Clinical efficacy and safety of conversion from cyclosporine A to tacrolimus-based regimen for different pathological types of chronic allograft nephropathy patients*★

Gao Sen[1], Gao Yi[1], Liu Yong-guang[2], Liu Ding[2], Guo Ying[2]

[1]Department of Hepatobiliary Surgery, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China
[2]Center for Organ Transplantation, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China

Gao Sen★, Studying for master's degree, Department of Hepatobiliary Surgery, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China nfygaosen@sina.com

Correspondence to: Guo Ying, Doctor, Associate professor, Center for Organ Transplantation, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China guohanjing001@163.com

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Abstract

BACKGROUND: Recent studies have suggested that conversion from cyclosporine A (CsA) to tacrolimus (FK 506)-based regimen can improve renal allograft function and survival rate. But little is known about whether the conversion from CsA to tacrolimus(FK 506) plus mycophenolate mofetil (MMF)-based regimen exhibits the same or similar clinical efficacy.

OBJECTIVE: To investigate the clinical efficacy and safety of converting CsA to FK506 plus MMF in treatment of different types of chronic allograft nephropathy (CAN).

DESIGN, TIME AND SETTING: An observational and controlled trial was performed at the Center for Organ Transplantation, Zhujiang Hospital, Southern Medical University from January 2005 to October 2007.

PARTICIPANTS: Fifteen-nine enrolled patients received CsA-based regimen after renal allografting. Following pathological confirm and typing, all patients were assigned to two groups: CAN with chronic rejection (CR, *n* = 31) and CAN without chronic rejection (non-CR, *n* = 28). FK 56 was purchased from Fujisawa Pharmaceutical Company, Ltd., Japan. MMF was sourced from Shanghai Roche Pharmaceutical Co., Ltd., China.

METHODS: When patients were diagnosed CAN, the CsA regimen was conversed to FK506 plus MMF regimen. FK506 initiated at a dose of 0.08 mg/kg per day and then was adjusted to achieve steady-state whole blood trough levels of approximately 5−8 μg/L. MMF was used at a fixed dosage, 1.0 g/d, twice a day, only if relative adverse events occurred. All patients were followed up at least 6 months.

MAIN OUTCOME MEASURES: Serum creatinine(Scr), total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), 24-h proteinuria, glomerular filtration rate (GFR), and complications.

RESULTS: All initial 59 patients were included in the final analysis. At 6 months after regimen conversion, the levels of Scr, TC, TG, LDL, and 24-hour proteinuria were significantly reduced in non-CR, in particular CR, groups, compared with prior to conversion ($P < 0.05$). GFR was markedly increased in both the CR and non-CR groups ($P < 0.05$). In the CR group, 20 patients obtained improved results, 7 got stable results, and 4 showed ineffective results. The effective rate of regimen conversion was 64.5% and 32.1% in the CR and non-CR groups, respectively, and significant difference existed between the two groups ($P < 0.05$). Compared with prior to conversion, the incidence of hypertension and hyperlipemia was significantly decreased after regimen conversion ($P < 0.05$). There was no significant difference in diabetes mellitus, opportunistic infection, and malignancy between prior to and after regimen conversion.

CONCLUSION: FK506 plus MMF-based regimen can markedly improve the function of renal graft of CAN, in particular CR, patients.

INTRODUCTION

Despite the enormous advancement of immunosuppressive therapy and a significant improvement in short-term graft survival rate after renal allografting, CAN is the leading cause of late renal allograft loss and a headache problem to clinicians[1-4].

Recent studies have suggested that conversion to tacrolimus reduces cyclosporine (CsA) toxicity and immunosupression can improve allograft function, but the clinical efficacy and safety are discrepant[5-6]. For this reason, such an intervention has been considered to produce different outcomes in different pathological types of CAN. The present study performed CsA conversion to FK506 in different pathological types of CAM.

SUBJECTS AND METHODS

Patients and study design

A total of 59 patients consisting of 33 males and 26 females received CsA-based regimen immunosuppressive theray after cadaveric renal allografting at the Center for Organ Transplantation, Zhujiang Hospital, Southern Medical University from January 2005 to October 2007. All patients were pathologically diagnosed with CAN and assigned to a CAN with chronic rejection (CR) group (*n* = 31) and a CAN without CR (non-CR) (*n* = 28) group. The baseline data are shown in Table 1. There was no significant difference in baseline data between CR and non-CR groups.

