

Cardiovascular Risk Factors in Renal Transplant Patients: Cyclosporin A *Versus* Tacrolimus

GERRY LIGTENBERG, RONALD J. HENÉ, PETER J. BLANKESTIJN,
and HEIN A. KOOMANS

Department of Nephrology and Hypertension, University Medical Center, Utrecht, The Netherlands.

Abstract. The hypertensive and hyperlipidemic effects of cyclosporin A (CsA) may contribute to the high cardiovascular morbidity in renal transplant patients and to the development of chronic transplant nephropathy. Tacrolimus is reported to have less effect on BP and lipids, but steroids, other drugs, and renal function may confound this. This study assessed 24-h BP and lipid profile in stable renal transplant recipients ($n = 17$) while they were receiving CsA, after 4 wk of receiving tacrolimus, and again after 4 wk of receiving CsA. Antihypertensives were stopped at least 3 wk before. A few patients used low-dose steroids and lipid-lowering drugs, which were not changed during the study. Mean daytime BP decreased from 149 ± 12 and 95 ± 8 mmHg to 138 ± 13 and 87 ± 9 mmHg ($P < 0.001$)

after patients were switched to tacrolimus. Mean nighttime BP also decreased, from $140 \pm 12/86 \pm 7$ mmHg to $132 \pm 17/79 \pm 10$ mmHg ($P < 0.05$). Total and low-density lipoprotein cholesterol decreased from 6.1 ± 0.7 and 3.84 ± 0.79 mmol/L to 5.1 ± 0.8 and 2.98 ± 0.75 mmol/L ($P < 0.001$). Return to CsA caused an increase in BP and cholesterol to values similar as during the first CsA period. The conclusion is that tacrolimus has fewer unfavorable effects on BP and lipids than does CsA. Elective conversion from CsA to tacrolimus in stable renal transplant recipients may lead to attenuation of cardiovascular morbidity and chronic transplant nephropathy in the long term.

Cardiovascular morbidity and mortality in renal transplant patients are dramatically increased compared with the general population (1). Cyclosporin A (CsA), the mainstay of immunosuppressive treatment, contributes importantly to the cardiovascular risk in transplant recipients because of its hypertensive and hyperlipidemic effects (2). In addition, hypertension and maybe also hyperlipidemia are risk factors for the development of chronic transplant nephropathy (3,4). Recently, it was shown that both short-term and long-term survival of kidney grafts have substantially increased in the past 10 yr (5). Nevertheless, chronic transplant nephropathy is an important cause of graft failure, and it is possible that the hypertensive and hyperlipidemic effects of chronic use of CsA are involved in its pathogenesis.

Tacrolimus, an immunosuppressive agent that has been used for several years in liver transplantation, is increasingly prescribed in renal transplantation (6,7). Its immunosuppressive working mechanism is virtually identical to that of CsA (8). It has been shown that tacrolimus allows early steroid withdrawal (9) and is effective as a rescue agent for renal allograft rejection failing conventional antirejection therapy (10).

The side-effect profile of tacrolimus is less well studied.

Hirsutism and gingival hyperplasia, common with CsA, are not seen with tacrolimus (6,7). In most clinical studies, similar nephrotoxic effects as with CsA are reported (6,7,11). Neurotoxicity seems to be worse than with CsA, in particular early after transplantation when high dosages are used (6,7). The incidence of posttransplantation diabetes mellitus is increased with tacrolimus compared with CsA (6,7), but this may also be a dose-dependent effect. Recently, it was shown that with lower trough levels and with rapid tapering of steroids, the diabetogenic effect of tacrolimus is minimal (12). It has been suggested that tacrolimus causes less hypertension (6,13,14) than CsA, but controlled studies have not been conducted. Hence, differences in BP may be ascribed to steroid dose, renal function, or the use of other drugs that influence BP, rather than to the use of tacrolimus instead of CsA. Hypercholesterolemia also occurs more often during treatment with CsA than with tacrolimus (6,7,13,14). Again, this was found in studies that were designed to look at differences in rejection rate and in which renal function and the use of other drugs may have differed. In one study of hyperlipidemic patients, who were randomized for conversion to tacrolimus or continuation of CsA, conversion to tacrolimus led to a decrease of cholesterol and low-density lipoprotein (LDL). However, in this study, the use of lipid-lowering drugs varied (15).

