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CLINICAL STUDY

Long-Term Comparative Results of C_0 and C_2 Monitoring of CyA in Renal Transplanted Patients

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The purpose of this study was to evaluate the effects of CyA monitoring using C_0 monitoring (fasting level after 12 h from last dose), and C_2 monitoring (2 h after morning dose) on renal functions, lipid levels, CyA levels, and daily dosages of CyA in renal transplanted patients in the posttransplant period from the first month to the 36th month. In our center between 1992–2003, 37 of the 54 renal transplanted patients were treated with CyA, prednisolone, and mycophenolate mofetil or azathioprine. The mean age was 32.36±10.32 and 35.00±10.23 (p=0.39) in C_0 (M/F: 18/7) and in C_2 (9/3), respectively. Cadaveric donor (d), living related d, and living unrelated d were in four patients (p), 17 p and four p in C_0, and two p, seven p, and three p in C_2, respectively (p=0.79). Chronic allograft nephropathy (CAN) developed in 13 p (52%) and one p (8.3%) in C_0 and in C_2, respectively (p=0.013). Creatinine clearance values were 72.31±23.10 mL/min and 78.73±22.42 mL/min (p:0.621) at first month, 64.97±22.58 mL/min and 78.00±19.90 mL/min (p:0.065) at sixth month, 56.50±19.62 mL/min and 76.62±21.06 mL/min (p:0.006) at 12th month, 50.28±24.79 mL/min and 80.87±18.24 mL/min (p<0.001) at 24th month, and 55.15±19.21 mL/min and 86.65±14.97 mL/min (p:0.004) at 36th month in C_0 and C_2, respectively. The mean daily dosages of CyA were 354.35±122.63 and 266.67±64.95 mg/d (p:0.031) at first month, 277.17±77.94 and 250.00±73.31 mg/d (p:0.228) at sixth month, 247.92±58.48 and 211.36±62.61 mg/d (p:0.09) at 12th month, 232.95±56.90 and 170.45±41.56 mg/d (p:0.003) at 24th month, and 240.63±52.34 and 153.57±46.61 mg/d (p:0.002) at 36th month in C_0 and C_2, respectively. In C_2, systolic and diastolic blood pressure, uric acid, total cholesterol (C), LDL-C, and triglyceride levels were lower than those monitored with C_0. In C_2, HDL-C levels were also higher than those monitored with C_0. None of these patients returned to dialysis or died in this period. In conclusion, during the first 36 months with monitoring C_2, preservation of renal function, control of blood pressure serum lipids and uric acid were better than those with monitoring C_0. In addition, daily dose of CyA was lower in C_2 method and, at the same time, this effect of C_2 can be accepted as cost effective.

Keywords renal transplantation, cyclosporine, C_0-C_2 monitoring

INTRODUCTION

Cyclosporine (CyA) has been using as a primary immunosuppressant agent in renal transplantation for 20 years. Its use in renal transplantation has resulted an improvement in graft survival. But nephrotoxicity is an important side effect of CyA in transplanted patients. The area under the concentration time curve (AUC) of CyA represents sensitive predictors for acute rejection (AR). It was realized that the level of C_0 did not correlate well with AUC because of the individual absorption variability of CyA. Recently, the level of CyA 2 (C_2) hours post dosing was found to correlate much better with AUC. In the literature, some investigators claimed that C_2 levels were more appropriate for posttransplantation monitoring of CyA.[1] But, still, in most of the transplant centers, C_0 monitoring is standard. In our center, we have been adjusting CyA dosage according to C_2 monitoring in renal transplanted patients since the beginning of 2000. In this

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Table 1
Patient characteristics

Patient characteristics	C_0	C_2	*P*:Significance
Age	32.3±10.3	35.0±10.2	0.29
Sex (M)	18	9	1.0
Donors (C, LR, LUR)	4, 17, 4	2, 7, 3	0.79
Cys A+steroid+MMF	—	8	—
Cys A+steroid+Aza	20	3	—
Cys A+Aza	5	1	—
Antihypertensive agent	21	9	—
Statin	3	2	—
Allopurinol	4	—	—

study, we investigated the effect of C_0 and C_2 monitoring on blood pressure, renal function serum glucose, serum uric acid, lipid profile, and CyA dosages.

