Application of low-dose calcineurin inhibitors in living-related donor renal transplantation☆

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Abstract

BACKGROUND: Adequate preparation of donors and recipients prior to living-related donor renal transplantation, short warm and cold ischemia time for donor kidney, good histocompatibility of human leukocyte antigen match, and low postoperative rejection incidence provide feasibility for use of low-dose immunosuppressive agents after living-related donor renal transplantation.

OBJECTIVE: To investigate the safety and effectiveness of low-dose calcineurin inhibitors (CNI), an immunosuppressive agent, in living-related donor renal transplantation.

METHODS: A total of 38 recipients who underwent living-related donor renal transplantation at the Center of Renal Transplantation of the First Affiliated Hospital of Nanjing Medical University from January 2006 to June 2008 were randomized for treatment with mycophenolate mofetil (750 mg twice a day), prednisone, and either standard-dose CNI (*n*=18) or low-dose CNI (*n*=20) during 12 months post-transplantation. Ciclosporin A was given orally (starting dose, 6 and 4 mg/kg per day, respectively) in two divided doses to achieve the 12-hour whole blood concentration as measured by fluorescence polarization immunoassay. The starting dose of tacrolimus was 0.12 and 0.08 mg/kg per day respectively, and its whole blood concentration was measured by enzyme-multiplied immunoassay technique. After transplantation, patients were followed up. Renal function, pulmonary infection, liver dysfunction, and CNI nephrotoxicity at different time periods were compared between different regimens.

RESULTS AND CONCLUSION: During 12 months post-transplantation, patient death occurred in one of 18 patients (5.6%) in the CNI standard-dose group and none of 20 patients (0%) in the CNI low-dose group. There was no significant difference in renal function and acute rejection between CNI standard-dose and CNI low-dose groups ($P > 0.05$). The incidence of liver dysfunction and CNI nephrotoxicity was significantly lower in the CNI low-dose group than in the CNI standard-dose group ($P < 0.05$). In addition, a low-dose CNI regimen helped recipients to lessen the economic burdens. These findings indicate that it is effective, safe and economical to use a low-dose CNI regimen in living-related donor renal transplantation.

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INTRODUCTION

Renal transplants from living-related donors have accounted for an increasing proportion of our renal transplant program over the past several years due to a severe shortage of cadaver kidneys in China. The long-term safety and benefit of a low-dose calcineurin inhibitors (CNI) such as cyclosporine A (CsA) and tacrolimus (FK506) in cadaveric renal transplantations have recently been demonstrated in randomized trials[1]. Low-dose CNI should be even safer in living-related renal transplants as these patients have received 'immunologically advantaged' grafts[2]. But so far there have been no consistent and concrete schemes in China. In our single center trial, recipients were randomized for treatment with a low-dose or a standard-dose of CNI, in combination with mycophenolate mofetil and prednisone. In this study, we prospectively compared an immunosuppressive maintenance regimen of a low-dose CNI with the standard-dose CNI and analyzed the results to evaluate its efficacy in living-related donor renal transplantation.

SUBJECTS AND METHODS

Design

A retrospective clinical study.

Time and setting

The included patients received living-related donor renal transplantation at the Center of Renal Transplantation of the First Affiliated Hospital of Nanjing Medical University from January 2006 to June 2008.

Subjects

A total of 38 recipients who underwent living-related donor renal transplantation at the Center of Renal Transplantation of the First Affiliated Hospital of Nanjing Medical University from January 2006 to June 2008 were selected and randomly divided into CNI standard-dose group (*n*=18) and CNI low-dose group (*n*=20). Adult recipients of a first renal transplantation from a living-related donor were eligible for this study. The recipients who had liver function disturbances, peptic ulcer, diarrhea, leukocytopenia, or thrombocytopenia were excluded. All donors contributed their kidneys of their own accord. The study design was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, and written informed consent was obtained from all participants before renal transplantation.

Methods

Immunosuppressive regimens

All patients received an immunosuppressive regimen consisting of CNI, mycophenolate mofetil and prednisone. Mycophenolate mofetil were given (750 mg twice a day), and 20 mg of prednisone was orally given and gradually reduced to 5 mg per day. Cyclosporine A was given orally (starting dose, 6 and

4 mg/kg per day, respectively) in two divided doses to achieve the 12-hour whole blood concentration as measured by fluorescence polarization immunoassay. The starting dose of tacrolimus was 0.12 and 0.08 mg/kg per day respectively, and its whole blood concentration was measured by enzyme-multiplied immunoassay technique. The target trough levels of cyclosporine A and tacrolimus are shown in Table 1. The sources of immunosuppressive agents are shown in Table 2.

