Original Article
Five-year follow-up after conversion from calcineurin inhibitor to sirolimus-based treatment in kidney transplant patients with chronic allograft nephropathy

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Abstract: Chronic allograft nephropathy (CAN) is a major cause of graft loss in long-term kidney transplant recipients. To identify the safety and efficacy of conversion from calcineurin inhibitors (CNI) to sirolimus (SRL) in patients with CAN, we investigated 92 biopsy demonstrated CAN patients during a 5-year follow-up.45 patients were converted to sirolimus treatment (SRL group) and remaining 47 patients continued CNI immunosuppression (CNI group). Renal function, proteinuria, hepatic function, lipid level and blood routine examination were observed for 60 months in each group. During the period of conversion, serum creatinine was superior in SRL group to CNI group. It dropped significantly from (174.0 ± 62.8) umol/L to (150.7 ± 83.4) umol/L in SRL group whereas increased to (200.9 ± 73.5) umol/L in CNI group (P < 0.05). However, SRL group showed increased proteinuria, triglycerides and decreased Plt (P < 0.05). We also found those patients in SRL group with a good baseline of renal function (serum creatinine < 200 umol/L or proteinuria < 800 mg/day at conversion) would ameliorate the impaired renal function from CAN at 60 months. In conclusion, it is safe and effective to convert from CNI to SRL for patients with CAN in our long-term observation. Early conversion is associated with an improvement of renal function.

Keywords: Sirolimus, chronic allograft nephropathy, conversion treatment

Introduction

One-year renal graft survival has improved markedly during the last 30 years up to more than 90% after introduction of new immunosuppressive protocols. Nonetheless, a commensurate increase in long-term graft survival has not been attained [1, 2]. Among all factors influencing the survival of the patients, chronic allograft nephropathy (CAN) is the most common cause of late renal graft dysfunction. Both immunological and non-immunological factors play a role in the development of CAN, and calcineurin inhibitor (CNI) therapy like Cyclosporine A (CsA) and Tacrolimus (Tac, FK506) has been identified to be an important non-immunological cause [3, 4]. Histologic features of CNIs nephrotoxicity include such as arteriolar hyalinosis, glomerulosclerosis, and tubulo-interstitial damage. These irreversible lesions lead to functional decline and insufficiency of the graft. Therefore, the use of antiproliferative drugs in combination with a reduction or withdrawal of CNI has become an interesting concept in treating CNI toxicity.

Sirolimus (SRL) is a macrolide antibiotic produced by the fungus Streptomyces hygroscopicus [5], with a mechanism of action and safety profile distinct from that of CNIs [6]. It inhibits the interleukin-2-mediated signal transduction pathway through binding to a specific cell cycle regulator protein called mammalian target of sirolimus (mTOR) and offers a potent immunosuppressive alternative to CNIs, with lower nephrotoxicity [7-9]. Sirolimus is also an effective immunosuppressant in preventing the acute allograft rejection [10]. Conversion to sirolimus has improved and stabilized renal graft function in some patients with biopsy-proven CNIs nephrotoxicity.

In present study, we observed the clinical indicators in patients showing histological signs of CAN from CNI-based protocols to SRL-based regimens and made the corresponding compar-

Table 1. Demographic data of SRL and CNI group

	SRL	CNI
	N = 45	N = 47
Age (year)	43.6 ± 8.9	42.4 ± 12.2
Gender (F/M)	15/30	18/29
Donor (Living/Death)	6/39	7/40
First/Second Tx	41/4	43/4
Rejection before conversion (times)	0.9 ± 0.7	1.2 ± 0.9
Mean grade of CAN	1.7±0.5	1.8 ± 0.7
Beginning time of creatinine elevation after Tx (month)	37.8 ± 19.2	35.4 ± 18.1
Infection (CMV/pneumonia)	5/4	6/6
BP before conversion (mmHg)	138 ± 9/81 ± 7	139 ± 5/80 ± 4

There were no significant differences between SRL and CNI group for the criteria mentioned in this table.

ison. The aim is to identify those patients who are likely to benefit from conversion from CNI to SRL and to analyze the safety and efficacy of this conversion in a large cohort of CAN patients for a five-year follow-up.

Methods

It is a retrospective controlled clinical study performed in two centers including all patients who were accepted kidney transplantation and regular follow-up starting from February 1999.