MATERIAL AND METHOD

Between 1992–2003, 54 renal transplanted patients using CyA were analyzed. It was noticed that the patients were on follow-up from the first posttransplantation month.

All patients were treated with CyA, azathioprine, or mycophenolate mofetil (MMF) and prednisone for immunosuppression. The number of patients who discontinued steroid administration was five for C_0, one for C_2. Physical examination and serum glucose, BUN, creatinine (Cr), creatinine clearance (Ccr), AST, ALT, uric acid, total protein, albumin, lipid levels, sedimentation rate, hematocrit, white blood count, and CyA dosage were recorded. Twelve patients who were converted to C_2 monitoring from C_0 monitoring were analyzed separately and the last levels of Ccr, uric acid, cholesterol, triglyceride, and blood pressure on C_0 monitoring (36–48 months) were compared with the levels of the 12th and 36th months on C_2 monitoring.

Table 2
Serum glucose, renal functions, CyA levels, and dosages of the patients

Month number	Glucose mg/dL	BUN mg/dL	Cr mg/dL	CrCl ml/dk	Cyclosporine level ng/ml	Cyclosporine mg/day
1						
C_0 25	94.00±15.94	19.87±8.23	1.17±0.32	72.31±23.10	251.44±143.33	354.35±122.63
C_2 12	95.00±12.91	16.11±6.49	0.97±0.29	78.73±22.42	1382.85±536.29	266.67±64.95
p	*p*: 0.062	*p*: 0.26	*p*: 0.11	*p*: 0.621	*p*<0.001	*p*: 0.031
6						
C_0 25	93.65±13.30	19.48±6.97	1.36±0.42	64.97±22.58	238.53±130.54	277.17±77.94
C_2 12	95.27±18.42	17.09±6.67	1.03±0.20	78.00±19.90	1066.43±448.69	250.00±73.31
p	*p*: 0.91	*p*: 0.30	*p*: 0.019	*p*: 0.065	*p*<0.001	*p*: 0.228
12						
C_0 24	89.79±11.33	20.00±8.22	1.43±0.40	56.50±19.62	175.38±82.77	247.92±58.48
C_2 11	102.82±21.82	17.00±6.26	1.05±0.13	76.62±21.06	774.85±202.24	211.36±62.61
p	*p*: 0.09	*p*: 0.43	*p*: 0.006	*p*: 0.006	*p*<0.001	*p*: 0.09
24						
C_0 22	93.68±15.19	24.55±15.97	1.86±1.15	50.28±24.79	188.21±155.66	232.95±56.90
C_2 11	96.00±12.15	15.27±4.31	1.03±0.13	80.87±18.24	821.60±144.77	170.45±41.56
p	*p*: 0.51	*p*: 0.053	*p*: 0.001	*p*<0.001	*p*<0.001	*p*: 0.003
36						
C_0 16	91.38±13.47	27.75±16.39	1.46±0.52	55.15±19.21	128.03±69.49	240.63±52.34
C_2 7	90.57±24.68	15.29±5.44	0.99±0.13	84.65±14.97	715.84±226.58	153.57±46.61
p	*p*: 0.53	*p*: 0.047	*p*: 0.039	*p*: 0.004	*p*<0.001	*p*: 0.002

