum creatinine (Scr) < 132 μmol/l. All patients were admitted to our nephrology department during the period of January 2003 to November 2005. Steroid dependence was defined as two consecutive relapses during the tapering of steroid therapy or within 14 days of cessation of steroid treatment. All patients showed negative steroid effects and relapsed upon decrease of prednisone to a dose ≤ 0.5 mg/kg/day or within 2 weeks after cessation of steroid treatment. The criteria for exclusion were systemic diseases, active infection, abnormal glucose tolerance test, liver function test abnormalities, active peptic ulcer disease and previous therapy with CYC, MMF and CYA (other than corticosteroids).

**Indications for therapy**

Patients were assigned to two cohorts: the TAC group (oral TAC in combination with oral prednisone) and the CYC group (intravenous CYC in combination with oral prednisone). For both groups, we started oral prednisone at 0.5 mg/kg/day (maximum dose 40 mg/day) until remission (protein-free urine on three consecutive days) and maintained this dose for 2 weeks after remission. Then we tapered the prednisone dose over ~4 weeks by 5 mg per week to a dosage of 20 mg on alternate days and maintained this dose for 4 weeks. Then, we tapered the prednisone dose to complete cessation in 6–8 weeks. For patients with partial remission or no remission, we maintained the dose of prednisone at 0.5 mg/kg/day throughout the 24-week therapy period. For the TAC group, we initiated TAC treatment at 0.05 mg/kg/day, divided into two doses over 12-h intervals. We adjusted the dose according to the trough blood level, with a target of 4–8 ng/ml. For the CYC group, we administered CYC intravenously at 750 mg/m2 body surface once every 4 weeks. We continued TAC and CYC treatment for 24 weeks. For patients who experienced partial remission at the end of the 24-week therapy period, we prolonged the treatment for another 12 weeks. For patients who had no response to the 24 weeks of therapy, we proposed that they quit the study. We administered increasing prednisone dosage to 0.5 mg/kg/day to patients who relapsed during therapy. Patients who relapsed during the follow-up period and quit the trial were given prednisone (1 mg/kg/day).

**Outcome variables**

The primary outcome measure was cumulative number of patients who experienced complete remission (CR). The secondary outcome measures were time required for CR, change in the steroid response status, cumulative number of sustained remissions, relapse rate, renal function during treatment and follow-up, side effects and compliance with therapy and TAC dosing and serum levels.

**Definitions**

CR was defined as when loss of oedema and return of proteinuria to normal range (<0.3 g/day) was obtained. Non-nephrotic proteinuria (0.3–3.5 g/day) with loss of oedema was considered to be partial remission (PR). Persistence of nephrotic-range proteinuria, hypoalbuminemia was considered as no response (NR). Relapse was identified as reappearance of more than 1+ albuminuria by dipstick for 3 consecutive days or recurrence of nephrotic syndrome. The time required for CR was defined as the time from the start of therapy to the first day on which we observed CR. Sustained remission was defined as 6 or more months of remission. One relapse over a period of 6 months was considered an infrequent relapse. Frequent relapse was defined as two or more relapses over a period of 6 months.

**Follow-up**

We performed follow-ups weekly for the first 4 weeks, and then monthly. At each visit, we obtained complete blood counts, serum levels of creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose, urine dipsticks and daily proteinuria. We estimated creatinine clearance (Ccr) from Scr levels and urinary creatinine levels. We measured trough TAC level every 2 weeks until it was stable and then measured it every 4 weeks.

