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Original Article

Comparison of efficacy and safety between tacrolimus and cyclosporine combined with corticosteroids in patients with idiopathic membranous nephropathy: a randomized controlled trial

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Abstract: Objectives: Immunosuppressive therapy plays an important role in patients with idiopathic membranous nephropathy (IMN). Evidence regarding the optimal kind of calcineurin inhibitors (CNIs) in treatment of IMN remains unclear. The objective of this study was to examine whether tacrolimus (TAC) is more effective and safe than cyclosporine (CsA) in treating IMN patients. Methods: We conducted a prospective randomized controlled study in 31 IMN patients, who were diagnosed by laboratory examination and renal biopsy. Among them, 16 patients received TAC combined with corticosteroids and 15 patients received CsA combined with corticosteroids. The follow-up period was 6 months. Results: After 6 months of therapy, no patient was lost to follow-up, complete remission (CR) occurred in 7 (43.8%) of the TAC group and 5 (33.3%) of the CsA group; partial remission (PR) occurred in 7 (43.8%) and 6 (40.0%) treated with TAC and CsA, respectively. The probability of remission (either CR or PR) was higher in the TAC group than in the CsA group, but there was no significant difference (P=0.116, by log-rank test). Furthermore, a greater incidence rate of hyperuricemia, new-onset hyperglycemia and hand tremor was observed in the TAC group compared with the CsA group. But the incidence rate of hypertrichosis, gingival hyperplasia was lower than that in the CsA group. Conclusion: TAC or CsA combined with corticosteroids was both useful for adults with IMN. But TAC was not inferior to CsA in efficacy. Otherwise, TAC and CsA had different side effects, so CNIs should be used in individualized way in patients with IMN.

Keywords: Idiopathic membranous nephropathy, tacrolimus, cyclosporine, efficacy, safety

Introduction

Idiopathic membranous nephropathy (IMN) is one of the most common causes of nephrotic syndrome in adults [1]. The fundamental pathological mechanism of IMN is that immune complex deposits under glomerular basement membrane (GBM) and the GBM diffusely thicken with spikes. The granular deposition of IgG (mainly IgG4) and C3 is visible along the glomerular capillary wall. It is found that electron dense only deposits in glomerular epithelial and/or in the basement membrane by electron microscopy. Its pathogenesis is still unclear, abnormal activation of the immune system is essential for the occurrence and development of IMN, but IMN is also regarded as a podocytopathy and podocytes play an important role in the process of proteinuria and renal function loss [2]. The clinical natural course of IMN is variable and not easy to predict. Generally, about one third of patients achieve spontaneous remission, but another one third of patients are likely to develop end-stage renal disease (ESRD) [3]. Due to the large difference of prognosis, different susceptibility to therapy and great relapse rate after drug withdrawal, the treatment has been controversial. Reich H et al recommended that immunosuppressive therapy should be given to the patients whose urinary protein excretion exceeds 3.5 g/24 h with renal function injury or proteinuria exceeds 8 g/24 h [4].

The best proven therapy for patients with IMN is the combined of cyclophosphamide (CTX) and corticosteroids. However, the potential side effects (such as gonadal dysfunction, marrow toxicity, lymphoma and bladder cancer) associated with the use of CTX [5, 6] and high recurrence rate after 12 months of treatment [7] have left many physicians reluctant to use this regimen. So choosing an effective and low toxic immumosuppressant has always been a clinical problem to be solved. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend calcineurin inhibitors (CNIs) as the replacement strategies of initial treatment for IMN patients [8]. A domestic contrast research about using cyclosporine (CsA) and CYC to treat the patients with IMN shows that the remission time of CsA was shorter than that of CYC, but the remission rate of the two groups was of no statistical significance [9]. Li et al, chen et al and Peng et al demonstrated that tacrolimus (TAC) combined corticosteroids was more rapid and more effective in inducing the remission of IMN and had tolerable adverse effects compared with CTX and mycophenolate mofetil (MMF) [10-12]. The study conducted by Choudhry S et al suggested that TAC combined with low-dose corticosteroids was not more effective than CsA in inducing remission in children with steroid-resistant nephrotic syndrome (SRNS), but had lower risks in cosmetic side effects [13]. In a word, in previous studies, investigators performed trials to compare the effectiveness between different kinds of immunosuppresants in the treatment of IMN. But there is a lack of randomized controlled study comparing the efficacy and safety between different kinds of CINs (TAC, CsA) in treating adult patients with IMN. Therefore, we admitted 31 patients with IMN to compare the efficacy and safety between TAC and CsA combined with corticosteroids in this randomized research.