Inclusion criteria were (i) transplantation more than 3 months before conversion, (ii) confirmed CAN by biopsy and conversion from a CNI-based protocol to a Sirolimus-based protocol, (iii) the absence of histological signs of acute rejection and (iv) on therapy with sirolimus for at least 5 years after conversion. Lesions suggestive of CAN were graded according to the BANFF 03 classification.

The conversion was performed by two methods according to the reduction of CNI on the day of introduction of SRL with or without a SRL loading dose. (1) to give SRL 4~5 mg dose in CNI sudden withdrawal's day, and then everyday 2~3 mg to maintain, adjustment according to trough concentration; (2) the first day of CNI reduction 50%, overlapping SRL 2 mg, the CNI was then gradually withdrawn over a period of 1-4 weeks. Target SRL trough levels were 5~12 ng/ml. In order to reduce drug interaction, SRL was given 4 hours after CsA. After complete CNI withdrawal SRL was administered in the morning.

Before conversion the immunosuppression dose: CsA 3~5 mg/kg/d or Tac 0.05~0.1 mg/kg/d, bid; MMF 0.5~2.0 g/d; Pred10~15 mg/d. After conversion SRL immunosuppressive pro-

tocol: SRL + MMF + Pred. Monitoring the concentration of SRL to guide medication at initial conversion stage and to adjust drug dosage timely according to the different immune status of patients in the follow-up process.

Follow-up time after conversion was 5 years. In each follow-up visit, a laboratory screening (allograft function, blood routine, liver function tests, triglycerides TG, total cholesterol TC, and blood glucose), SRL trough concentration, and ultrasound scan of the transplant kidney were recorded. Adverse events were also included.

Patients with biopsy-proven CAN were divided into SRL group and CNI group according to whether they received sirolimus treatment. We compared every clinical indicator of each phase (3 months, 6 months, 1 year, 2 years, 3 years, 4 years and 5 years) between two groups. We also compared graft function with a different baseline (serum creatinine and proteinuria) in SRL group between before and after conversion in order to determine a good conversion timing for the CAN patients.

The data were analyzed using GraphPad prism software (version 5.0, GraphPad Software, San Diego, CA, USA) and STATA for windows (version 13.1). Mann-Whitney test or Kruskal-Wallis test were used as appropriate. Continuous variables were showed to mean ± standard deviation. All statistical tests were two-sided. Two-sided p-values less than 0.05 were considered to indicate statistical significance.
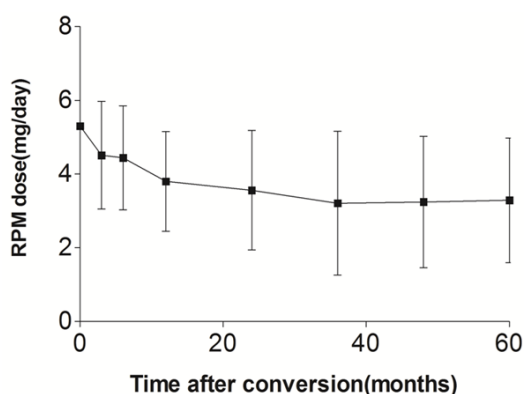
Results

Patients and treatments

In a total amount of 942 regular follow-up transplant patients, 92 cases who were confirmed
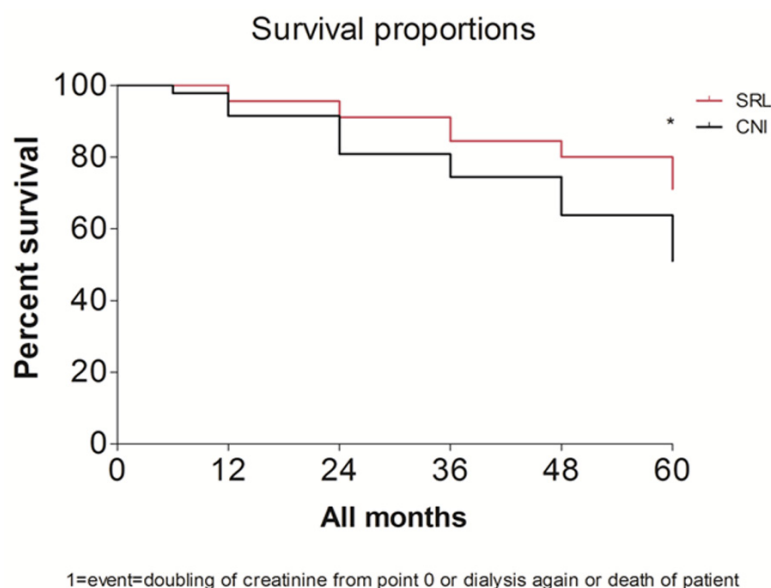
Figure 1. Renal graft survival proportions in two groups during follow-up time. The percent survival of graft are about 71% and 51% in SRL and CNI group respectively. *P < 0.05.