**Statistical analysis**

Data are expressed as means ± SD. We compared differences for normally distributed continuous variables between two groups by an independent t-test and performed a paired t-test to analyze changes within each group during therapy. We expressed nonparametric variables as median and range and compared them using the Mann–Whitney test. We used the chi-square test to compare the cumulative proportion of patients who had complete or sustained remission with patients who had relapses. A P value of ≤ 0.05 was considered statistically significant.
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Table 1. Baseline characteristics of patients receiving CYC or TAC

<table>
<thead>
<tr>
<th>CYC group</th>
<th>TAC group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 14)</td>
<td>(n = 12)</td>
<td></td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>5/9</td>
<td>4/8</td>
</tr>
<tr>
<td>Age at onset of disease (years)</td>
<td>31.7 ± 12.0</td>
<td>22.7 ± 10.6</td>
</tr>
<tr>
<td>Age at treatment (years)</td>
<td>33.8 ± 12.1</td>
<td>25.0 ± 10.5</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>25.3 ± 11.3</td>
<td>28.6 ± 16.5</td>
</tr>
<tr>
<td>Number of relapses per patient</td>
<td>2.86 ± 0.77</td>
<td>2.83 ± 1.03</td>
</tr>
<tr>
<td>Cumulative steroid dosage (mg/kg)</td>
<td>297.0 ± 81.7</td>
<td>301.1 ± 99.9</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>81.7 ± 30.1</td>
<td>301.1 ± 99.9</td>
</tr>
<tr>
<td>Serum creatinine (mol/l)</td>
<td>82.1 ± 9.7</td>
<td>73.2 ± 7.7</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>5.1 ± 0.7</td>
<td>5.61 ± 1.37</td>
</tr>
<tr>
<td>Daily proteinuria (g)</td>
<td>18.9 ± 5.1</td>
<td>16.7 ± 7.1</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>82.1 ± 24.8</td>
<td>86.0 ± 29.7</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>80.0 ± 22.4</td>
<td>75.5 ± 29.1</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.1 ± 9.0</td>
<td>124.4 ± 7.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.9 ± 9.2</td>
<td>73.2 ± 7.0</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>4.92 ± 0.70</td>
<td>4.55 ± 0.80</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD (range) or number of patients.

Results

Twenty-six adult patients met the enrollment criteria and agreed to participate. Twenty-four patients relapsed upon prednisone withdrawal and two patients relapsed within 2 weeks of prednisone withdrawal. Twelve patients were self-assigned to the TAC group and 14 were self-assigned to the CYC group. There were no differences between the two groups in the main baseline characteristics (Table 1). Twenty-four patients (11 in TAC and 13 in CYC group) completed the 24-week therapy and were included in the subsequent evaluation of TAC and CYC efficacy. One patient from each group discontinued treatment because of severe drug-related adverse effects.

During the 24-week period of treatment, the mean dose of TAC was 3.1 ± 1.1 (range 2.0–7.5) mg/day, corresponding to 0.05 ± 0.02 (range 0.03–0.11) mg/kg/day. The mean TAC trough blood level was 5.1 ± 2.6 (range 1.2–8.8) ng/ml. The mean cumulative prednisone dosage was 66.3 ± 23.1 mg/kg in the CYC group and 50.6 ± 25.0 mg/kg in the TAC group, a statistically insignificant difference (P = 0.127).

Response to therapy

We evaluated efficacy according to the outcome of patients who completed the 24-week therapy. Of the patients who completed this therapy, 76.9% of CYC patients and 90.9% of TAC patients achieved CR. TAC patients tended to have higher cumulative CR rates after 2 and 4 weeks of therapy (Figure 1). The mean time for achieving CR in the TAC group (31.5 ± 25.8, range 12–98 days) was significantly less (P = 0.031) than that in the CYC group (59.9 ± 28.3, range 18–105 days). Patient number 12 in the CYC group and patient number 7 in TAC group were still in PR after 24 weeks of treatment, so we extended their treatment by an additional 12 weeks. Regardless, both patients failed to achieve CR (Figure 2). No response was seen in two (15.4%) patients of the CYC group after 24 weeks’ treatment.

The mean serum albumin levels after 2, 4 and 12 weeks of treatment were significantly higher in the TAC group than in the CYC group (P = 0.012, P = 0.002 and P = 0.005 respectively; Figure 3A). In addition, the TAC group had significantly lower daily proteinuria at the end of 2 and 8 weeks of therapy (P = 0.034 and P = 0.026 respectively; Figure 3B).