We hypothesized that maintenance use of tacrolimus in stable renal transplant recipients causes less hypertension and hyperlipidemia than does CsA. We measured ambulant BP, lipid profile, and renal function during treatment with cyclosporin and after 4 wk of treatment with tacrolimus. Measurements were repeated again 4 wk after return to cyclosporin treatment, to abolish the effect of time on the studied variables.

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Correspondence to Dr. Gerry Ligtenberg, Department of Nephrology and Hypertension, University Medical Center, Room F03.226, Post Box 85500, 3508 GA, Utrecht, The Netherlands. Phone: 00-31-30-2507329; Fax: 00-31-30-2543492; E-mail: gligtenb@digd.azu.nl

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The design of the study, *i.e.*, switch from CsA to tacrolimus and back to CsA, and unchanged concomitant medication throughout the study allows for elimination of potential confounding factors.

Materials and Methods

Patients

We studied 17 renal transplant patients with stable renal function who were at least 1 yr after transplantation (Table 1). Patients with diabetes were excluded. Patients received CsA as immunosuppressive monotherapy ($n = 13$) or in combination with prednisone ($n = 4$) with a maximum of 5 mg/d. The prednisone dose was not changed during the study. Fourteen patients used antihypertensive drugs, either Ca-entry blockers (9 patients) or angiotensin-converting enzyme inhibitors (3 patients) or both (1 patient). These drugs were stopped at least 3 wk before the study. One patient was on diuretic therapy, which was continued throughout the study. Four patients took an hepatic 3-methylglutaryl coenzyme A reductase inhibitor, which was continued in an unchanged dose throughout the study.

Study Design

After an overnight fast, blood was sampled for measurement of serum creatinine, lipids, serum glucose and uric acid, and CsA trough level. BP was recorded for 24 h. In the morning of the next day, patients took their last dose of CsA. In the evening of the same day, tacrolimus was started at a dose of 0.10 mg/kg, and on the following days, tacrolimus was taken twice daily (total daily dose, 0.20 mg/kg). This initially high dose was chosen because our experience with conversion from CsA to tacrolimus was limited and we wanted to prevent acute rejection during conversion. Trough levels were measured after 1 wk, and the dose was adjusted to reach trough concentrations of 5 to 15 ng/ml, which is the recommended target trough level during maintenance use. After 4 wk of treatment with tacrolimus, fasting blood sampling and 24-h ambulant BP measurement were repeated. The next day, patients switched to CsA, taking the same dose as before the switch to tacrolimus. After 4 wk of treatment with CsA, fasting blood sampling and 24-h ambulant BP measurement were repeated again. The study protocol was approved by the Medical Ethics Committee of the University Hospital Utrecht, and all patients gave informed consent.

24-H BP Monitoring

The oscillometric SpaceLabs model 90207 monitor (Redmond, WA) was used. BP was measured in the nondominant arm. During the day (7 p.m. to 11 a.m.), BP was measured quarterly; during the night (11 a.m. to 7 p.m.), BP was measured every hour. From these measurements, a mean daytime BP and a mean nighttime BP were calculated.

CsA and Tacrolimus Trough Levels

CsA 12-h trough blood concentrations were measured in whole blood using an HPLC method (16). Tacrolimus 12-h trough blood concentrations were measured in whole blood by microparticle enzyme immunoassay technology using the IMX Tacrolimus II assay (Abbott Laboratories, Abbott Park, IL).

Statistical Analyses

Data are presented as mean \pm SD. Statistical analysis was performed by one-way ANOVA for repeated measurements. If variation among means reached statistical significance ($P < 0.05$), the Student-Newman-Keuls multiple comparisons test was used. A value of $P < 0.05$ was considered significant.

Results

Clinical Characteristics

Seventeen kidney transplant recipients (nine men, eight women) were studied. Their mean age was 49.7 ± 12.4 yr, and mean time after transplantation was 70 ± 40 mo (range, 12 to 144 mo). Body weight was 76.1 ± 17.5 kg and did not change during the study period. At the start of the study, the mean daily dose of CsA was 290 ± 69 mg, resulting in a mean trough concentration of 122 ± 45 ng/ml. After 4 wk of treatment with tacrolimus, the mean daily dose was 9 ± 2.6 mg, resulting in a mean trough concentration of 9.9 ± 3.5 ng/ml (Table 1).