Converting scheme

When CAN was pathologically confirmed, the CsA regimen was conversed to FK506 plus MMF regimen. FK506 initiated at a dose of 0.08 mg/kg per day and then was adjusted to achieve steady-state whole blood trough levels of approximately 5−8 μg/L. MMF was used at a fixed dosage, 1.0 g/d, twice a day, only if relative adverse events occurred. All patients were followed up at least 6 months. FK506 dosage adjustment was based on the following principles: ① When the blood

concentration > 10 ng/mL, 1/4–1/3 of the FK506 dosage was reduced and the blood concentration was retested 1 week later. ② When Scr kept going up and exceeded its baseline more than 30%, 1/4–1/3 of the FK506 dosage was reduced and Scr level was retested 1 week later, if it kept going up, Fk506 was reduced to half of its basic dosage or even withdrawn. ③ When the patients were complicated by hyperglycemia, FK506 was reduced to half of its dosage. ④ When the patients were complicated by server infection, immunosuppressants were withdrawn for a few days and the primary immunosuppressive protocol was reassumed as soon as the infection was brought under control.

Table 1 Baseline data of CR and non-CR groups

Item	CR group (n = 31)	Non-CR group (n = 28)	P value
Heat ischemia time (min)	14.1±4.0	14.9±3.6	0.900[a]
Cold ischemia time(h)	5.3±1.7	5.4±1.5	0.709[a]
Age (yr)	40.8±10.9	43.3±12.0	0.537[a]
Gender(% males)	20(64.5%)	16(57.1%)	0.562[c]
HLA mismatches	2.6±0.7	2.0±1.2	0.541[a]
PRA (%)	24.5±31.4	21.4±28.5	0.487[a]
Dialysis time(mon)	8.9±3.6	10.0±4.5	0.161[a]
Delayed renal allograft function (%)	3(9.7%)	2(7.1)	0.727[b]
Primary cause of renal failure [n (%)]			0.499[b]
Chronic glomerulonephritis	19(61.35)	16(57.15)	
Diabetes mellitus	2(6.5%)	3(10.7%)	
Polycystic kidney disease	2(6.5%)	0(0.0%)	
Others/Unknow	8(25.8%)	9(32.1%)	

CR: chronic allograft nephropathy with chronic rejection; non-CR: chronic allograft nephropathy without chronic rejection; HLA: human leukocyte antigen; PRA: panel-reactive antibody; Values are expressed as Mean ± Standard Deviation or number (percentage); a for Student's t test, b for Pearson's chi-squared test

Clinical criteria

Effectiveness was defined as follows: improved: a decrease of serum creatinine (Scr) of more than 10%, which persisted during follow-up period; stable: Scr remained within 10% of the previous level at the end of follow-up; failed: either a persistent deterioration of renal function or failure to stabilize. Dialysis was necessary for graft failure patients.

Laboratory parameters

Scr, total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), 24-hour proteinuria, glomerular filtration rate (GFR) were examined. The cardiovascular risk profile was assessed by the incidence of hypertension, hypercholesterolemia and post-transplant diabetes mellitus (PTDM). Hypercholesterolemia was defined as TC greater than 5.8 mmol/L (224 mg/dL) or requiring lipid-lowering agent. The use of drugs for hypertension or hypercholesterolemia was established from the medical record. PTDM was defined as fasting blood glucose more than 7 mmol/L (126 mg/dL) on two occasions at any time after transplantation in those patients with no previous history of diabetes mellitus.

Statistical analysis

All data were analyzed using SPSS 13.0 software and were expressed as Mean±SD. Baseline data were compared using Student's t test, Pearson's X^2 test or Fisher's exact test where appropriate. The rate of adverse events between CR and non-CR groups was compared using Pearson's X^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

Quantitative analysis of subjects

All initial 59 patients were included in this study.

Laboratory examination results

At 6 months after regimen conversion, the levels of Scr, TC, TG, LDL, and 24-hour proteinuria were significantly reduced in non-CR, in particular CR, groups, compared with prior to conversion ($P < 0.05$). GFR was markedly increased in both the CR and non-CR groups ($P < 0.05$, Table 2).