Relapses during therapy and follow-up

The mean follow-up period after cessation of therapy was 23.0 ± 10.1 months (CYC group: 22.2 ± 9.9, range 12–46 months; TAC group: 23.7 ± 10.7, range 13–43 months). Eight of 13 (61.5%) patients in the CYC group versus 8 of 11 (72.7%) patients in the TAC group (no significant difference, P = 0.683) successfully withdrew from steroids for more than 2 weeks and their status changed from steroid dependence to sustained remission. Among patients who attained CR, the percentage of patients who maintained remission at the end of therapy was 80% for both TAC and CYC patients, 70% for CYC and 60% for TAC at the 24-week follow-up, 60% for CYC and 50% for TAC at the 48-week follow-up and 60% for CYC and 50% for TAC at the final post-therapy follow-up (23.0 ± 10.1 months). At least one relapse occurred in 40% of CYC patients versus 50% of TAC patients. Two CYC patients and one TAC patient who relapsed during the therapy period relapsed again during a subsequent follow-up period. Two patients of the TAC group who relapsed during the therapy period were found to have lower trough level (1.5 and 2.6 ng/ml) and quickly achieved CR again with adjustments to the target TAC dose. Two CYC patients experienced frequent relapse. There was no significant difference in the cumulative number of sustained remissions or relapse rate between the two groups.

Changes in renal function

The changes of Scr and Ccr are presented in Figure 4A and B. The differences of Scr and Ccr between the two groups during the period of therapy and follow-up were not significant. At the last observation, no patient in either...
Fig. 2. Outcome of the patients receiving CYC (top) or TAC (bottom). Mean observation period after starting therapy was 29.2 ± 10.3 months (CYC group: 28.8 ± 10.1, range 18–52 months; TAC group: 29.5 ± 10.6, range 18–49 months). All relapses in both groups occurred before 108-week observation period after initiation of CYC or TAC therapy.

Fig. 3. Changes of serum albumin (A), daily proteinuric (B) in patients receiving CYC or TAC.

Fig. 4. Changes of serum creatinine (A) and creatinine clearance (B) in patients receiving CYC or TAC.
MCNS. Furthermore, we also observed that TAC patients can be an effective treatment in inducing remission for SD-MCNS. The difference is statistically insignificant, it indicates that TAC of CYC patients were in complete remission. Although this 24 weeks of treatment, 90.9% of TAC patients and 76.7% of SD-MCNS patients. Of the patients who completed the treatment of adults with SD-MCNS.

In our study, there is no evidence that TAC is effective in the present study, there is no evidence of TAC nephrotoxicity in the sections of either patient.

**Adverse effects**

In the CYC group, one patient did not complete the 24-week treatment because of leukopenia (WBC count: 2.1 × 10^9/l). In the TAC group, one patient had to discontinue therapy because of severe pulmonary infection. We detected some adverse effects in both groups during the treatment and follow-up periods (Table 2). The most common adverse effect was infections, which occurred in four (28.6%) CYC patients and three (25%) TAC patients. Hepatotoxicity, presented as an elevation of ALT (85–252 IU/l; normal: 3–50 IU/l) and AST (84–186 IU/l; normal: 3–40 IU/l), occurred in four CYC patients and one TAC patient. Gastrointestinal symptoms occurred in two patients of each group. New-onset hypertension occurred in one TAC patient who was given antihypertensive therapy.

**Discussion**

TAC is effective in treating patients with steroid-dependent and steroid-resistant nephrotic syndrome [12–15] and can control the proteinuria associated with MCNS due to its potent immunosuppressive effect and its suppression of vascular permeability factor production [11,16]. There is evidence that TAC has already been shown to be a promising alternative to CYA in several patients with SDNS [12]. However, a recent study by Sinha et al. [15] indicated that replacement of CYA by TAC did not lead to a better management of SDNS. Thus, there is debate about the effectiveness of TAC for treatment of SDNS and, prior to the present study, there is no evidence that TAC is effective in treatment of adults with SD-MCNS.