Materials and methods

Patients

This prospective randomized and controlled study was conducted from September 2015 to March 2016. Thirty one patients from the first affiliated hospital of Zhengzhou university were recruited to our study. Inclusion criteria: (i) age between 18 and 60 years; (ii) IMN (stage I-IV) proven by renal biopsy and laboratory examination; (iii) persistent proteinuria >8 g/d and met the diagnostic criteria for nephritic syndrome; (iv) serum creatinine levels <133 umol/L. Exclusion criteria: (i) serious complications such as thrombolism, renal failure and infection; (ii) serious diseases companied such as HIV, cardiac dysfunction, hepatitis B, hepatitis C or lever function test abnormalities, diabetes mellitus and other kidney diseases; (iii) received any cytotoxic drugs and immunosuppressant treatment in the past; (iv) pregnant women or lactating women; (v) poor adherence to the drug. This study was approved by the ethics committee of the first affiliated hospital of Zhengzhou university. All patients were signed informed consent.

Study design

The 31 patients were randomly administered TAC or CsA combined with corticosteroids. Patients were randomized into two groups according to a randomization list generated from the table of random numbers. Patients randomized to the TAC group were administered at 0.05-0.1 mg/kg/d and was divided into 2 equal doses at 12-hour intervals. The drug concentration was first checked after 1 week. We adjusted the dosage according to the whole blood concentration, with a target of 5-10 ng/mL. For the CsA group, patients received CsA at 3-5 mg/kg/d divided into two doses at intervals of 12 hours initially. The dose was adjusted to achieve a blood trough concentration of 100-200 ng/mL. Lower blood trough concentration levels of TAC or CsA were accepted if patients were in remission. Both groups received oral prednisone at a dose of 0.5 mg/kg/d. Then we further tapered the dosage slowly by 5 mg per month down to a dosage of 10 mg/d and maintained that dosage throughout the remainder of the 6-month therapy period.

Follow-up

Follow-up was scheduled weekly for the first month and then monthly. After initiation of TAC or CsA treatment, we monitored the blood concentration of TAC or CsA each week and adjusted the dosage until stable levels of TAC or CsA were achieved. The trough concentration of TAC and CsA in whole blood was measured by chemiluminescence microparticle immunoassay (CMIA) when limosis. Laboratory evaluation including serum levels of creatinine, albumin,

Table 1. Baseline clinical and laboratory parameters

	TAC (n=16)	CsA (n=15)	*p* Value
Female:Male	4:12	2:13	0.411
Age (y)	39.4±8.8	42.8±8.1	0.279
Hypertension (n)	3	4	0.598
Systolic (mmHg)	133.1±15.0	125.2±13.8	0.138
Diastolic (mmHg)	87.1±9.2	83.4±8.2	0.252
Bloodglucose (mmol/L)	4.9±1.9	4.8±0.9	0.933
Urinary protein (g/d)	9.5±1.9	9.7±2.5	0.697
Serum albumin (g/L)	22.8±3.8	23.2±5.8	0.820
T-CHO (mmol/L)	8.0±3.2	9.1±3.1	0.364
TG (mmol/L)	3.1±2.2	2.3±1.3	0.224
Scr (umol/L)	71.8±17.4	73.3±16.5	0.813
Renal biopsy			0.250
Stage I	1	3	
Stage II	11	11	
Stage III	4	1	
Stage IV	0	0	

Values are means ± SD, or number of patients; T-CHO = serum cholesterol; TG = serum triglycerides; Scr = serum creatinine; CKD = chronic kidney disease; A value of $P<0.05$ was defined as statistically significant.

alanine aminotransferase, glucose, total cholesterol, triglycerides, as well as complete blood counts and 24-hour urinary protein was measured at baseline and at monthly intervals for 6 months. Physical examination and screening for side effects were also performed at each visit. At 6th month, a photograph of the patient's teeth was compared with the initial one by a blinded observer. A picture of the back was assessed for hypertrichosis. Reversible nephrotoxicity was defined as an increase in serum creatinine level greater than 50% more than baseline that improved after reducing the dose of TAC or CsA by 50% for 15 days.

Symptomatic treatment

Antihypertensive agents were administered to achieve a target blood pressure (systolic <125 mmHg and diastolic <75 mmHg). Angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) and other antihypertensive drugs were prescribed in those patients who did not reach the above target values. Participants with serum cholesterol levels greater than 5.6 mmol/L were treated with rosuvast calcium tablets. Anticoagulant drugs, calcium carbonate and vitamin D were also prescribed to all the patients.