Table 2 Laboratory exmination results of CR and non-CR groups ($\bar{x}$±s)

Item	CR group (n = 31)	
	Prior to conversion	6 mon after conversion
Scr (μmol/L)	291.0±82.0	236.6±75.6[a]
GFR (mL/min per 1.73 m^2)	48.3±3.3	54.7±3.9[a]
Proteinuria (g/24 h)	3.7±0.8	2.0±0.3[a]
TC (mmol/L)	6.8±1.3	5.2±0.7[a]
TG (mmol/L)	3.1±1.1	1.9±0.8[a]
LDL (mmol/L)	3.9±1.0	2.5±0.5[a]
Item	Non-CR group (n = 28)	
	Prior to conversion	6 mon after conversion
Scr(μmol/L)	302.3±98.2	287.5±80.3[ab]
GFR(mL/min per 1.73 m^2)	48.8±3.4	50.9±3.5[ab]
Proteinuria (g/24 h)	3.5±0.6	2.8±0.5[ab]
TC (mmol/L)	6.9±1.8	6.0±0.9[ab]
TG (mmol/L)	2.9±1.0	2.5±0.9[ab]
LDL (mmol/L)	3.8±0.8	3.0±0.7[ab]

CR: chronic allograft nephropathy with chronic rejection; non-CR: chronic allograft nephropathy without chronic rejection; Scr: serum creatinine; GFR: glomerular filtration rate; TC: total cholesterol; TG: triglyceride; LDL: low density lipoprotein; [a]$P < 0.05$, vs. 6 mon in the CR and non-CR groups; [b]$P < 0.05$, vs. 6 mon in the CR group

According to clinical criteria, 20 patients were improved, 7 patients were stable, and 4 patients failed and received hemodialysis in the CR group; 9 patients were improved, 12 patients were stable, and 4 patients failed in the non-CR group. The effective rate of regimen conversion was 64.5% and 32.1% in the CR and non-CR groups, respectively, and significant difference existed between the two groups ($P < 0.05$). Compared with prior to conversion, the incidence of hypertension and hyperlipemia was significantly decreased after regimen conversion ($P < 0.05$). There was no significant difference in diabetes mellitus, opportunistic infection, and malignancy between prior to and after regimen conversion. There was statistical difference in clinical efficacy between the CR and non-CR groups ($P < 0.05$; Table 3). After regimen conversion, the incidence of hypertension and hypercholesterolemia was obviously decreased compared with prior to conversion, and there was no statistical difference in the incidence of diabetes mellitus, opportunistic infection, and malignancy among 59 cases ($P < 0.05$; Table 4).

Table 3 Clinical efficacy of CR and non-CR groups

	CR group (*n* = 31)	Non-CR group (*n* = 28)
Improved	20	9
Stable	7	12
Failure	4	7
Clinical effcacy	64.5%	32.1%

Table 4 Pre- and post-conversion complications of 59 patients (*n* /%)

Complication	Pre-conversion	Post-conversion	*P* value
Hypertension	39/66.1	25/42.4	0.010[b]
Hypercholesterolemia	29/49.2	18/30.5	0.039[b]
Diabetes mellitus	6/10.2	8/13.6	0.569[b]
Opportunistic infection	10/16.9	8/16.3	0.931[b]
Malignancy	0/0	0/0	1.000[b]