Our results show that a 24-week course of oral TAC or intravenous CYC, each administered with a tapering dose of prednisone, led to favorable remission in most adult SD-MCNS patients. Of the patients who completed the 24 weeks of treatment, 90.9% of TAC patients and 76.7% of CYC patients were in complete remission. Although this difference is statistically insignificant, it indicates that TAC can be an effective treatment in inducing remission for SD-MCNS. Furthermore, we also observed that TAC patients had a more rapid decrease in median daily proteinuria and increase in median serum albumin. Significantly, the mean time for response to TAC was less than that for CYC. In the literature, most steroid-sparing therapies that commonly failed to maintain remission in SDNS were concerned [1–4,12]. In our study, 72.7% of patients in the TAC group were successfully stopped from using steroids. TAC therapy also appeared to improve steroid response categories from ‘steroid dependent’ to ‘sustained remission’. During the follow-up period following therapy (23.0 ± 10.1 months), the proportion of patients with sustained remission was 50% in the TAC group and 60% in the CYC group. There were two frequent relapers in the CYC group. The maintenance of CR and relapse rates were similar in TAC and CYC patients. Our results show no significant superiority of TAC or CYC for treatment of adults with SD-MCNS.

CYA can relieve the steroid toxicity of SDNS patients, but many patients relapsed when CYA was withdrawn and were transformed into CYA-dependent cases [8,17]. In our study, 50% of TAC patients stayed in remission for more than 12 months after complete withdrawal of steroid and TAC. This is higher than that observed with CYA therapy in previous studies [1,8]. Two relapses of the TAC group during the treatment period because of low trough level of TAC responded with adjustments to the target TAC dose. No TAC patient immediately relapsed after withdrawal of TAC. The ratio of patients with anticalcineurin-dependent manner after TAC therapy may be lower than that with CYA-dependent manner after CYA therapy too. Prolonged treatment with low-dose TAC may reduce the incidence of relapse, but increase the risk of nephrotoxicity. Several recent studies indicate that MMF may be effective in treating steroid- or CYA-dependent patients without increasing the risk of nephrotoxicity [4,17,18]. It also appears that MMF is effective for the maintenance of remission in SDNS patients, with a response similar to that of CYA [19]. In the future, either TAC or MMF should be considered treatment options for treatment of steroid-dependent patients. Steroid toxicity is a significant problem in adults with SD-MCNS and may necessitate the use of other drugs [6]. All patients in our study had at least two relapses and received repeated treatment with high doses of steroids. They suffered from negative steroid effects before this study initiation and could not tolerate prolonged or repeated treatment with high doses of steroids. Thus, at initiation of the study, we administered a tapering dose of oral prednisone (0.5 mg/kg/day). This dose is lower than that used in most previous trials (for adults 1 mg/kg/day, for children 2 mg/kg/day) [1–4,12]. In most previous studies, steroid-sparing immunosuppressive agents are administered after achieving steroid-induced remission [1–3,12]. One improved steroid-sparing treatment protocol with MMF combined tapering doses of prednisolone resulted in significant steroid sparing and reduction in relapse rates in patients with SDNS and appeared to be a promising intervention in children with SDNS [4]. In our study, oral TAC or intravenous CYC, in combination with tapering doses of prednisone, was used early at the start of study to avoid insufficiency and toxicity of prednisolone. This protocol resulted in steroid sparing, with a reduction in prednisone dose. Although the mean cumulative prednisone dosage between the two groups had a statistically

<table>
<thead>
<tr>
<th>Side effects</th>
<th>CYC group (n = 14)</th>
<th>TAC group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>4 (28.6%)</td>
<td>3 (25.0%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>4 (28.6%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>2 (14.3%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>New-onset hypertension</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