Outcome parameters

The end point of this study was complete remission (CR) or partial remission (PR). CR was defined as a daily proteinuria level of less than 0.3 g, normal serum albumin (≥35 g/L), and stable renal function. PR was defined as proteinuria of 0.3-3.5 g/d that had declined to ≤50% of the baseline value with a serum albumin concentration of at least 30 g/L and a stable renal function. NO response (NR) was defined as a value for proteinuria ≥3.5 g/d and decease less than 50% of the baseline value. Total remission (TR) was defined as either CR or PR.

Statistical methods

Statistical analyses were performed with SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were described as the mean ± standard deviation (SD), and we compared differences for normally distributed continuous variables between groups by an independent *t*-test. Categorical variables are presented as numbers and percentages, chi-square test was used for comparison between groups. Kaplan-Meier analysis was used to determine the probability of complete remission and remission rate, and log-rank test was used to estimate the differences. A value of $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of patients

In this study, 16 patients were assigned to the TAC group and 15 to the CsA group. There was no difference between the two groups with respect to clinical characteristics, for example, age, blood pressure, blood glucose, proteinuria, serum albumin, liver enzymes, blood lipid, serum creatinine or pathological characteristics (**Table 1**).

Response to treatment

We evaluated efficacy according to the outcomes in patients who completed the 6-month therapy. During the observed time, no patients were lost to follow-up. As shown in **Figure 1**, NR occurred in 2 patients of the TAC group and 4 of

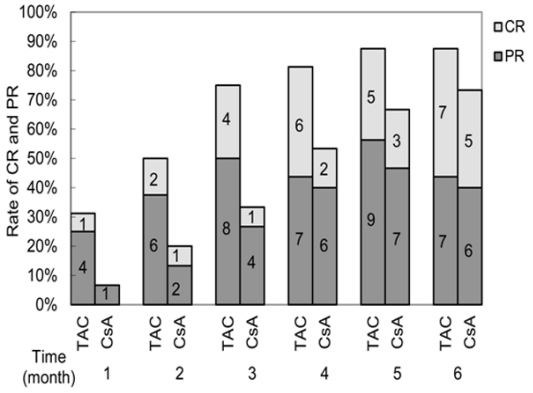

Figure 1. The remission rates in the tacrolimus and cyclosporine groups during 6 months. CR = complete remission; PR = partial remission; TAC = tacrolimus; CsA = cyclosporine.

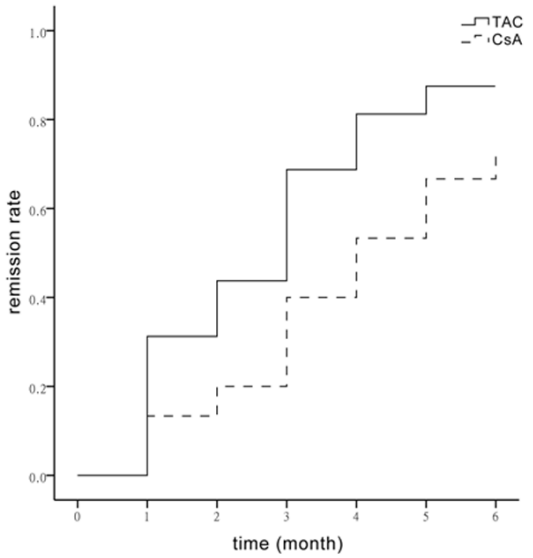

Figure 2. Kaplan-Meier curves for probability of remission (either partial remission or complete remission) in the tacrolimus (TAC) group and the cyclosporine (CsA) group (*P*=0.116, by log-rank test).

the CsA group at the end of 6th month. The percentages of remission (either CR or PR) in the TAC group vs. CsA group were 31.3% vs. 6.7%, by 1st month (*P*=0.083); 50.0% vs. 20.0% by 2nd months (*P*=0.081); 75.0% vs. 33.4% by 3rd months (*P*=0.020); 81.3% vs. 53.3% by 4th months (*P*=0.097); 87.5% vs. 66.7% by 5th months (*P*=0.166); 87.5% vs. 73.3% by 6th months (*P*=0.318), respectively. The percentages of complete remission (CR) in the TAC group vs. CsA group were 6.3% vs. 0.0%, by 1st month (*P*=0.325); 12.5% vs. 6.7% by 2nd months (*P*=0.583); 25.0% vs. 6.7% by 3rd months

