Tacrolimus as rescue therapy for adult-onset refractory minimal change nephrotic syndrome with reversible acute renal failure

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ABSTRACT

Background. Some adult patients with minimal change nephrotic syndrome (MCNS) who are refractory to steroid treatment or combination with immunosuppressive drug developed reversible acute renal failure (ARF) due to persistent severe hypoalbuminemia and proteinuria. It is a challenge to find rescue therapies that are effective and safe in treating such difficult patients.

Methods. In this prospective observational study, 13 patients with adult-onset MCNS, all unresponsive to treatment with a steroid or a steroid with other immunosuppressive drugs, were studied from January 2005 to February 2009. All patients developed ARF before enrollment. Oral tacrolimus (TAC) was started at 1 mg/day (target trough levels of 3–6 ng/mL) before serum creatinine (SCr) decreased to ≤133 μmol/L, and then increased doses were given (target trough level of 5–10 ng/mL) when SCr decreased to ≤133 μmol/L. Primary outcome variables were remission, and recovery from ARF. Secondary outcome variables were time to recovery from ARF, time to remission, relapse rate, changes in SCr and estimated glomerular filtration rate (eGFR).

Results. One patient discontinued TAC due to deterioration of ARF, and 12 patients recovered from ARF. The mean time to recovery from ARF was 15.8 ± 4.4 days. Nine patients (69.2%) experienced complete remission (CR) and two patients (15.4%) experienced partial remission (PR). The mean time to PR and CR was 4.8 ± 2.7 and 9.4 ± 2.3 weeks, respectively. After a mean follow-up of 69.6 months, 36.4% (4/11) of patients who had remission experienced relapses. One patient who was resistant to TAC therapy had a doubling of serum creatinine concentration during follow-up.

Conclusions. TAC may be a suitable therapeutic option for treatment of adult-onset refractory MCNS with reversible ARF.

INTRODUCTION

Minimal change nephrotic syndrome (MCNS) accounts for 10–15% of cases of primary nephrotic syndrome in adults. Previous research indicated that more than one-quarter of patients with MCNS are resistant to steroid treatment [1]. Second-line treatments for adults or children with steroid-resistant MCNS include pulse methylprednisolone, calcineurin inhibitors (CNIs), cyclophosphamide, mycophenolate mofetil and rituximab [2–5]. However, most previous studies have reported that these second-line agents have a therapeutic efficacy of <60%. Adult patients with MCNS often develop acute renal failure (ARF) at presentation of nephrotic syndrome or...
early after onset of severe hypoalbuminemia and proteinuria [1, 6, 7]. A retrospective review of adults with MCNS indicated that ARF occurred in 24 of 89 patients with MCNS [1]. Thus, there is a need for safe and effective rescue therapies for patients with ARF secondary to MCNS who are resistant to treatment consisting of a steroid or a steroid with another immunosuppressive drug, but such treatments are currently unavailable. CNIs may also be considered as a first therapeutic option for steroid-resistant nephrotic syndrome (SRNS) in children or adults according to KDIGO Clinical Practice Guideline for Glomerulonephritis [8]. However, there are concerns over acute and chronic CNI nephrotoxicity in the treatment of MCNS patients with ARF.

Oral tacrolimus (TAC) is a stronger immunosuppressant than cyclosporine and differs in the nature of its cytokine suppression, and this may explain its different effect on proteinuria in refractory MCNS [9]. Furthermore, the results of an observational study from kidney transplantation showed that in a group of patients with raised creatinine levels at entry, conversion from cyclosporine to tacrolimus resulted in improved graft function [10]. Recent reports indicate that TAC is a suitable therapeutic option for SRNS in adult and pediatric patients [11–15]. A single-center retrospective observational study reported that TAC may be a safe and effective alternative treatment for children with SRNS, with a 93.8% complete remission (CR) rate [12]. A randomized controlled trial indicates that TAC appears to be a promising alternative to cyclosporine because it is associated with a lower risk of relapses and does not have cosmetic side effects [11]. In addition, TAC is a potential option for rescue therapy of patients who failed therapy consisting of steroids in combination with cyclosporine or cytotoxic agents [12, 16]. Since 2004, we have used TAC as the preferred CNI in the treatment of adults with steroid-dependent MCNS, steroid-resistant MCNS and idiopathic membranous nephropathy. Our results indicate that TAC is more effective than cyclophosphamide in these patients [15–18]. The aim of this observational study was to evaluate the efficacy and safety of TAC as a rescue therapy for the treatment of patients with adult-onset MCNS who did not respond to treatment consisting of a steroid or a steroid with another immunosuppressive drug and developed reversible ARF.