Figure 2. The variety of SRL dose during the follow-up. The SRL dose decreased over time from 5.3 mg/day to 3.21 ± 1.65 mg/day for reaching the SRL trough concentration

CAN by biopsy were enrolled in this study (exclude pathological changes of acute CsA poisoning, recurrent glomerulonephritis and other specifics), among 45 patients with sirolimus conversion treatment, the remaining 47 patients continued previous immunosuppression. Male were 59 cases and female were 33 cases, age ranging from 26 to 59 years old, mean age (42.5 ± 11.3) years old. 8 cases of them were retransplantation and 13 cases were living donor kidney transplantation. All demographic data listed in **Table 1** did not differ significantly.

During the 5 years of follow-up, 7 cases died of cancers, infections and respiratory failures respectively in both two groups and 15 cases had deterioration of renal function and 5 patients were back to hemodialysis again, survival data shown in **Figure 1**. There was no acute rejection episode within the first half year after conversion in both two groups.

Before conversion the mean dose of CsA was 164 ± 63.2 mg/day (Tac 5.1 ± 1.2 mg/day); mean CsA trough concentration was 98 ± 9.6 ng/mL (Tac 4.8 ± 0.86 ng/mL). In our conversion scheme with a loading dose of SRL 4~5 mg/day as shown in **Figure 2**, most patients can reach the target range within the beginning 2 weeks. After that, we decreased SRL dose gradually and the mean dose was 3.29 ± 1.69 mg/day at 60 months. The mean SRL trough level maintained 6.1 ± 4.9 ng/mL.

Comparasion between SRL and CNI groups

In hematological features, there was a significant difference of platelet count between SRL and CNI group (5 years after conversion: 133.8 ± 41.3 vs. 219.1 ± 37.3 × 10^9/L, P < 0.05). The change did not appear in leukocyte. Although there were no significant changes of hemoglobin between two groups, a obvious declining trend was found in both groups, especially in SRL. (5 years after conversion: 101.3 ± 18.6 vs. 111.3 ± 17.9 g/L) (**Table 2**).

Hyperlipidemia was thought to be one of the major adverse effects of sirolimus [11]. Compared with CNI, there was no significant change of triglyceride level in SRL group in spite of an uptrend (5 years after conversion: 3.4 ± 0.6 vs. 2.6 ± 0.8 mmol/L). The same in total cholesterol (5 years after conversion: 7.1 ± 1.4 vs. 6.1 ± 1.2 mmol/L). In lipid profile change, there were some rising trends after sirolimus conversion, but it was not statistically significant.

As shown in **Table 2**, SRL group had significant difference to CNI group in proteinuria parame-

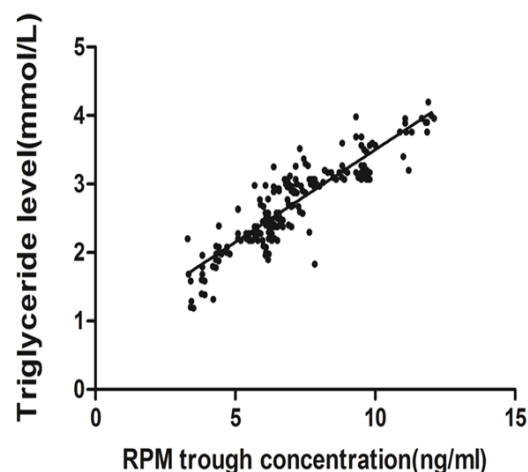**Table 2.** Comparison of clinical indicators in two groups during the follow-up