Table 1 The target trough levels of cyclosporine A and tacrolimus

Post-transplantation (mon)	Cyclosporine A (μg/L)		Tacrolimus (μg/L)	
	CNI standard-dose group	CNI low-dose group	CNI standard-dose group	CNI low-dose group
0-1	250-300	150-200	12-15	8-11
2-3	200-250	120-160	10-13	6-9
4-6	150-200	100-120	8-11	4-7
7-12	120-180	80-120	6-10	3-6

CNI: calcineurin inhibitors

Table 2 Source of immunosuppressive agents

Generic drug	Trade name	Source
Cyclosporine A (CsA)	Neoral	Novartis
Tacrolimus (FK506)	Prograf	Astellas
Mycophenolate mofetil (MMF)	CellCept	Roche
Prednisone (Pred)	prednisone	Xinhua

Main outcome measures

Post-transplantation follow-up data were collected, 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, and 12 months post-transplantation respectively. Data on serum creatinine, acute rejection episodes, mean arterial pressure, pulmonary infection, liver dysfunction, and CNI nephrotoxicity were recorded throughout the entire study period. Creatinine clearance rate was calculated using the standard formula.

Statistical analysis

The numeric variables were presented as Mean ± SD. Comparisons between different groups were performed using the Student's *t*-test. For other analyses, the incidences were compared using Fisher's exact test. SPSS software version 11.0 was used for statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Quantitative analysis of subjects

All patients were interviewed during a period of 12 months, and follow-up was performed from January 2006 to June 2009 in specific clinic service for renal transplantation. One patient died because of severe pulmonary cytomegalovirus infection at 3 months post-transplantation. Quantitative analysis of subjects is shown in Figure 1.

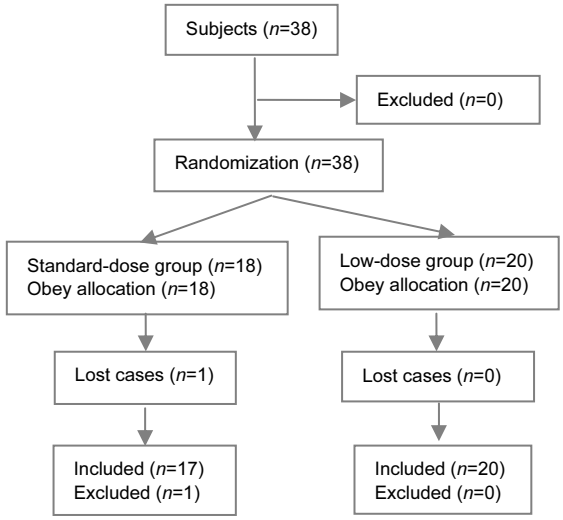

Figure 1 Quantitative analysis of subjects

Baseline data of patients

Baseline data of patients are shown in Table 3. There were no significant differences in age, gender, hepatic function, haematoglobin, glomerular filtration rate (of the donors) and blood type of both recipients and donors between the groups (data not shown). No significant difference in one haplotype human leukocyte antigen mismatch with the donor was found between the groups ($P > 0.05$). Lymphocytotoxicity test was negative and pretransplant panel-reactive antibody (PRA) was < 10% in all patients.

Table 3 Baseline data of patients

Item	CNI standard-dose group (*n*=18)	CNI low-dose group (*n*=20)
Recipient		
Gender (male/female, *n*)	15/3	16/4
Age ($\bar{x}$±*s*, yr)	28.7±4.0	31.6±9.5
Donor		
Father	3	3
Mother	12	13
Sister	3	4
Age ($\bar{x}$±*s*, yr)	45.2±15.9	48.2±16.7
HLA match		
6/6	1	1
4/6	3	3
3/6	14	16

HLA: human leukocyte antigen

Survival and renal function

During 12 months post-transplantation, the survival rate of renal graft was 94% (17/18) and 100% in the CNI standard-dose and low-dose groups, respectively, and the survival rate of recipients was 100% in both groups. No evidence of proteinuria was observed in all patients. There was no significant difference in serum creatinine (Scr) level between CNI standard-dose and low-dose groups at different stages post-transplantation ($P > 0.05$; Figure 2). Creatinine clearance rates did not differ between CNI standard-dose and low-dose groups (58.5± 27.1 mL/min *vs.* 56.3±26.6 mL/min at 3 months and 58.9± 29.8 mL/min *vs.* 59.4±27.5 mmol/L at 12 months

post-transplantation, $P > 0.05$).