**Subjects and Methods**

This prospective observational study was performed at a single center, the Kidney Disease Center of the First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, P. R. China). All enrolled patients were admitted from January 2005 to February 2009, were informed of the potential risks associated with steroid and TAC therapy and provided informed consent. The Ethics Committee of our hospital approved this study.

**Subjects**

All enrolled patients were older than 18 years and had adult-onset SRNS. Steroid resistance was defined as the absence of complete or PR despite at least 3 months of prednisone (1.0 mg/kg per day). In addition, some patients had resistance to a second-line agent such as pulse intravenous cyclophosphamide (750 mg/m² every 2 weeks, total dosage of at least 6 g), mycophenolate mofetil (at least 3 months at 1.5–2 g per day) or cyclosporine (at least 3 months with target trough concentration of 150–200 ng/mL). All patients developed ARF, defined as an increase in serum creatinine (SCr) to >50% above baseline. The initial histopathology of all patients indicated minimal change nephropathy (MCN). Exclusion criteria included SCr >353.6 µmol/L, urine output <800 mL/day after administration of oral or intravenous diuretics, focal segmental glomerulosclerosis or obvious acute tubular necrosis (ATN) on repeat renal biopsy, thrombotic events, dehydration, drug-induced side effect of drugs such as nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitor,

**Indications for therapy**

Oral TAC was started at 0.5 mg each 12 h to achieve a target trough level of 3–6 ng/mL until SCr decreased to ≤133 µmol/L; the dose was then increased to achieve a target trough level of 5–10 ng/mL. All patients were given oral prednisone at 0.5 mg/kg/day for 8–12 weeks according to the response; the dose was then reduced by 5 mg every 2 weeks to 20 mg on alternate days, and maintained for 8 weeks followed by tapering over 8–16 weeks until complete withdrawal. For patients who achieved CR following 24 weeks of TAC, we tapered the dose to achieve a target trough level of 3–6 ng/mL for an additional 24 weeks. Patients who relapsed during the tapering of TAC were given an increased dose until a trough level of 5–10 ng/mL was achieved.

We performed weekly follow-up for the first 4 weeks, and then monthly follow-ups. At each visit, proteinuria, complete blood count, SCr, albumin, glucose and alanine aminotransferase (ALT) were measured. The glomerular filtration rate (GFR) was estimated using the four-variable MDRD (Modification of Diet in Renal Disease) equation. After initiation of TAC, blood was drawn weekly and ultimately monthly to determine TAC trough levels.

**Outcome variables and definitions**

The primary outcome variables were cumulative number of complete or PRs, and recovery from ARF. The secondary outcome variables were relapse rate, time to recovery from ARF, time to CR and PR, changes in SCr and estimated glomerular filtration rate (eGFR), TAC dosing and serum trough levels and adverse effects.

CR was defined as a decrease in proteinuria to ≤0.3 g/day; PR was defined as a decrease in proteinuria from 0.3 to 3.5 g/day; no response was defined as the persistence of nephrotic proteinuria after 12 weeks of TAC treatment with trough levels of 5–10 ng/mL. The time to CR or PR was defined as the time from initiation of TAC therapy to the first day when CR or PR was observed. Relapse was defined as an increase in proteinuria to ≥3.5 g/day in patients who had remission. Recovery of ARF was defined as a decrease of SCr to ≤133 µmol/L. Time to recovery from ARF was defined as the time from the start of therapy to the first day when SCr decreased to ≤133 µmol/L.
Statistical analysis
All continuous variables are expressed as means ± standard deviations (SDs) or as medians and interquartile ranges (IQRs), and all categorical variables are expressed as percentages. The paired t-test was used to compare mean values obtained at different times during therapy. The Wilcoxon signed-rank test was used to compare nonparametric variables obtained at different times, and the χ² test or Fisher’s exact test were used to compare categorical variables. A P-value <0.05 was considered significant. All statistical analyses were performed with SPSS, version 14.0 (SPSS Inc, Chicago, IL).

