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Long-term use of ciclosporin on kidney transplant recipients surviving more than 10 years

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Objective: To evaluate the long-term use of ciclosporin on kidney transplant recipients who survived more than 10 years. *Methods:* We reviewed cadaveric kidney transplant patients who had survived 10 years or longer in this study. Patients were divided into five groups based on their ciclosporin concentration at one year: group 1 (> 250 ng/ml), group 2 (200-250 ng/ml), group 3 (150-200 ng/ml), group 4 100-150ng/ml) and group 5 (< 100 ng/ml). Lab parameters were compared among these groups over time. *Results:* There were no differences in lab parameters among the five groups. At five years, systolic blood pressures (SBP), TG, CH, DB, TB were significantly higher in groups 3, 4, and 5. Uric acid was also higher but albumin was lower in group 5 compared to those in all other groups. Prevalence of proteinuria in both groups 4 and 5 were lower. At 10 years, SBP in group 3 was lower while both uric acid and ALT in all groups were decreased. *Conclusion:* In patients who survived for more than 10 years after kidney transplantation, serum lipid levels were markedly elevated, indicating the increase of cardiovascular risk factors for patients, which might impact long-term survival benefit.

1. Introduction

Compared to dialysis, kidney transplantation offers remarkable survival benefit and life quality for ESRD patients (Yabu and Vincenti 2009). Application of immunosuppressants, particularly ciclosporin, significantly reduces acute rejection after kidney transplantation and improves survival. However, increased risks of infection, tumor and cardiovascular disease in long-term survivors by ciclosporin drew the attention of investigators (Heinze et al. 2009). The purpose of our study was to retrospectively evaluate kidney transplant recipients who were continuously administrated ciclosporin and had survived over 10 years (Opelz et al. 2009). We focused on the question how various ciclosporin concentrations impacted graft function and biochemical parameters 10 years after transplantation.

2. Investigations and results

2.1. Basic characteristics of patients

From 1976 to 1998, a total of 380 patients who were persistently on ciclosporin and had been surviving for at least 10 years were enrolled in our study. There were 280 males and 100 females with average age of 40.4 ± 8.8. The average follow-up time was 13.38 ± 3.98 years, dialysis time was 23.6 ± 20.3 months, and body mass index was $22.6 \pm 4.33\,kg/m^2$. Among these patients, 146 cases were on 2-drug regimen with ciclosporin and prednisone, 76 cases on 3-drug regimen with ciclosporin, prednisone and azathioprine and 158 cases on 3-drug regimen with ciclosporin, prednisone and mycophenolate mofetil.

Table 1: Biochemical parameters for renal transplant patients who were on ciclosporin and survived over 10 years

	1 year	5 years	10 years
SBP (mmHg)	134 ± 18	131 ± 17	126 ± 17
DBP (mmHg)	87 ± 11	86 ± 10	84 ± 10
Scr (μmol/L)	114 ± 33	108 ± 25	106 ± 40
UA (μmol/L)	412 ± 102	413 ± 100	397 ± 103
TG (mmol/L)	1.35 ± 0.51	1.58 ± 0.72	1.85 ± 1.14
CH (mmol/L)	5.01 ± 0.78	5.28 ± 0.98	5.38 ± 1.06
Albumin (g/L)	46.3 ± 5.2	44.9 ± 3.3	45.1 ± 4.8
GPT (u/L)	18 ± 14	15 ± 11	14 ± 10
DB (mmol/L)	3.24 ± 1.55	3.96 ± 1.77	4.24 ± 2.41
TB (mmol/L)	11.13 ± 3.78	12.71 ± 4.72	15.22 ± 6.16
Hb (g/L)	143 ± 23	139 ± 18	134 ± 19
WBC ($\times 10^9$/L)	7.48 ± 2.4	7.38 ± 2.21	7.26 ± 2.06
Proteinuria (%)	7.7	12.5	29.4

2.2. Comparison of biochemical parameters at 1 year, 5 years and 10 years

Among 380 cases, triglycerides (TG), cholesterol (CH), direct bilirubin (DB), total bilirubin (TB), and incidence of proteinuria were remarkably elevated whereas hemoglobin (Hb) was declined, No difference was found otherwise (Table 1). Based on ciclosporin concentrations, 380 cases were categorized into five groups as shown below.