b for Pearson's chi-squared test

DISCUSSION

CAN has become a major cause of renal dysfunction and renal allograft loss after transplantation. Both FK506 and CsA belong to calcineurin inhibitors (CNI). But CsA has a series of side effects such as nephrotoxicity, hypertension, metabolic disturbances of blood lipids, etc, which are primary causes of CAN in the triple immunosuppressive regimen[7-8]. FK506 had been proved more effective than CsA for CAN. Scientists further researched FK506 and concluded that FK506 can suppress the progression of CAN. The potential mechanisms include: ① The immunosuppressive efficacy of FK506 is 50–100 times than that of CsA, it can not only be used as basal immunosuppressants to prevent rejection but also be effective to steroid-resistant and intractable rejection. Thus the administration of FK506 will play an important part in preventing CAN[9].② The nephrotoxicity of CNI is a very important factor in the progression of CAN. As the dosage of FK506 clinically prescribed is much lower than that of CsA, it will notably lessen the nephrotoxicity of CNI and slow the progression of CAN[10]. ③ Hypertension and hyperlipidemia are important risk factors in the occurrence and progression of CAN. CsA can activate rennin-angiotensin system and influence the constriction/dilation function of renal vessels to cause hypertension, It can also cause a high level of LDL and enhance the side effects of steroids to cause hypertension. On the contrary, FK506 would not bring these side effects. So after conversion, hypertension and hyperlipidemia will be more efficiently controlled and the renal allograft function will be improved[11]. In the present study, at 12 months after conversion, the level of Scr, TC, TG and LDL in both groups was lower and GFR was higher than prior to conversion. Comparisons between pre- and post conversion in both groups reveal significant statistical difference. In the CR group, the level of Scr, TC, TG and LDL was (236.6±75.6) μmol/L, (5.2±0.7), (1.9±0.8), and (2.5±0.8) mmol/L respectively, and they were all at a significantly lower level than the non-CR group. The mean GFR was significantly higher in the CR group than in the non-CR group ($P < 0.05$, Table 1). ④CsA can injure P-glycoprotein and make it accumulated in the cells. The accumulation will injure proximal tubule and finally cause tubular interstitial fibrosis[12]. *In vivo* and *in vitro* experiments reveal that CsA stimulate the expression of tumor growth factor beta 1, which will cause fibrosis and stimulate the expression of platelet derived growth factor and finally cause smooth muscle cell hyperplasia. This plays an important role in the progression of graft arteriosclerosis. Different from CsA, FK506 has the same binding site with tumor growth factor beta receptor (TGF-β), which is called FKBP-12. It will interfere the expression of TGF-β by competitive combination, and may ameliorate graft fibrosis and finally slow the progression of CAN[13]. Proteinuria is one of the important characteristics in the progression of CAN. Meantime, protein in the urine will subside in the basement membrane and protein cast will block the tubule, which will accelerate the progression of CAN[14].

In the present study, at 12 months after conversion, proteinuria in the both groups was significantly lower than prior to conversion, the level of 24-hour proteinuria in the CR group was decreased from (3.7±0.8) g to (2.0±0.3) g, which was significantly lower compared with the non-CR group ($P < 0.05$, Table 3). This indicates that FK506 could efficiently improve proteinuria in CAN patients, in particular CR patients, and delay the progression of renal dysfunction. The present results suggest that conversion from CsA to FK506 markedly improve the allograft function and slow the progression of renal failure. The side effects and toxicity of FK506 have positive correlation with its dosage. The 5–10 ng/mL target FK506 is considered to be safe at 6 months after renal allografting[15].

In the present study, there was no significant statistical difference in the incidence of side effects and toxicity between the CR and non-CR groups. Compared with a prospective, randomized, multicenter, clinical trail[16] , we found low dosage of FK506 and well controlled blood concentration would not increase the allografting risk.

There are several limitations in the present study, and protocol biopsies are not a part of the routine practice in our center. Without histological information, subclinical rejection and CNI toxicity cannot be diagnosed early or accurately. This may influence our observation results. Based on early diagnosis and recognition of these disorders, proper FK506 adjustment in our immunosuppressive regimen may improve the worse outcomes. The mechanisms as to why FK506 produces different efficacies in treatment of different pathological types of CAN need to be further investigated.

REFERENCES

[1] Zisman AL, Sprague SM. Chronic Allograft Nephropathy. Adv Chronic Kidney Dis. 2006;13(1):56-61.
[2] Kosch M, Hausberg M, Suwelack B. Studies on effects of calcineurin inhibitor withdrawal on arterial distensibility and endothelial function in renal transplant recipients. Transplantation. 2003;76(10):1516-1519.
[3] Nankivell BJ, Chapman JR. Chronic allograft nephropathy: current concepts and future directions. Transplantation. 2006; 81(5):643-654.
[4] Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. N Engl J Med. 2003;349(24): 2326-2333.