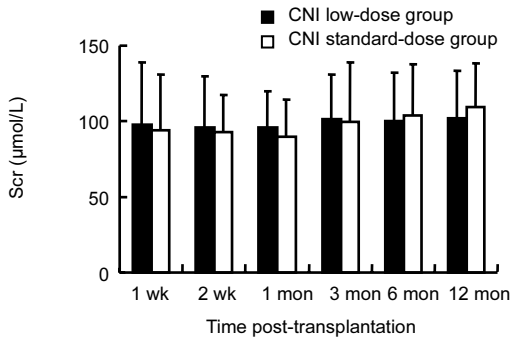

Figure 2 Comparison of serum creatinine (Scr) levels in recipients between calcineurin inhibitors (CNI) standard-dose and low-dose groups (w: week; m: month)

Acute rejection

No evidence of hyperacute rejection was observed in all patients. There was no significant difference in the incidence of biopsy-proven rejection within 12 months between the CNI standard-dose and low-dose groups [17% (3/18) *vs*. 20% (4/20)]. No histological severity of biopsy-proven rejections was observed between these two groups. All patients who suffered from acute rejection were given methylprednisolone stoss therapy.

Blood pressure

Throughout the study period, mean arterial pressure did not differ between the CNI standard-dose and low-dose groups: (101.3±16.0) mm Hg (1 mm Hg = 0.133 kPa) *vs*. (99.3± 12.1) mm Hg at 12 months post-transplantation. There were no differences between the two groups regarding the number of cases using antihypertensive drugs.

Pulmonary infection

One patient (5%) in the CNI low-dose group developed slight pulmonary infection at 6 months post-transplantation and was effectively treated with antibiotics. In the CNI standard-dose group, three patients (17%) developed pulmonary infection. One patient died 3 weeks later because of severe pulmonary cytomegalovirus infection in the CNI standard-dose group. The incidence did not show significant differences between the two groups ($P > 0.05$), but the severity of pulmonary infection in the CNI low-dose group was lower compared with the CNI standard-dose group.

Liver dysfunction

Throughout the study period, episodes of liver function disturbances occurred in 4 of 18 patients (22%) in the CNI standard-dose group, but no incidence occurred in the CNI low-dose group. Episodes of liver function disturbances in the CNI standard-dose group were significantly higher compared with the CNI low-dose group ($P < 0.05$). Total bilirubin, total cholesterol and triglyceride in the CNI standard-dose group increased as compared with the corresponding pre-transplantation values, and triglyceride had the highest increase. There were no significant differences in total bilirubin, total cholesterol and triglyceride in the CNI low-dose group between post-transplantation and pre-transplantation (data not shown).

CNI nephrotoxicity

A biopsy was performed in cases of deteriorating graft function without an obvious prerenal or postrenal cause. According to the criteria described previously[3], no evidence of CNI nephrotoxicity was observed in the CNI low-dose group, but 5 of 18 patients (28%) in the CNI standard-dose group were found to have developed it. Episodes of CNI nephrotoxicity in the CNI low-dose group were significantly lower compared with the CNI standard-dose group ($P < 0.05$).

DISCUSSION

Although CNI had improved the first-year graft survival rates, they have a significant adverse impact on renal and cardiovascular functions, and long-term graft survival has not yet been achieved[4]. Considering the good histocompatibility between donors and recipients and therefore few rejections, it was advisable that the dosage of CNI be reduced in living-related donor renal transplantation[5]. Although many studies have reported low-dose CNI use in cadaveric or living-related donor renal transplants[6-7], there had been no unified regimens in China. The purpose of this prospective pilot study was to investigate the feasibility of application of low-dose CNI.