After 5 years, systolic blood pressure (SBP) in group1 and 2 were significantly higher than those in groups 3, 4, and 5. However, no difference in diatsolic blood pressure (DBP), TG, CH,

Table 2: Comparison of baseline biochemical parameters among different groups

	Group 1	Group 2	Group 3	Group 4	Group 5
Scr (μmol/L)	128 ± 26	115 ± 35	108 ± 30	102 ± 19	115 ± 55
UA (μmol/L)	432 ± 98	403 ± 101	411 ± 93	420 ± 110	404 ± 113
TG	1.37 ± 0.45	1.36 ± 0.52	1.34 ± 0.45	1.33 ± 0.48	1.35 ± 0.53
CH (mmol/L)	5.01 ± 0.75	5.13 ± 0.81	5.11 ± 0.76	5.00 ± 0.67	4.87 ± 0.56
Albumin (g/L)	45 ± 7	45 ± 3	47 ± 4	48 ± 5	45 ± 3
GPT (u/L)	20 ± 17	19 ± 17	14 ± 8	18 ± 14	17 ± 7
DB (mmol/L)	3.1 ± 0.6	3.2 ± 1.3	3.3 ± 1.2	3.1 ± 1.7	3.3 ± 2.1
SB (mmol/L)	11.2 ± 2.7	10.9 ± 3.8	12.2 ± 3.2	11.1 ± 2.3	11.16 ± 3.8
Hb (g/L)	152 ± 25	140 ± 25	136 ± 18	145 ± 20	143 ± 24
WBC ($\times 10^9$/L)	7.8 ± 2.4	7.1 ± 1.8	7.7 ± 2.8	6.4 ± 1.8	8.9 ± 2.7
Proteinuria (%)	7.9	2.9	5.6	3.4	25

serum creatinine (Scr), GPT, DB, TB, Hb, and white blood cell count (WBC) was found among the five groups. Uric acid (UA) in group 5 was significantly lower than those in other groups (Table 2). Albumin was elevated in group 5 compared to other four groups. Incidence of proteinuria was lower in groups 4 and 5 than in other groups (Table 3).

After 10 years, both systolic blood pressure and diastolic blood pressure in group 3 were remarkably lower. Additionally, no differences in TG, CH, Scr, Alb, Hb, and WBC were found between these groups. Although being not statistically significant, UA and GPT in all groups and DB and TB in group 5 showed a trend to decline (Table 4).

3. Discussion

We found elevated lipid panels after 1 year, 5 years and 10 years in 380 long-term survivors who were continuously on ciclosporin, indicating that long-term survivors had an increased risk of cardiovascular disease. Elevated direct and total bilirubin may be associated with the long-term use of ciclosporin through affecting bile metabolism. Therefore, long-term survivors should also be closely followed up (Anil Kumar et al. 2008; Ortiz et al. 2013; Ruiz and Klintmalm 2012; Prokai et al. 2012; Casey and Meier-Kriesche 2011). Our data also showed a higher prevalence of proteinuria, which may be due to higher incidences of chronic allograft nephropathy over time. Kidney biopsies on 78 patients with higher creatinine and proteinuria confirmed that 56 cases developed chronic allograft nephropathy, and 22 had either acute rejection, chronic rejection, transplant renal or glomerulonephritis.

At 5 years and 10 years after transplantation, patients of group 1 and group 2 who had higher blood concentration of ciclosporin presented with higher BP and lower UA levels compared to other groups of lower drug concentration. The possible interpretation is that lower ciclosporin levels have fewer adverse effects on blood pressure and uric acid.

At 5 years and 10 years, there were no differences in graft function between groups of different drug concentrations. Some other actors may have affected graft function. One of the possible biases of our study was that graft dysfunction and death cases were excluded by our strict criteria. Therefore, further analysis of these excluded cases may be helpful to support our findings. However, several studies from other investigators indicated that no difference in either 5-year or 10-year survival benefit was identified among patients of different drug concentration and even different immunosuppressant regimens. The only difference was the incidence of post transplant complication.

In conclusion, ciclosporin improves long-term survival in kidney transplant recipients. A long-term use of ciclosporin may result in drug-related adverse effects. In patients who survived for more than 10 years after kidney transplantation, serum lipid levels were markedly elevated, indicating an increase of cardiovascular risk factors for patients, which might impact long-term survival benefit.

4. Experimental

4.1. Study design

This is a retrospective study evaluating cadaveric kidney transplant patients who had been surviving over 10 years and had persistently received ciclosporin.