The switch from CsA to tacrolimus and back was not complicated by acute graft rejection. Two patients reported gout after the switch to tacrolimus, which responded rapidly to short-term treatment with colchicine.

Table 1. Plasma creatinine and lipids in 17 renal transplant patients during CsA treatment and TAC treatment^a

	CsA 1	Tacrolimus	CsA 2
Plasma creatinine ($\mu\text{mol/L}$)	134 ± 49	148 ± 56^b	141 ± 53
Total cholesterol (mmol/L)	6.1 ± 0.7	5.1 ± 0.8^c	6.0 ± 0.9^d
HDL (mmol/L)	1.41 ± 0.48	1.34 ± 0.47	1.41 ± 0.50
LDL (mmol/L)	3.84 ± 0.79	2.98 ± 0.75^c	3.77 ± 0.80^d
Triglycerides (mmol/L)	1.84 ± 1.23	1.58 ± 0.91	1.86 ± 1.56
CsA or TAC dose (mg/d)	290 ± 69	9 ± 2.6	290 ± 69
CsA or TAC trough level (ng/ml)	122 ± 45	9.9 ± 3.5	132 ± 38

^a CsA, cyclosporin A; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAC, tacrolimus. Statistical analysis was performed by one-way ANOVA for repeated measurements.

^b $P < 0.01$: TAC versus CsA 1.

^c $P < 0.001$: TAC versus CsA 1.

^d $P < 0.001$, CsA 2 versus TAC.

24-H BP Recordings

Reliable ambulatory BP recordings were obtained for all patients but one. Two patients switched the monitor off during the night because it disturbed their sleep. Therefore, day and night BP data of 14 patients are shown (Figure 1, Table 2). During CsA treatment, most patients were hypertensive (in 11 patients, mean daytime systolic BP > 140 mmHg and/or mean daytime diastolic BP > 90 mmHg). BP at night was lower than during the day (140 ± 12 and 86 ± 7 mmHg; 149 ± 12 and 95 ± 8 mmHg). Eight patients had a nocturnal decline in mean arterial pressure of 10 mmHg or more, and six patients had a nocturnal decline in mean arterial pressure of more than 10% of the daytime average.

Switch to tacrolimus resulted in a profound decline in BP during the day as well as during the night (Figure 1, Table 2). From the 11 patients who had hypertension during CsA treatment, 5 became normotensive during tacrolimus treatment. During tacrolimus treatment, six patients had a more than 10 mmHg and a more than 10% decrease of daytime mean BP during the night. During the second CsA treatment period, BP rose to values identical to those in the first CsA phase (Figure 1, Table 2). The dipping patterns in mean arterial BP could also be reproduced: Seven of eight patients had again a decline of more than 10 mmHg in mean arterial BP during the night. Heart rate did not differ between CsA and tacrolimus treatments.

Laboratory Measurements

Mean plasma creatinine increased from 134 ± 49 mol/L to 148 ± 56 mol/L after 4 wk of treatment with tacrolimus ($P < 0.01$; Table 1). Uric acid did not change (0.42 ± 0.11 and 0.43 ± 0.11 mmol during CsA treatment and 0.42 ± 0.11 during tacrolimus treatment). Fasting glucose levels remained similar throughout the study (5.5 ± 0.7 and 5.4 ± 0.7 mmol/L during CsA treatment and 5.5 ± 0.5 mmol/L during tacrolimus treatment). Total cholesterol levels decreased markedly during treatment with tacrolimus, from 6.0 ± 0.7 to 5.1 ± 0.8 mmol/L ($P < 0.001$), and increased to 6.0 ± 0.9 mmol/L 4 wk after

return to treatment with CsA. The same pattern was seen in LDL cholesterol levels (Table 1). High-density lipoprotein cholesterol and serum triglycerides did not change.

Discussion

Our study shows that 4 wk of tacrolimus treatment in renal transplant patients results in a favorable cardiovascular risk profile compared with CsA. BP as well as total and LDL cholesterol decreased markedly after switching from CsA to tacrolimus. The subsequent rise in BP and total and LDL cholesterol after return to CsA and that all other medication was kept constant give definite proof that the switch to tacrolimus caused the fall in BP and lipids.