RESULTS

Characteristics of subjects
Table 1 summarizes the baseline characteristics of the enrolled patients. 13 patients with steroid-resistant adult-onset MCNS with ARF met our enrollment criteria and agreed to participate. The mean total course of steroids before study entry was 33.4 ± 9.9 weeks, and the mean course of full-dose steroids was 12.6 ± 1.5 weeks. Five patients were also resistant to cyclophosphamide, three were resistant to mycophenolate mofetil, and two were resistant to cyclosporine. The mean duration of the ARF before study entry was 16.2 ± 6.3 days. Repeat renal biopsies were performed in nine patients during episodes of ARF and prior to initiation of TAC. Interstitial oedema was present in all repeat biopsies, and was moderate in seven patients and severe in two patients. Seven biopsies indicated no evidence of ATN, and two biopsies indicated mild ATN. Twelve patients completed at least 12 weeks of TAC therapy. One patient discontinued TAC treatment because of deterioration to ARF.

Trough levels and dosage of TAC
Figure 1 shows the trough levels of TAC during the study period. The mean dose of TAC was 1.8 ± 0.9 mg/day (range 0.03–0.08 mg/kg/day) during the first 4 weeks, 3.1 ± 0.5 mg/day (range, 0.02–0.06 mg/kg/day) during the following 20 weeks, and 2.0 ± 0.6 mg/day (range 0.03–0.08 mg/kg/day) during the final 24 weeks.

Response to therapy
Eleven of 13 patients (84.6%) had complete or PR and 9 of 13 patients (69.2%) had CR (Figure 2). The mean time to PR and CR was 4.8 ± 2.7 weeks and 9.4 ± 2.3 weeks, respectively. One patient (Patient 3) developed resistance to TAC therapy after 16 weeks and stopped TAC therapy.

Figure 3A and B show the proteinuria and serum albumin levels of patients before (Week 0) and during TAC therapy. The median proteinuria decreased from 6.5 g/day (range 4.6–12.0 g/day) at baseline to 3.3 g/day (range, 0.2–8.4 g/day) at Week 4 (P < 0.001), 0.2 g/day (range 0.1–5.8 g/day) at Week 24 (P < 0.001) and 0.2 g/day (range 0.1–8.4 g/day) at Week 48 (P < 0.001). The median serum albumin increased from 11.0 g/L (range 8.9–17.9 g/L) at baseline to 29.6 g/L (range 10.8–42.5 g/L) at Week 4 (P < 0.001), 43.5 g/L (range 15.6–49.5 g/L) at Week 24 (P < 0.001) and 43.2 g/L (range 14.5–54.4 g/L) at Week 48 (P < 0.001).

Among the 11 patients who experienced remission, 4 (36.4%) experienced relapses during TAC therapy or the follow-up period. One patient suffered two relapses. The first relapse occurred at Week 36, while TAC therapy being given with a tapering of the dose, and the second relapse occurred 10 weeks after cessation of therapy. Other patients relapsed at Weeks 12, 21 and 192 after cessation of TAC therapy.

Recovery of ARF and changes in renal function during follow-up
Figure 4C and D show the SCr and eGFR of each patient before (Week 0), during therapy, and at the last follow-up [69.6 ± 47.6 months (range 36–85 months) after initiation of treatment]. All patients who completed at least 12 weeks of TAC therapy experienced recovery from ARF by Week 4. The mean time to recovery from ARF was 15.8 ± 4.4 days (range 7–23 days). Five of 13 patients (38.5%) required three to eight sessions of hemodialysis for severe edema, despite the use of diuretics. Patient 7 suffered an exacerbation of ARF with SCr increasing from 235 µmol/L before TAC therapy to 416 µmol/L.

Table 1. Baseline characteristics of patientsa,b

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
</tr>
<tr>
<td>Male sex, n(%)</td>
<td>8 (61.5)</td>
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<tr>
<td>Age at onset (years)</td>
<td>21.5 ± 7.1</td>
</tr>
<tr>
<td>Age at treatment (years)</td>
<td>22.6 ± 7.0</td>
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<tr>
<td>Duration of disease (months)</td>
<td>8.8 ± 2.5</td>
</tr>
<tr>
<td>Duration of ARF (days)</td>
<td>16.2 ± 6.3</td>
</tr>
<tr>
<td>Initial/late steroid resistance, n(%)</td>
<td>10 (76.9)/3 (23.1)</td>
</tr>
<tr>
<td>Treatments, n(%)</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>13 (100)</td>
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<tr>
<td>Cyclophosphamide</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>3 (23.1)</td>
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<tr>
<td>Cyclosporine</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2 (15.4)</td>
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<tr>
<td>Systolic BP (mmHg)</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td>Proteinuria (g/day)</td>
<td>7.0 ± 1.9</td>
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<tr>
<td>Serum albumin (g/L)</td>
<td>11.6 ± 2.5</td>
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<tr>
<td>Serum creatinine (µmol/L)</td>
<td>234.9 ± 52.7</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>30.7 ± 8.8</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, median (interquartile range) or number (percent).