Table 3
Serum uric acid, lipid levels, and blood pressure of the patients

Month number	Uric acid mg/dL	T. Cholesterol mg/dL	HDL-Cholesterol mg/dL	LDL-Cholesterol mg/dL	Triglyceride mg/dL	Systolic blood pressure mmHg	Diastolic blood pressure mmHg
1							
C_0 25	7.94±2.02	243.78±63.51	47.04±14.44	152.13±46.65	228.04±75.08	129.13±14.74	86.74±11.24
C_2 12	6.14±0.66	235.67±76.95	51.33±11.06	136.22±51.53	154.00±39.77	118.89±11.67	77.78±6.67
p	*p*: 0.008	*p*: 0.433	*p*: 0.246	*p*: 0.246	*p*: 0.008	*p*: 0.064	*p*: 0.027
6							
C_0 25	8.00±2.20	226.09±46.84	45.87±14.63	154.52±43.93	248.22±122.74	133.52±37.58	86.30±15.68
C_2 12	6.26±0.93	203.82±34.41	53.27±17.74	115.55±32.13	153.64±51.10	119.09±17.00	78.18±9.82
p	*p*: 0.007	*p*: 0.153	*p*: 0.258	*p*: 0.012	*p*: 0.004	*p*: 0.106	*p*: 0.133
12							
C_0 24	7.88±1.86	234.54±57.18	45.83±15.64	152.17±48.14	226.13±95.37	143.96±25.66	94.17±15.01
C_2 11	6.10±1.14	203.36±25.05	50.18±14.80	117.73±24.82	130.27±40.24	125.91±15.30	83.64±8.97
p	*p*: 0.005	*p*: 0.186	*p*: 0.409	*p*: 0.009	*p*: 0.001	*p*: 0.033	*p*: 0.036
24							
C_0 22	8.01±1.73	236.41±48.95	43.59±12.97	148.00±42.03	200.86±74.56	138.86±25.54	89.09±15.71
C_2 11	6.31±0.99	191.91±38.21	49.09±13.43	111.45±25.03	148.64±46.14	118.18±13.28	71.82±10.79
p	*p*: 0.004	*p*: 0.019	*p*: 0.281	*p*: 0.014	*p*: 0.048	*p*: 0.009	*p*: 0.002
36							
C_0 16	8.66±1.59	234.94±48.93	49.50±17.44	142.13±55.50	269.31±154.69	141.88±28.74	93.13±18.87
C_2 7	6.82±2.31	206.57±38.08	63.86±17.40	126.14±35.88	133.00±66.65	117.86±6.99	75.71±9.76
p	*p*: 0.065	*p*: 0.198	*p*: 0.065	*p*: 0.492	*p*: 0.015	*p*: 0.089	*p*: 0.039

Serum levels of CyA were measured by CSA cobas integra (Roche). The blood samples were collected according to C_0 monitoring (a fasting level at 9–11 h after evening administration) or C_2 monitoring (2 h after morning administration). Target serum levels of CyA were 300–400 ng/mL at the first month, 100–300 ng/mL at sixth month, <200 ng/mL at 12th month, and after 1 year <200 ng/mL for C_0 monitoring. They were 1700 ng/mL at first month, 1500 ng/mL at second month, 1300 ng/mL at third month, 1100 ng/mL between fourth and sixth months, 900 ng/mL between seventh and 12th month, and 800 ng/mL after 1 year for C_2 monitoring.[2,3]

Mann-Whitney-U test was used for statistical analysis.

RESULTS

The mean age was 32.3±10.3 years and 35.0±10.2 years in C_0 group and in C_2 group, respectively. There

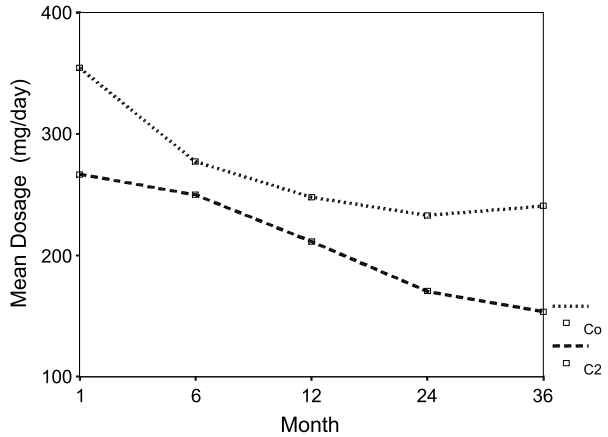


Figure 1. Mean dosages of the patients.