**Table 2.** Adverse effects in patients receiving CYC or TAC

TAC responded with adjustments to the target TAC dose. No TAC patient immediately relapsed after withdrawal of TAC. The ratio of patients with anticalcineurin-dependent manner after TAC therapy may be lower than that with CYA-dependent manner after CYA therapy too. Prolonged treatment with low-dose TAC may reduce the incidence of relapse, but increase the risk of nephrotoxicity. Several recent studies indicate that MMF may be effective in treating steroid- or CYA-dependent patients without increasing the risk of nephrotoxicity [4,17,18]. It also appears that MMF is effective for the maintenance of remission in SDNS patients, with a response similar to that of CYA [19]. In the future, either TAC or MMF should be considered treatment options for treatment of steroid-dependent patients. Steroid toxicity is a significant problem in adults with SD-MCNS and may necessitate the use of other drugs [6]. All patients in our study had at least two relapses and received repeated treatment with high doses of steroids. They suffered from negative steroid effects before this study initiation and could not tolerate prolonged or repeated treatment with high doses of steroids. Thus, at initiation of the study, we administered a tapering dose of oral prednisone (0.5 mg/kg/day). This dose is lower than that used in most previous trials (for adults 1 mg/kg/day, for children 2 mg/kg/day) [1–4,12]. In most previous studies, steroid-sparing immunosuppressive agents are administered after achieving steroid-induced remission [1–3,12]. One improved steroid-sparing treatment protocol with MMF combined tapering doses of prednisolone resulted in significant steroid sparing and reduction in relapse rates in patients with SDNS and appeared to be a promising intervention in children with SDNS [4]. In our study, oral TAC or intravenous CYC, in combination with tapering doses of prednisone, was used early at the start of study to avoid insufficiency and toxicity of prednisolone. This protocol resulted in steroid sparing, with a reduction in prednisone dose. Although the mean cumulative prednisone dosage between the two groups had a statistically
insignificant difference, our data show a tendency toward lower mean prednisone dosage in the TAC group. This may be because quicker remission occurred in TAC patients than in CYC patients.

In general, patients with MCNS have favorable long-term outcomes and high probability of preserved renal function. In our study, renal function was well preserved during the treatment and follow-up periods. TAC was a CNI and drug-associated nephrotoxicity was concerned [13, 15]. An observational study by Falkiewicz et al. [10] showed that TAC-treated patients exhibited significantly faster recovery from tubular phosphate reabsorption impairment compared with CYA-treated patients. In addition, TAC-based immunosuppression led to better kidney allograft function during a 2-year observation period and, in comparison with CYA, TAC appeared to reduce the adverse effect profile for renal dysfunction [9, 20]. Acute reversible nephrotoxicity has been recorded as a side effect of TAC therapy when started at a dose 0.15 mg/kg/day; there was no new acute reversible nephrotoxicity when using a lower dose (0.08 mg/kg/day) [13]. In our study, we adjusted TAC dose so as to achieve a level of 4 to 8 µg/l to avoid TAC-associated adverse effects, especially TAC-associated nephrotoxicity. During the mean observation period of 29.5 months after initiation of TAC therapy, there was no evidence of deleterious effects on renal function. However, we are limited in that we performed repeat renal biopsy on only two TAC patients. Due to the relatively short follow-up period, we cannot exclude the possibility of a long-term negative impact of TAC on renal function. Hypertension and elevated blood glucose are the most prominent TAC-associated adverse effects. From the results of our study, new-onset hypertension occurred in only one TAC patient who needed antihypertensive therapy. The most common side effect in both groups was infection, most of which occurred during the period of prednisone combined TAC or CYC therapy. With earlier combined immunosuppressive therapy at the start of the study, the danger of infections may develop. The incidence of hepatotoxicity and leukopenia was higher among CYC patients than TAC patients. This study is limited in that patients were not randomly assigned to treatment groups and in that it was performed at a single medical center. Although our mean follow-up period was only 23.0 months, most patients continue to visit our medical center and we believe that longer follow-up periods will verify the results presented here.

Conclusion

This cohort study shows that a 24-week course of TAC administered with tapering doses of prednisone is an effective treatment for Chinese adults with SD-MCNS. The TAC treatment protocol that we used appears to induce earlier and more rapid remission than the CYC treatment protocol. Based on the mean observation period of 29.5 months after initiation of TAC, we found no evidence of TAC-associated nephrotoxicity. We suggest that our results provide an important foundation for the development of large, prospective, randomized, multi-center trials to address the effectiveness of TAC as a first-line steroid-sparing agent for treatment of steroid-dependent forms of nephritic syndrome.

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Conflict of interest statement. We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.


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