Only circumstantial evidence was obtained that patients who use tacrolimus have lower BP and lipid levels than during the use of CsA. These studies focused on the action of tacrolimus to prevent acute rejection and on graft survival (6,7,17). We believed, therefore, that there was a place for the present controlled study. Interestingly, we found that the use of tacrolimus reduced the incidence of hypertension and blood cholesterol levels to that in the pre-CsA era (18,19). Introduction of CsA was accompanied by an increase in the prevalence of hypertension from 40 to 70% of renal transplant patients (18). Besides its nephrotoxic and sodium-retaining effects, increased systemic vascular resistance and impaired vasodilation also play a role (20–22). Plasma renin activity is usually normal or low, supporting the existence of an expanded plasma volume (23). In animal experiments, renal and muscle sympathetic nervous activity was consistently elevated after acute CsA treatment (24–26). Sympathetic hyperactivity could also be demonstrated in cardiac transplant recipients and in patients who have myasthenia gravis and are receiving maintenance CsA (20). However, this could not be confirmed in other studies in cardiac transplant recipients (27), in patients with rheumatoid arthritis (22), and in patients with familial Mediterranean fever (28). Endothelium-dependent vasodilation is impaired in CsA-treated patients (21), and L-arginine administration in rats protects against CsA-induced vasoconstriction, suggesting that nitric oxide-induced vasorelaxation is inhibited by CsA (29). Furthermore, urinary endothelin has been found to be increased in CsA-treated transplant patients (30). To summarize, there has to be a vasoconstrictive factor that causes CsA-induced hypertension, but it is unknown whether this is of hormonal, neuronal, or endothelial origin.

Tacrolimus seems to be as nephrotoxic as CsA. Renal vascular resistance is similarly increased in CsA- and tacrolimus-treated liver transplant patients (31), although identical as in our patients, BP was increased during CsA treatment only. Renal morphologic changes in renal biopsy material from patients who were treated with tacrolimus are identical to those seen in patients who were treated with CsA (32). Indeed, in our study, plasma creatinine did not change in nine patients and increased slightly in eight after the switch to tacrolimus. In the long term, an improvement in renal function has been described (13). The decline in BP can be explained by a decrease either in extracellular fluid volume or in systemic vascular resistance. We did not measure cardiac output or extracellular

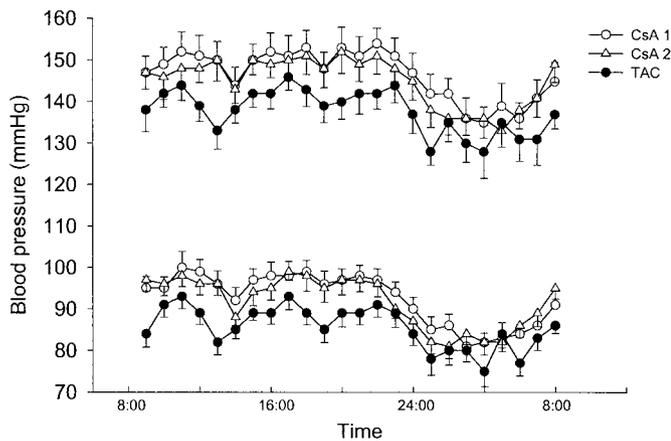


Figure 1. Twenty-four-h systolic and diastolic BP during treatment with cyclosporin A (CsA 1 and CsA 2) and during treatment with tacrolimus (mean values \pm SEM).

Table 2. Mean daytime and nighttime ambulant BP in 14 renal transplant recipients during CsA treatment and TAC treatment^a

	CsA 1	TAC	CsA 2
Daytime			
systolic BP (mmHg)	149 ± 12	138 ± 13 ^b	148 ± 12 ^e
diastolic BP (mmHg)	95 ± 8	87 ± 9 ^b	95 ± 8 ^e
mean arterial pressure (mmHg)	114 ± 9	104 ± 10 ^b	113 ± 9 ^e
heart rate (beats/min)	79 ± 11	80 ± 11	80 ± 13
Nighttime			
systolic BP (mmHg)	140 ± 12	132 ± 17 ^c	138 ± 12 ^f
diastolic BP (mmHg)	86 ± 7	79 ± 10 ^c	86 ± 7 ^f
mean arterial pressure (mmHg)	104 ± 9	97 ± 12 ^d	104 ± 9 ^g
heart rate (beats/min)	67 ± 7	71 ± 7	69 ± 10

^a Statistical analysis was performed by one-way ANOVA for repeated measurements.