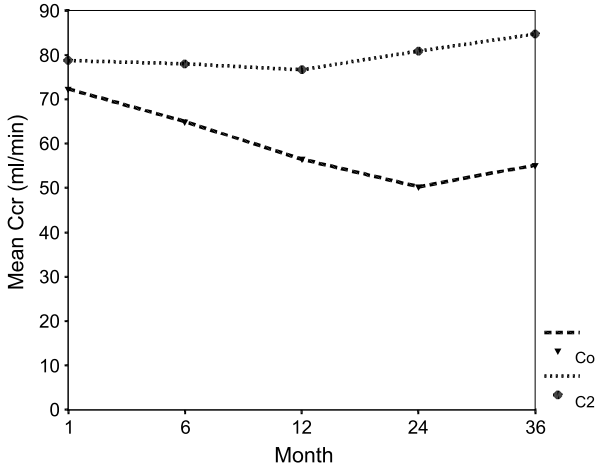


Figure 2. Ccr of the patients.

Table 4
Ccr, lipid levels, uric acid, and blood pressures of the patients who converted to C_2 from C_0

Parameters	Last levels on C_0 monitoring (1)	12th month on C_2 monitoring (2)	36th month on C_2 monitoring (3)	p: Significance
Ccr (mL/min)	51.8±7.3	66.3±9.2	65.1±6.7	p_{1-2}: 0.288 p_{1-3}: 0.342
T. cholesterol mg/dL	239.1±15.9	198.7±15.4	199.0±14.1	p_{1-2}: 0.161 p_{1-3}: 0.133
Triglyceride mg/dL	222.6±22.7	122.7±15.7	115.2±17.2	p_{1-2}: 0.006 p_{1-3}: 0.011
Uric acid mg/dL	8.9±0.7	6.9±0.4	7.1±0.5	p_{1-2}: 0.015 p_{1-3}: 0.011
Systolic blood pressure (mmHg)	134.4±4.8	135.0±5.9	124.0±5.9	p_{1-2}: 0.928 p_{1-3}: 0.167
Diastolic blood pressure (mmHg)	93.7±3.2	84.4±4.8	77.5±3.5	p_{1-2}: 0.117 p_{1-3}: 0.028

was no statistical difference between these two groups (p=0.295) Sixteen patients who were treated at other centers previously were excluded from this study. One patient who was receiving antituberculosis treatment was also excluded. In total, 37 renal transplanted patients (25 in C_0 group, 12 in C_2 group) were analyzed. The characteristics of the patients were summarized in Table 1. Chronic allograft nephropathy developed in 13 p (52%) and one p (8.3%) in C_0 and in C_2, respectively (p=0.013).

Renal functions, serum glucose, CyA levels, and CyA dose were shown in Table 2. Uric acid, lipid profile, and blood pressure measurements were shown in Table 3. Mean daily dosages of CyA and Ccr of the patients were shown in Figures 1 and 2. Blood pressure, triglyceride, uric acid, and Ccr of 12 patients who were converted to C_2 monitoring were compared to the last levels of C_0 with the levels of the 12th and 36th months on C_2 monitoring. Mean levels and significances were shown in Table 4. Ccr of the patients who converted to C_2 from C_0 were shown in Figure 3.