[5] Meier M, Nitschke M, Weidtmann B, et al. Slowing the progression of chronic allograft nephropathy by conversion from cyclosporine to tacrolimus: a randomized controlled trial. Transplantation. 2006;81(7):1035-1040.
[6] Kaplan B, Schold JD, Meier-Kriesche HU. Long-term graft survival with neoral and tacrolimus: a paired kidney analysis. J Am Soc Nephrol. 2003;14(11):2980-2984.
[7] Banasik M, Klinger M. Chronic allograft nephropathy--immunologic and nonimmunologic factors. Ann Transplant. 2006;11(1):7-10.
[8] Flechner SM, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clin Transplant. 2008;22(1):1-15.
[9] Artz MA, Boots J, Ligtenberg G, et al. Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. Am J Transplant. 2004;4(6):937.
[10] Cheung CY, Wong KM, Chan HW, et al. Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. Transplant International. 2006;19(8):657-666.
[11] Waid T. Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure. Clin Transplant. 2005;19(5):573-580.
[12] Anglicheau D, Pallet N, Rabant M, et al. Role of P-glycoprotein in cyclosporine cytotoxicity in the cyclosporine-sirolimus interaction. Kidney Int. 2006;70(6):1019-1025.
[13] Bing P, Maode L, Li F, et al. Expression of renal transforming growth factor-beta and its receptors in a rat model of chronic cyclosporine-induced nephropathy. Transplant Proc. 2006;38(7):2176-2179.
[14] Fernandez-Fresnedo G, Plaza JJ, Sanchez-Plumed J, et al. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. Nephrol Dial Transplant. 2004;19 Suppl 3: i47-i51.
[15] Krämer BK, Montagnino G, Del Castillo D, et al. Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results. Nephrol Dial Transplant. 2005;20(5):968-973.
[16] Stoves J, Newstead CG, Baczkowski AJ, et al. A randomized controlled trial of immunosuppression conversion for the treatment of chronic allograft nephropathy. Nephrol Dial Transplant. 2004;19(8):2113-2120.

他克莫司替代环孢素 A 为基础方案治疗不同病理类型慢性移植肾肾病：有效性和安全性**★

高　森[1]，高　毅[1]，刘永光[2]，刘　丁[2]，郭　颖[2]（南方医科大学珠江医院，[1]肝胆二科，[2]器官移植中心，广东省广州市　510282）

高　森★，男，1982 年生，汉族，安徽省巢湖市人，南方医科大学在读硕士，主要从事生物人工肝功能性研究研。

通讯作者：郭　颖，博士，副教授，南方医科大学珠江医院器官移植中心，广东省广州市　510282

摘要

背景：研究证实以他可莫司代替环孢素 A 的免疫抑制方案能够改善移植肾的功能，提高移植肾的生存率，但国内外尚未报道这种以他可莫司联合霉酚酸酯为主的免疫抑制方案是否对所有病理类型的慢性移植肾肾病(chronic allograft nephropathy，CAN)都有相同或相似临床有效性。

目的：观察以他可莫司联合霉酚酸酯为基础的免疫抑制方案对不同病理类型 CAN 的有效性和安全性。

方法：59 例接受尸体供肾移植患者，移植后均接受以环孢素 A 为主的免疫抑制方案；经病理证实和分型后分为 2 组：CAN 伴慢性排斥组(n=31)和 CAN 不伴慢性排斥组(n=28)。所有患者在被病理证实为 CAN 时，立即停止环孢素 A，转换为他可莫司联合霉酚酸酯为主的免疫抑制方案，他可莫司的起始剂量为 0.08 mg/(kg·d)，其目标血药质量浓度为 5~8 μg/L，霉酚酸酯按固定剂量 1.0 g/d，2 次/d，根据患者的自身情况和药物的副作用调整药物剂量。随访期间，所有患者血肌酐、总胆固醇、三酰甘油和低密度脂蛋白、24 h 蛋白尿和肾小球滤过率及并发症发生情况。

结果与结论：59 例患者均进入结果分析。随访 6 个月后，CAN 伴慢性排斥组和 CAN 不伴慢性排斥组患者血肌酐、总胆固醇、三酰甘油和低密度脂蛋白和 24 h 蛋白尿均较转换前明显降低(P < 0.05)，CAN 伴慢性排斥组更明显(P < 0.05)，两组肾小球滤过率均明显升高(P < 0.05)。CAN 伴慢性排斥组中 20 例患者好转，7 例患者稳定，4 例患者无效；CAN 不伴慢性排斥组中 9 例患者好转，15 例患者稳定，4 例患者无效。两组有效率分别为 64.5%，32.1%，差异有显著性意义(P < 0.05)。与转换前相比较，患者高血压的发病率和高脂血症的发病率有显著性下降(P < 0.05)，而糖尿病、机会性感染和恶性肿瘤的发病率无统计学意义。提示以他可莫司联合霉酚酸酯为基础的免疫抑制方案可以显著性的改善 CAN 患者移植肾肾功能，尤其是对 CAN 伴慢性排斥反应患者。

关键词：慢性移植肾肾病；环孢素 A；他克莫司；霉酚酸酯；慢性排斥反应；肾移植

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