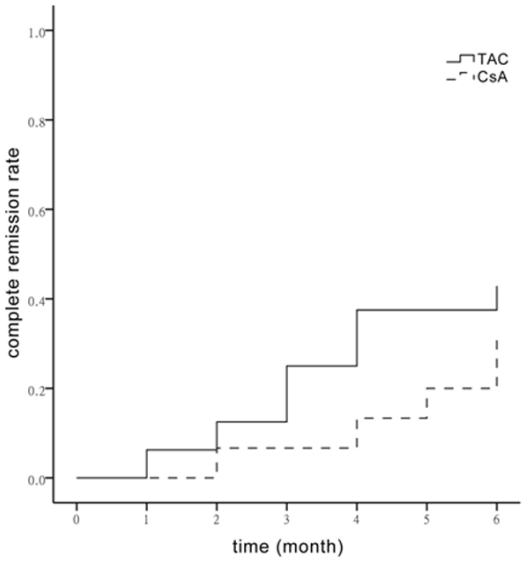

Figure 3. Kaplan-Meier curves for probability of complete remission in the tacrolimus (TAC) group and the cyclosporine (CsA) group (*P*=0.438).

(*P*=0.165); 37.5% vs. 13.3% by 4th months (*P*=0.124); 31.3% vs. 20.0% by 5th months (*P*=0.474); 43.8% vs. 33.3% by 6th months (*P*=0.552), respectively. As estimated by the Kaplan-Meier method, the probability of the remission (either CR or PR) was similar between the TAC group and the CsA group (*P*=0.116, by log-rank test) (**Figure 2**), and the probability of CR had no statistical difference between the 2 groups (*P*=0.438) (**Figure 3**). In addition, mean time to PR was 2.4±1.3 months in the TAC group vs. 3.5±1.6 months in the CsA group. And there was a statistically significant difference between the 2 groups (*P*=0.045).

Adverse effects

Side effects were monitored in all follow-up periods for all of the patients. The adverse events during the treatment period were listed in **Table 2**. Common adverse effects in the TAC group included hyperuricemia, hyperglycemia and hand tremor, which occurred in 8 patients (50.0%), 3 patients (18.8%), 4 patients (25.0%), respectively. However, 12 patients (80.0%) and 8 patients (53.3%) in the CsA group suffered from hypertrichosis and gingival hyperplasia, and this reached statistical significance.

Discussion

IMN accounts for 20% to 40% of primary nephrotic syndrome in adult patients. Consi-

Table 2. Side effects associated with the use of tacrolimus versus cyclosporine

	TAC (N=16)	CsA (N=15)	*p* Value
Pneumonia	1 (6.3%)	1 (6.7%)	0.962
Hepatotoxicity	3 (18.8%)	3 (20.0%)	0.930
Diarrhea	2 (12.5%)	1 (6.7%)	0.583
Hyperglycemia	3 (18.8%)	2 (13.3%)	0.682
Worsening of hypertension	1 (6.3%)	2 (13.3%)	0.505
Hand tremor	4 (25.0%)	1 (6.7%)	0.165
Hypertrichosis	0 (0.0%)	12 (80.0%)	<0.001
Gingival hyperplasia	1 (6.3%)	8 (53.3%)	0.004
Reversible nephrotoxicity	1 (6.3%)	1 (6.7%)	0.962
Hyperuricemia	8 (50.0%)	5 (33.3%)	0.347

Values are numbers of patients (%). TAC = tacrolimus; CsA = cyclosporine. A value of $P<0.05$ was defined as statistically significant.

dering the toxic effects of immunosuppressant and the high spontaneous remission rate of IMN, some scholars recommend delaying treatment for those adult patients with IMN who are incipient and had non-nephritic proteinuria. So the choice of immunosuppressive agents and the treatment time is crucial to the remission and the improvement of prognosis of the IMN patients. In our study, patients whose proteinuria was greater than 8 g/d received immunosuppressive therapy for the purpose of reliving proteinuria, reducing the complication and preventing progression to renal failure. Past studies had shown that patients in this group were less likely to achieve spontaneous remission [14]. In this study, treatment with TAC or CsA combined with corticosteroid was effective in patients with IMN. During the 6-month observation period, we found that the remission rate in the TAC group (87.5%) was lower than that in previous study in which investigator used similar dose of TAC (91.7%) [10]. The reason may be that the level of proteinuria was higher at the admitted time in our study. The remission rate in the CsA (73.3%) group was close to that found in two previous trials (70.7% and 71.5%, respectively) [15, 16] in which similar dose of CsA was used. Although the remission rate in TAC group was higher than CsA group, there was no statistical difference. Our study also indicated that the mean time of attaining PR was 2.4±1.3 months in the TAC group, and 3.5±1.6 months in the CsA group, and it showed significant differences between the two groups ($P=0.045$). This result demonstrated that compared with CsA therapy, TAC induced remission more quickly and significantly shorted the duration of treatment in patients with IMN, which may have contributed to protect renal function in these patients. What's more, not all patients achieved complete remission, but studies had seen that achieving partial remission also could effectively improve the prognosis of patients [17].