ARF, acute renal failure; eGFR, estimated glomerular filtration rate.

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L after 2 weeks of therapy. SCr decreased from 416 µmol/L to 243 µmol/L 1 week after discontinuation of TAC, 198 µmol/L 2 weeks after discontinuation of TAC. At the last follow-up, the eGFR remained stable in all patients with CR or PR. SCr of Patient 3 changed from 321 µmol/L before TAC therapy to 89 µmol/L at Week 4, 84 µmol/L at the time of discontinuation of TAC. Deterioration of renal function of this patient was observed at Week 8 after cessation of TAC therapy.

**Adverse effects**

Table 2 shows the adverse events during the period of TAC therapy. One patient suffered reversible acute nephrotoxicity after 2 weeks of TAC therapy, and this patient recovered following treatment cessation. Two patients developed infections, one patient developed hepatotoxicity, as determined by an elevation of ALT (86 IU/L; normal: 3–50 IU/L), one patient experienced new-onset hypertension and was given antihypertensive therapy, and one patient developed gastrointestinal symptoms, characterized by nausea with vomiting.

**DISCUSSION**

This prospective observational study tested the efficacy and safety of TAC as rescue therapy for treatment of adult-onset refractory MCNS with reversible ARF. The treatment of such patients is challenging for several reasons. First, all patients in this study failed to respond to initial therapy, which consisted of a steroid or steroid with another immunosuppressant. Second, all patients suffered from ARF. Effective treatment of adults with refractory MCNS, especially those with ARF, has not yet been established. Second-line agents for adults or children with refractory MCNS include cyclosporine, cyclophosphamide, mycophenolate mofetil, and TAC, and these are often given in cases of steroid resistance [3, 4, 11]. CNIs have been recommended as first agents for the treatment of SRNS [3, 8, 11], but these agents are associated with acute and chronic nephrotoxicity, so their safety, especially in the presence of ARF, is a concern. To the best of our knowledge, this is the first report to investigate the efficacy and safety of TAC as rescue therapy for the treatment of adult-onset idiopathic nephrotic syndrome with reversible ARF.
The mechanism of TAC in the treatment of steroid-resistant idiopathic nephrotic syndrome is unknown, but is presumably related to its immunosuppressive effects [9]. A recent study reported that the beneficial effect of a CNI on proteinuria results from stabilization of the actin cytoskeleton of podocytes [19]. These results indicate a novel calcineurin signaling pathway and shed light on its use as a potential treatment for refractory idiopathic nephrotic syndrome. Furthermore, TAC appears to be a more potent immunosuppressant than cyclosporine, in that it inhibits cell-mediated and humoral immune responses [20]. Several case reports indicated that TAC was effective in the treatment of some patients with nephrotic syndrome that were resistant to steroids or other immunosuppressants [11–16]. Our previous study indicated that TAC may have definite efficacy in the treatment of steroid or cyclophosphamide-resistant nephrotic syndrome [15, 16]. In this study, we administered TAC to adults with MCNS who were nonresponsive to a steroid or a steroid in combination with cyclophosphamide, mycophenolate mofetil or cyclosporine. A total of 84.6% had remission, and 69.2% had CR.

### Table 2. Adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>1</td>
</tr>
<tr>
<td>New-onset hypertension</td>
<td>1</td>
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</tbody>
</table>
Furthermore, our TAC protocol induced a rapid effect, with PR attained after a mean of 4.8 weeks and CR attained after a mean of 9.4 weeks. Interestingly, the relatively low trough levels of TAC, which were 3–6 ng/mL at the beginning of treatment and 5–10 ng/mL after recovery from ARF, were sufficient for remission.