^b $P < 0.001$: TAC versus CsA 1.

^c $P < 0.05$: TAC versus CsA 1.

^d $P < 0.01$: TAC versus CsA 1.

^e $P < 0.001$: CsA 2 versus TAC.

^f $P < 0.05$: CsA 2 versus TAC.

^g $P < 0.01$: CsA 2 versus TAC.

volume, but the stable body weight implies no important changes. This suggests that the lower BP is caused by a lower peripheral vascular resistance. Little is known of the effects of tacrolimus on vasoconstrictive factors in humans. Experimental data are scarce. In cultured tubular cells (33) but not in bovine aorta cells (34), tacrolimus caused endothelin release. However, in contrast to CsA, tacrolimus did not inhibit nitric oxide synthase in rat aortic smooth muscle cells (35). Renal sympathetic nervous activity was increased after CsA and tacrolimus treatment in rats (25). Human data on the effects of tacrolimus on systemic vasoconstrictive factors are lacking. However, our and earlier data (31) suggest that tacrolimus has a dissociated effect on renal and peripheral hemodynamics, leading to similar renal vasoconstriction but less peripheral vasoconstriction than CsA.

CsA impairs the nocturnal BP fall in organ transplant recipients (36). Approximately half of our patients had a nocturnal mean arterial BP decline of more than 10 mmHg, or of more than 10% of the daytime average. The total BP load is important for the development of organ damage (37). The number of dippers did not change during tacrolimus, but 24-h BP load was lower because overall BP decreased. This also may reduce the cardiovascular risk in the transplant population.

The hyperlipidemic effect of CsA not only is important for cardiovascular morbidity and mortality, but is also associated with the development of chronic transplant nephropathy (38). CsA-induced hyperlipidemia consists mainly of an elevated LDL cholesterol level, caused by a reduction of LDL catabolism in liver cells (39). In several studies, it was noted that tacrolimus did not have this effect, or to a lesser extent (7,13,15). However, changes in steroid dose and concomitant use of lipid-lowering drugs in those studies prohibit a clear conclusion. We eliminated steroids and lipid-lowering drugs as confounding factors and thus proved that conversion to tacroli-

mus decreases total and LDL cholesterol. It is conceivable that this reduction in lipids will have beneficial effects not only on cardiovascular morbidity but also on the development of chronic transplant nephropathy.

We did not see any effect on glucose levels. Fasting glucose levels were normal in all patients and did not change after conversion to tacrolimus. The use of tacrolimus in organ transplantation has been associated with an increase in the incidence of diabetes mellitus early after transplantation (6,7). However, this may be related to high initial tacrolimus levels. Maintenance dosages of tacrolimus do not impair glycemic control (12).

The recommended trough levels for CsA and tacrolimus during maintenance treatment are 100 to 250 ng/ml and 5 to 15 ng/ml, respectively. It is possible that the low levels of CsA in our patients were not equivalent to the obtained levels of tacrolimus with regard to nephrotoxicity, which may account for the small but significant increase in serum creatinine after the switch to tacrolimus. It seems clear that the nephrotoxicity of both CsA and tacrolimus is dose dependent, which makes comparison of the two drugs difficult. More recently, lower levels for maintenance use of tacrolimus have been used (13). However, even with relatively high levels of tacrolimus, the reduction of BP and cholesterol level after the switch to tacrolimus was pronounced. A lower dose of tacrolimus probably would have enhanced even the differences as presently found.

In conclusion, we have demonstrated in stable renal transplant recipients that conversion from treatment with CsA to treatment with tacrolimus leads to a marked decline in BP and in total and LDL cholesterol. There is circumstantial evidence that these effects are sustained during long-term follow-up (7,13–15). In view of the dramatic cardiovascular morbidity in the transplant population, we suggest that this reduction of car-

diovascular risk factors warrants elective conversion to tacrolimus in renal transplant recipients who are treated with CsA.

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