	TG (mmol/L)		TC (mmol/L)		GPT (IU/L)		GLU (mmol/L)	
	SRL	CNI	SRL	CNI	SRL	CNI	SRL	CNI
0 year	2.3 ± 0.7	2.5 ± 0.6	5.6 ± 1.4	5.7 ± 1.5	12.9 ± 4.8	13.2 ± 4.5	5.5 ± 0.8	5.6 ± 0.7
1 year	2.7 ± 0.8	2.6 ± 0.4	6.1 ± 1.4	5.7 ± 1.4	14.1 ± 5.6	13.9 ± 4.1	5.7 ± 0.6	5.9 ± 0.9
2 year	3.0 ± 0.5	2.4 ± 0.8	6.5 ± 1.2	5.9 ± 1.3	14.4 ± 5.9	14.8 ± 4.9	5.4 ± 0.9	6.0 ± 0.5
3 year	3.1 ± 0.6	2.4 ± 0.9	6.8 ± 1.5	6.1 ± 1.3	14.7 ± 5.8	15.2 ± 4.1	5.8 ± 0.8	6.2 ± 0.8
4 year	3.3 ± 0.5	2.5 ± 0.7	6.9 ± 1.3	6.1 ± 1.6	14.2 ± 5.1	15.3 ± 4.8	6.0 ± 0.9	6.2 ± 1.2
5 year	3.4 ± 0.6	2.6 ± 0.8	7.1 ± 1.4	6.0 ± 1.2	14.8 ± 6.2	15.5 ± 5.9	6.1 ± 0.7	6.1 ± 1.8

	Hb (g/L)		WBC (10^9/L)		Plt (10^9/L)*		Proteinuria (g/d)*	
	SRL	CNI	SRL	CNI	SRL	CNI	SRL	CNI
0 year	121.3 ± 16.3	123.2 ± 13.5	7.8 ± 2.6	7.5 ± 2.8	249.1 ± 45.6	251.2 ± 37.3	0.99 ± 0.65	1.01 ± 0.56
1 year	113.3 ± 17.2	120.5 ±1 2.8	7.9 ± 2.9	8.5 ± 3.6	218.4 ± 45.5	245.1 ± 38.7	1.42 ± 0.52	1.12 ± 0.45
2 year	111.7 ± 17.8	118.3 ± 18.6	7.6 ± 2.4	7.6 ± 2.6	181.1± 47.6	247.2 ± 38.9	1..64 ± 0.85	1.21 ± 0.88
3 year	106.6 ± 19.4	118.1 ± 19.4	8.0 ± 2.6	7.9 ± 3.8	163.5 ± 45.6	238.2 ± 37.3	1.89 ± 0.97	1.26 ± 0.67
4 year	104.4 ± 15.2	112.3 ± 18.7	7.7 ± 2.1	8.6 ± 2.6	151.1 ± 47.7	227.9 ± 34.9	2.04 ± 0.88	1.28 ± 0.81
5 year	101.1 ± 18.6	111.3 ± 17.9	8.1 ± 3.1	7.9 ± 3.3	133.8 ± 41.3	219.1 ± 37.3	2.43 ± 0.96	1.31 ± 0.77

*$P < 0.05$.
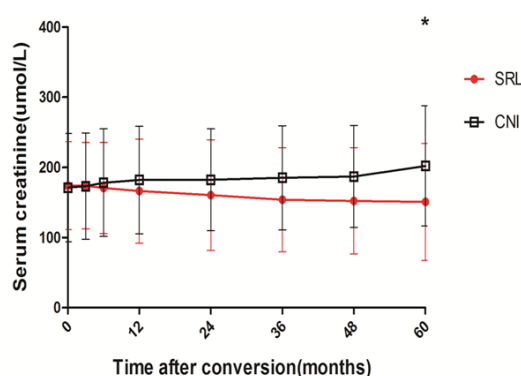
Figure 3. Mean serum creatinine (SCcr) levels between SRL and CNI group during the conversion period. Following conversion to SRL, serum creatinine of patients with CAN declined gradually. *$P < 0.05$.
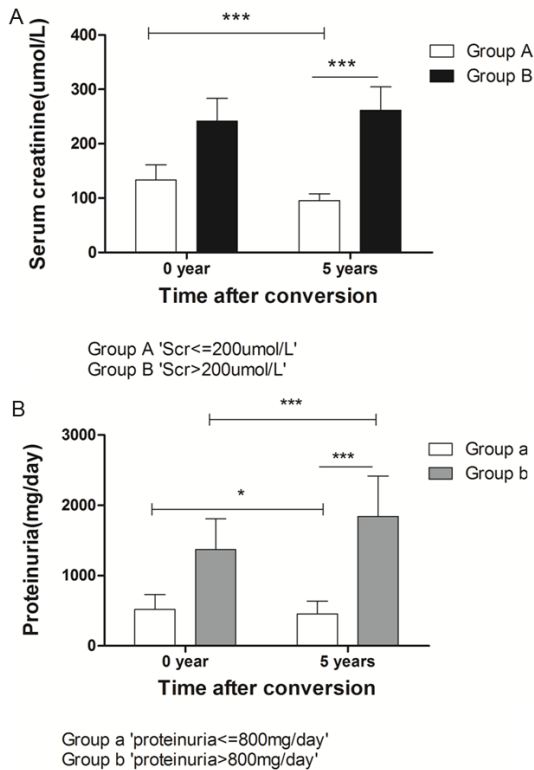