ARF in the presence of MCNS has been well documented in the literature and typically occurs in 25–30% of adult patients [1, 6, 7]. The pathophysiology basis of ARF in such patients is still not understood. ARF in the presence of MCNS could be consistent with severe plasma volume depletion, acute tubular injury, interstitial edema, changes in glomerular permeability, and/or bilateral renal vein thrombosis [1, 7, 21–23]. Most renal biopsies of adults with MCNS at the time of ARF have features suggestive of acute tubular injury with interstitial inflammation and edema [1]. A renal biopsy study showed numerous protein droplets, flattening of epithelial cells, and focal detachment of cells from the basal membrane in proximal tubules of patients with MCNS and reversible ARF [24]. Previous results showed that ARF patients with MCNS had lower serum albumin and greater protein excretion than non-ARF patients [1, 7]. Proteinuria is a well-known risk for acute kidney injury [25]. In the present study, ARF occurred in the presence of persistent severe hypoalbuminemia (median, 11.0 g/L) and heavy proteinuria (median, 6.5 g/day). Thus, persistent hypoalbuminemia and heavy proteinuria may have a major role in the onset of ARF in the presence of refractory MCNS. Pathological examination in repeat biopsies of nine patients enrolled in this study indicated interstitial edema with no conspicuous evidence of ATN or interstitial inflammation. Acute renal damage induced by severe nephrotic syndrome should be a diagnostic possibility in most of these patients. ARF in adult patients with MCNS is often reversible. Remission of MCNS with correction of proteinuria and hypoalbuminemia might favor recovery from ARF. TAC treatment can obtain a high remission rate and a rapid effect on serum albumin levels in idiopathic nephrotic syndrome based on our experience [15–17], therefore we tested TAC as a rescue therapy for refractory MCNS with reversible ARF. The results of this study show that most patients recovered from ARF during the first 4 weeks, and the mean time for recovery was only 15.8 days. Interestingly, recovery from ARF in most of our cases paralleled the increase of serum albumin and urinary output, but preceded the decrease of proteinuria.

Previous reports indicated that TAC-based immunosuppression led to better kidney allograft function than cyclosporine [10, 26, 27]. A regimen of low-dose tacrolimus may be advantageous for renal function, allograft survival, when compared with regimens of either cyclosporine or sirolimus [26]. Tacrolimus-treated patients exhibit significantly faster recovery from tubular phosphate reabsorption impairment compared with cyclosporine-treated recipients [27]. However, TAC is a CNI, so acute and chronic nephrotoxicity is a concern [28–32]. To reduce the risks of acute CNI nephrotoxicity, we excluded patients who had SCr >353.6 µmol/L, urine output <800 mL/day or severe ATN in the second renal biopsy. Renal toxicity has been reported to be associated with TAC dose and TAC trough level [29, 32], so we administered a low dosage with target trough levels of 3–6 ng/mL before recovery of ARF. From the results of the present study, we found that one patient in this group suffered deterioration of renal failure for acute TAC nephrotoxicity. The low incidence of worsening of ARF after TAC therapy of this study was most likely due to the precautions used including the exclusion of patients with severe kidney impairment or severe ATN based on repeat renal biopsies, and the use of low TAC dose and target trough levels. Although these strategies of safeguards were used, worsening of ARF after starting TAC therapy is possible and close monitoring of these patients is required. Long-term use of a CNI is associated with chronic nephrotoxicity [28–31]. Thus, we followed our patients for a mean of 69.6 months after initiation of TAC therapy, and found that renal function remained stable in all patients who experienced remission of nephrotic syndrome and recovery from ARF. We had no clinical evidence of deleterious effects on renal function based on the measurements of SCr and eGFR, except for one patient who experienced an increase in SCr and a decrease in eGFR because of resistance to TAC therapy. Our favorable results may be due to our use of low dosage TAC therapy that was given for only 48 weeks. However, we cannot identify the pathological mechanism of the observed effect because we do not have any histological evidence. More caution should be owed to the risk of renal toxicity of TAC in treating these patients.

In summary, our results show that TAC therapy rapidly and effectively induces remission of nephrotic syndrome, resulting in recovery from reversible ARF. TAC seems to be a suitable immunosuppressive drug for the treatment of adult-onset MCNS which failed to respond to initial therapy with a steroid or with a steroid and another immunosuppressive drug. However, controlled studies with more patients are needed to determine whether TAC is truly an effective and safe agent for treatment-resistant MCNS with reversible ARF.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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