4.2. Groups

The patients were allocated into five groups according to trough level of ciclosporin blood concentrations one year after transplantation as follows: Group 1: > 250 ng/ml; Group 2: 200-250 ng/ml; Group 3:150-200 ng/ml; Group 4: 100-150 ng/ml; Group 5: < 100 ng/ml

Table 3: Biochemical parameters in various groups 5 years after renal transplantation

	Group 1	Group 2	Group 3	Group 4	Group 5
SCr (μmol/L)	114 ± 24	105 ± 29	107 ± 23	105 ± 27	107 ± 27
UA (μmol/L)	427 ± 106	436 ± 83	404 ± 83	401 ± 122	373 ± 112
TG	1.6 ± 0.8	1.5 ± 0.8	1.8 ± 0.7	1.5 ± 0.6	1.3 ± 0.6
CH (mmol/L)	5.1 ± 1.2	5.4 ± 1.1	5.5 ± 0.9	5.1 ± 0.8	4.4 ± 0.1
Albumin (g/L)	44.7 ± 4.2	44.3 ± 3.1	45.0 ± 2.6	45.0 ± 3.0	47.0 ± 3.0
GPT (u/L)	17 ± 13	14 ± 10	14 ± 10	16 ± 12	17 ± 11
DB (mmol/L)	3.2 ± 0.8	4.0 ± 1.7	3.8 ± 1.4	4.1 ± 1.9	7.0 ± 4.4
TB (mmol/L)	11.2 ± 2.7	13.0 ± 4.8	12.2 ± 3.2	12.1 ± 3.3	12.0 ± 3.1
Hb (g/L)	140 ± 14	141 ± 20	138 ± 20	141 ± 19	132 ± 23
WBC ($\times 10^9$/L)	7.6 ± 2.3	7.0 ± 1.8	7.7 ± 2.0	7.3 ± 2.4	7.1 ± 2.8
Proteinuria (%)	10.5	17.6	16.7	3.45	6.25

Table 4: Comparison of biochemical parameters among different groups 10 years after renal transplantation

	Group 1	Group 2	Group 3	Group 4	Group 5
Scr (μmol/L)	113 ± 52	95 ± 29	106 ± 39	107 ± 35	111 ± 37
UA (μmol/L)	389 ± 97	414 ± 119	395 ± 94	399 ± 103	380 ± 108
TG	1.8 ± 1.4	1.8 ± 0.9	1.8 ± 0.6	2.1 ± 1.6	1.7 ± 0.5
CH (mmol/L)	5.0 ± 0.9	5.5 ± 1.1	5.8 ± 1.0	5.5 ± 0.9	4.3 ± 1.4
Albumin (g/L)	44 ± 7	44 ± 4	46 ± 3	46 ± 4	47 ± 3
GPT (u/L)	16 ± 14	16 ± 11	11 ± 5	15 ± 10	11 ± 6
DB (mmol/L)	3.4 ± 1.2	4.8 ± 2.9	4.6 ± 2.7	4.1 ± 2.0	3.9 ± 3.5
SB (mmol/L)	12 ± 4	18 ± 6	15 ± 6	14 ± 4	15 ± 8
Hb (g/L)	136 ± 20	136 ± 15	132 ± 19	132 ± 22	132 ± 21
WBC ($\times 10^9$/L)	7.0 ± 1.9	7.0 ± 1.8	7.7 ± 2.1	7.2 ± 2.1	7.4 ± 2.4
Proteinuria (%)	23.7	32.3	41.7	24.1	0

4.3. Immunosuppressant regimen

Two ciclosporin-based immunosuppressant regimens were administered: Two-drug immunosuppressant regimen: ciclosporin + corticosteroid; three-drug immunosuppressant regimen: ciclosporin + corticosteroid with or without mycophenolate mofetil (or) azathioprine. Dosage varied on an individual basis.

4.4. Laboratory data

Patient's general condition included age, gender, weight, blood pressure, date of transplantation, date of dialysis, kidney age, hot and cold ischemic time, immunosuppressant regimen and dosage, presence or absence of acute rejection, presence or absence of infection and presence or absence of tumor. Patient's biochemical indicators included serum creatinine (sCr), uric acid (UA), glucose (Glu), cholesterol (CH), triglyceride (TG), GPT, direct bilirubin (DB), total bilirubin (TB), albumin (Alb), hemoglobin (Hb), white blood cell count (WBC), and presence or absence of proteinuria.

Acute rejection was defined as remarkable elevated serum creatinine, either confirmed by kidney biopsies, or reversed by bolus glucocorticoids. Post transplant infection was defined as lung or urinary tract infections requiring hospitalization. The urinary tract infection following transplant complications due to urinary obstruction or autologous renal infection was excluded.

4.5. Statistical analysis

Statistical analysis was done using SPSS 13.0. Continuous variables were expressed with mean and standard deviation and then analyzed with one way-ANOVA. Comparison of graft function or biochemical parameters was performed over five different groups at one year, five years and ten years. Meanwhile, we also compared the dosage of immunosuppressant, incidence of acute renal allograft rejection, infection and tumor among difference groups. $P < 0.05$ was considered to be significant.

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