In patients with IMN, the immunosuppressive effects of CNIs could partially explain its therapeutic effects. However, previous study confirmed that CNIs can also reduce proteinuria in nonimmunological disease, for example Alport syndrome [18]. In addition to its immunological effects, CNIs could have other therapeutic targets for its antiproteinuria activity in IMN. Study conducted by Peng L et al verified that TAC can reduce angiopoietin-like-4 in podocytes to promote podocyte repair in an animal-model of IMN in the early stage [19]. The actin cytoskeleton of podocytes is a direct target of the antiproteinuric effect of CsA [20]. These two effects may be able to demonstrate the efficacy of TAC and CsA in treating IMN. Nevertheless, the predominance effect of CNIs is currently unclear. Compared with CsA, TAC is a more potent inhibitor of antigen-driven T cell activation, cytokine production, and lymphocyte proliferation in vitro [21]. This may be the mechanism by which TAC induced remission earlier than CsA, but whether it is related to the non-suppressive effect or not is still unknown.

In our study, we did not strictly limited the levels of the medication. Although we aimed for trough levels of TAC 5 to 10 ng/mL, and CsA 100 to 200 ng/mL, we accepted the lower levels if the patients were in remission. The mean dose of TAC was 0.04 mg/kg/d, and the trough level at 4 weeks was 4.84 ng/mL. Similarly, dosages and blood concentration of CsA were lower compared with other reports. It is worth noting that the dose and blood concentration were lower in two groups, however, 87.5% of patients on TAC therapy and 73.3% on CsA therapy were in remission at the end of 6 months. Comparing with study [11] in which investigators had used greater dose of TAC or CsA, we got the similar remission rate. The randomized prospective cohort study conducted by He et al

also demonstrated that low-dose TAC accompanied by prednisone was enough to induce remission in the majority of patients with IMN [22]. In their study, 28 patients received oral TAC (target whole blood concentration of 2-4 ng/mL) plus prednisone and the remission rate reached 82.1% after the treatment of 6 months. Similarly, Dimitrios's study also reported that low dose of CsA (2-3 mg/kg/d) could also induce remission (remission rate 85%) [23]. It is speculated that the use of lower doses of medications may have implications in minimizing their adverse effects.

Cosmetic side effects including gingival hyperplasia, hypertrichosis and hypertention were found in a large proportion of adults treated with CsA. TAC could produce more common adverse effects such as hyperuricemia, hand tremor and hyperglycemia, similar to that noted by other investigators [13]. All of those side effects were mild, transient and under control after drug withdrawal or expectant treatment. No serious consequences were caused. In a word, the side effects of drugs in two groups are different; we can give an individualized administration of drugs according to particular case in the clinical work.

Limitations of this study were as follows. (i) It was conducted at a single medical center, which limited the sample size. (ii) The time of follow-up was short. Although acquisition of partial remission is assumed to reduce the progression of kidney disease, the long-term benefits and safety of these agents was unclear. (iii) The patients were at pathological stage I to III. Due to the limitation of sample size, we can't compare the corresponding remission rate between the pathological stages. (iv) Monitoring drug levels was not rigorous. Despite these limitations, this is the first prospective randomized controlled study comparing the efficacy and safety between TAC and CsA combined with corticosterioids for treatment of patients with IMN. Meanwhile, we monitored side effects of the two immunosuppressants closely in our study.

Findings from this study suggested that therapy with TAC or CsA combined with corticosteroids had the similar efficacy in inducing remission in a considerable proportion of patients with IMN. But compared with the CsA group, patients treated with TAC could achieve remission more rapidly. The side effects in two group different from each other. However long-term randomized prospective controlled study should be conducted to evaluate the safety and efficacy.

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Disclosure of conflict of interest

None.

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