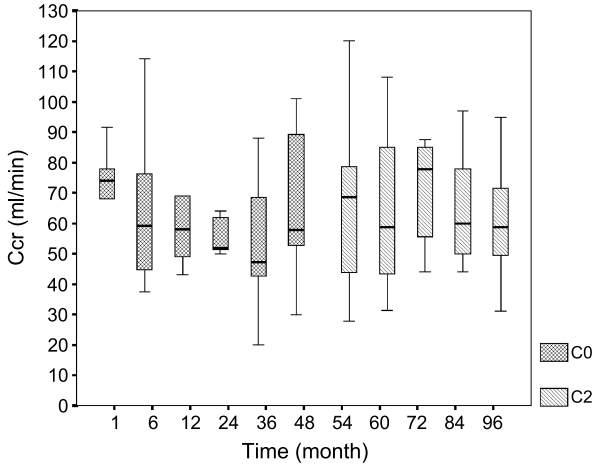


Figure 3. Ccr of the patients who converted to C_2 from C_0.

DISCUSSION

Gender, donation, systolic blood pressure, CCr, Serum Cr, and lipid profile were similar in the C_0 and C_2 groups. But, Ccr were higher and serum Cr levels were lower in the C_2 group after the first month (6, 12, 24, 36 months) than in the C_0 group.

The bioavailability of CyA shows wide intrapatient and interpatient variation in absorption.[4] Low oral bioavailability is associated with AR, and high exposure is a significant risk factor for CAN.[5,6]

AUC is known to be the most accurate way to adjust CyA dosage.[1] However, this method is not practical. MOZART study showed that the microemulsion form of CyA with C_2 monitoring was associated with excellent short-term efficacy and safety in renal transplant patients.[7] In our study, allograft functions of the patients were kept more reliable in patients monitored with the C_2 monitoring than those with the C_0 monitoring for long periods. This improvement was seen after the sixth month and continued for 36 months.

We obtained optimal target C_2 levels with lower doses of CyA in C_2 monitoring. There was no increase in the incidence of rejection or infection in C_2 monitoring. In the literature, the comparison of C_0 and C_2 monitoring for posttransplantation in the first 6 months was investigated and the superiority of the C_2 monitoring was claimed by some investigators. However, to

achieve recommended C_0 and C_2 levels at the first month was not found to be expected. The incidence of cytomegalovirus (CMV) infections associated with C_2 monitoring were demonstrated to be increased in C_2 monitoring in the first month, probably reflecting the higher doses of CyA.[8] But, in this study, our patients were studied after the first month and increases in AR episodes or increases in the number of infections were not seen.

Also, when we evaluate all of the patients ($n=54$), excluded and included, similar results were obtained. Another finding that supported superiority of the C_2 method was that the renal functions were similar in 12 patients who converted to C_2 monitoring from C_0, even in succeeding years with transplantation. Also, in the follow-up period, there were no differences between the C_0 method and the C_2 method regarding Δcr and ΔCcr after 36 and 48 months.

This finding might show that lower and efficient doses of CyA achievement with C_2 monitoring could improve allograft functions. Hyperlipidemia is very important in renal transplanted patients, and the major cause of death in posttransplantation period is cardiovascular disease.[9] In our study, we demonstrated significantly lower serum levels of LDL, triglyceride, total cholesterol in C_2 group. An increase in HDL levels was not statistically important. Systolic and diastolic blood pressure measurements were lower in the C_2 group than in those with the C_0 monitoring.

In patients who converted to C_2 from C_0, serum levels of triglyceride, uric acid, and blood pressure measurements were decreased. In our study, lower serum levels of uric acid seem to be more related to lower doses of CyA and improvement in renal function. Finally, this might reduce the risk of cardiovascular disease, gout, and renal failure in transplanted patients.

In conclusion, C_2 monitoring can be safer than C_0 in renal transplanted patients, regarding improvement in renal functions. The best results for renal functions tests were found in patients who converted to C_2 monitoring, especially after 36–48 months of transplantation. Blood pressure, LDL, triglyceride, and uric acid were lower. The optimal target level CyA was achieved with proper C_2 monitoring. Also, the patients with the C_2 monitoring had been treated with daily lower doses of CyA. Finally, monitoring of C_2 to adjust CyA was found to be useful in regard to CyA nephrotoxicity, and it was also cost effective.

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