Figure 4. Linear correlation analysis between SRL trough concentration and average triglyceride level of the patients in SRL intra-group comparaision during the conversion period.

ter. SRL group showed (0 year vs. 5 years after conversion: 0.99 ± 0.65 vs. 2.43 ± 0.96 g/d) while CNI group showed (0 year vs. 5 years after conversion: 1.01 ± 0.56 vs. 1.31 ± 0.77 g/d).There was no obvious difference in CNI group between before and after conversion but in SRL group proteinuria parameter increased markedly during the follow-up ($P < 0.05$).

In comparison of renal function, serum creatinine of SRL group was from (174.0 ± 62.8) umol/L before conversion to (150.7 ± 83.4) umol/L after conversion while this of CNI was from (171.2 ± 77.3) umol/L to (200.9 ± 73.5) umol/L.A great change in kidney function was found between two groups, as shown in **Figure 3** ($P < 0.05$). Serum creatinine of patients with

CAN in SRL group declined gradually, but a deteriorative trend in serum creatinine was found in keeping using CNIs.

There was no difference in live function (GPT) and GLU between SRL and CNI group during the conversion time.

Comparison within SRL group

In two groups comparasion above,we found hyperlipidemia was common in patients with sirolimus. For investigating the relationship between sirolimus usage and hyperlipidemia,

Group A 'Scr<=200umol/L'
Group B 'Scr>200umol/L'

Group a 'proteinuria<=800mg/day'
Group b 'proteinuria>800mg/day'

Figure 5. The changes in serum creatinine (A) and proteinuria (B) levels with a different baseline before and after conversion in SRL group. *P < 0.05. ***P < 0.01.

we observed the patients' change of SRL trough concentration and average triglyceride level during the conversion period. Linear correlation analysis was shown in **Figure 4** ($r^2 = 0.80$). It is clear that hyperlipidemia prevalence is related to the increase of SRL concentration in this project.

For investigating the effect of different conversion timing and program on graft function, we divided SRL patients into the following groups according to their different baseline of renal function and urinary protein excretion before conversion: Patients with serum creatinine of 200 umol/L or less were assigned to Group 'A' and more than 200 umol/L were assigned to Group 'B'; patients with proteinuria of 800 mg/day or less were assigned to Group 'a' and more than 800 mg/day were assigned to Group 'b'.

The patients in Group 'A' showed a decrease of serum creatinine after conversion (0 year vs. 5 years: 133.1 ± 27.9 vs 95.4 ± 12.5 umol/L) while Group 'B' showed an increase of serum creatinine at the same time (0 year vs 5 years:

241.4 ± 41.9 vs 263.1 ± 43.1 umol/L) (**Figure 5A**). On the other hand, it was shown a decline of proteinuria from 519.5 ± 221.6 mg/day to 453.6 ± 199.5 mg/day in the patients in Group 'a' who had a lower baseline proteinuria, but outcome of Group 'b' patients with a higher baseline proteinuria was opposite, gradually increasing proteinuria (**Figure 5B**).