In this study, according to the criteria described previously[8-9], the target trough levels of CsA and FK506 were established for Chinese. CNI levels were measured frequently and doses were adjusted repeatedly, and mean CNI trough levels in both groups reached the desired range satisfactorily. Acute rejection episode showed no significant difference between the CNI standard-dose and low-dose groups. Although some studies had suggested that an increased risk of acute rejection was associated with low-dose CNI levels, others had demonstrated that MMF played a so-called 'CsA-sparing' effect and therefore a low-dose CNI could prevent acute rejection efficiently in renal transplantation[10-11]. Our findings suggested that a low-dose CNI regimen did not increase the incidence or the severity of acute rejection in living-related donor renal transplantation. Graft function, as measured by Scr and creatinine clearance levels, did not show significant difference between the CNI standard-dose and low-dose groups. Our study had documented inferior graft function 3 months post-transplantation in patients who maintain a low-dose CNI therapy as compared with those who underwent the standard-dose CNI. However, the Scr levels in the CNI low-dose group were slightly lower than those in the CNI standard-dose group at 6 months post-transplantation. As we know, CNI had a revolutionary effect on the overall success of renal transplantation by reducing early immunological injuries and decreasing acute rejection rate. Nevertheless, the CNI had a significant adverse impact on renal function such as CNI nephrotoxicity[12-13]. A low-dose CNI immunosuppressive regimen is a desirable strategy to limit nephrotoxicity and a great benefit to the graft function 6 months post-transplantation[14-15].

The costs of CsA and FK506 were expensive for Chinese, and cost savings in the CNI low-dose group helped recipients to lessen the economic burdens. The cost savings in the CNI low-dose group amounted to approximately $1 000 per patient during the first 12 months post-transplantation, which means a reduction by 30%.

Results from this study suggested that a low-dose CNI regimen

is a safe and effective way to prevent acute rejections. In addition, the incidences of liver lesion and CNI nephrotoxicity were reduced, which clearly demonstrated that low-dose CNI had beneficial effects on long-term graft function and tended to produce fewer side effects. In addition, by reducing CNI dosage, a significant drop of medical expenditure could be obtained, which would contribute to relieving the financial burdens of living-related renal transplant recipients. Therefore, low-dose CNI immunosuppressive agent is a safe, effective and economical regimen.

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亲属活体供肾移植后低剂量钙调蛋白酶抑制剂的应用☆

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摘要

背景：亲属活体肾移植供、受者移植前准备充分，供肾热、冷缺血时间较短，HLA 配型的组织相容性好，移植后排斥反应发生率低，为亲属活体供肾肾移植后采用低剂量免疫抑制剂方案提供了可能性。

目的：探讨亲属活体供肾移植后低剂量钙调蛋白酶抑制剂的安全性和有效性。

方法：选取 2006-01/2008-06 在南京医科大学第一附属医院肾移植中心行亲属活体供肾移植的受者 38 例，移植后常规使用环孢素 A/他克莫司+吗替麦考酚酯+泼尼松的三联免疫抑制方案。将 38 例患者随机分为两组：CNI 常规剂量组(n=18)，移植后初始药物剂量为环孢素 A 6 mg/(kg•d)或他克莫司 0.12 mg/(kg•d)；CNI 低剂量组(n=20)，术后初始药物剂量为环孢素 A 4 mg/(kg•d)或他克莫司 0.08 mg/(kg•d)；两组吗替麦考酚酯和泼尼松使用剂量相同。移植后密切随访，比较两组患者移植后不同时期的肾功能以及急性排斥反应、肺部感染、肝功能损害、肾毒性等并发症的发生情况。

结果与结论：随访 12 个月，CNI 常规剂量组重度肺部感染死亡 1 例，CNI 低剂量组无死亡病例。两组移植肾功能及急性排斥反应发生率比较差异均无显著性意义(P > 0.05)；CNI 低剂量组肝功能损害、钙调蛋白酶抑制剂肾毒性发生率显著低于 CNI 常规剂量组(P < 0.05)。此外，采用低剂量钙调蛋白酶抑制剂免疫抑制方案明显减轻了亲属肾移植患者的经济负担。说明亲属活体供肾移植后采用低剂量钙调蛋白酶抑制剂的免疫抑制剂方案安全、有效。

关键词：亲属活体供肾；低剂量；免疫抑制剂；钙调蛋白酶抑制剂；肾移植
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