Discussion

Chronic allograft nephropathy remains an important issue in renal transplantation compromising long-term renal allograft survival. CNI nephrotoxicity is thought to be a major non-immune factor in the pathogenesis of CAN [12, 13]. The conversion of a CNI-based protocol to a non-nephrotoxic regimen seems to be an effective treatment in CAN, but it also must maintain an adequate immunosuppressive effect. Previous clinical studies suggest that sirolimus not only inhibits the proliferation of T and B cells, but also inhibits the proliferation of fibroblast, endothelial, and smooth muscle cells stimulated by growth factors or cytokines. Sirolimus also has protective effects on endothelium and smooth muscle cells in vascular injury. Therefore, sirolimus may antagonize or relieve the pathological changes of CNI-caused renal fibrosis and endarterial hyperplasia as well as other kinds of CAN [14, 15]. Moreover, some clinical trials suggest that sirolimus may allow discontinuation or dose reduction of CsA with less acute rejection episodes [16]. These evidences provide a theoretical rationale for the benefits of sirolimus in CAN.

In the comparison between two groups of present study, conversion to SRL achieved an improvement or stabilization of allograft function in CAN patients. We found that 64% (29/45) patients' kindney function in SRL group were successfully rescued but in CNI control group most allograft function had no improvement or had progressive deterioration. Some previous studies also had similar results. Citterlo et al converted 19 kidney transplant patients with progressive chronic renal allograft dysfunction from CNI to SRL using a protocol of rapid withdraw of CNI. They observed amelioration or stabilization of renal function in 57% of patients. No acute rejection or major infections occurred [14]. Fritz Diekmann et al. divided 59 renal transplant patients with CAN into responders and non-responders according to whether they received SRL therapy and found allograft func-

tion in responders were significantly better than non-responders [17].

As other studies showed, major clinical adverse reactions of sirolimus were hyperlipidemia and myelosuppression [18, 19]. Hyperlipidemia is mainly caused by the inhibition of lipoprotein lipase and the lower metabolism of apoB100 [20]. In our study, the average lipid elevation began at 6 months after initiation of therapy and we also found the positive relationship between hyperlipidemia and SRL trough concentration. Aggressive treatment with lipid-lowering agents may be necessary despite the potentially protective effects of SRL on vascular endothelium. The myelosuppression is caused by inhibition of mTOR, hence leading to decreased cell proliferation in G1 and S phase [20]. Our observations showed that the mean levels of WBC and Hb did not change significantly. Meanwhile, the mean platelets level decreased significantly 1 year after conversion (**Table 2**).

The other important objective of this study is to decide a proper timing of the conversion, although it is still controversial. In the comparison within SRL group of our study, we observed that the different status of grafts before conversion had a different results after treatment. The patients with Scr > 200 umol/L before conversion had a much worse renal function after treatment than those with Scr ≤ 200 umol/L. Similarly, the proteinuria in those patients who had a higher baseline proteinuria (> 800 mg/day) at conversion increased significantly after conversion, but Sirolimus seems to be protective to the patients who had a lower baseline proteinuria. Our findings are in accordance with several other studies. Diekmann et al. reported proteinuria over 800 mg/24 h as a risk factor for CAN development [17]. In JC Ruiz et al study, the increase of proteinuria appeared mainly within the first 3 months after conversion and was observed in two-thirds of the patients. They also found increase of proteinuria > 500 mg/day was associated with a worse outcome in terms of post-conversional creatinine and the quartile of patients with a baseline proteinuria above 792 mg/day showed a deterioration of serum creatinine within the first 6 months after conversion [21]. It has been demonstrated by Mota A et al. that early CsA withdrawal followed by SRL-based protocols provided significant improvement in renal histology and

function in the first 3 years [22]. Combining with our data, we found that beneficial effects of conversion to SRL depended on the right timing of conversion before CAN development.

In conclusion, we first demonstrate that conversion from CNI to SRL is effective in patients with mild or moderate CAN. Second, the use of SRL in CAN is relatively safe in spite of some side effects such as hyperlipidemia, myelosuppression and proteinuria. Last but not least, proper conversional time is important for getting a beneficial effect of SRL. Patients with low pre-conversional serum creatinine and proteinuria show a significantly improved effect after conversion.

Disclosure of conflict of interest

None.

Abbreviations

SRL, Sirolimus; CNI, Calcineurin inhibitor; CAN, Chronic allograft nephropathy; CsA, Cyclosporine A; Tac, Tacrolimus; MMF, Mycophenolate mofetil; TG, Triglycerides; TC, Total cholesterol; GPT, Glutamate Pyruvate Transaminase; Hb, Hemoglobin; GLU, Glucose.

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