Immunosuppression Modifications and Graft Outcome in Patients With Chronic Allograft Nephropathy

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Abstract

Objectives: **This retrospective study was done to assess the efficacy and safety of immunosuppression conversion on progression of chronic allograft nephropathy**

Materials and Methods: **One hundred seventy-four cyclosporine-treated renal transplant recipients were studied. Patients were included if they had biopsy-proven chronic allograft nephropathy (mild to moderate) with a serum creatinine level of 300 *μ*mol/L or less. The treatments groups were (1) mycofenolate mofetil and reduced-dosage cyclosporine (group MMF/CsA; n=132) and (2) azathioprine and reduced-dosage tacrolimus (group Aza/Tac; n=42). Patient records were checked for graft function, survival, and comorbidities after conversion.**

Results: **Mean follow-up before conversion was 52.2 ± 31.1 and 47.9 ± 27.4 month in groups MMF/CsA and Aza/Tac, respectively. There was a significant deterioration of graft function in group Aza/Tac after 5 years (*P* < .05). Ten-year actuarial graft survival in group MMF/CsA was 38%; in group Aza/Tac it was 19% (*P* = .04). Nine patients started dialysis within 12 months. Tacrolimus-treated patients had a lower insignificant incidence of hyperlipidemia (*P* = .05) but a significantly higher incidence of diabetes mellitus (*P* = .04). There were no significant changes or differences in blood pressure between the groups.**

Conclusions: **Our results suggest that in patients with chronic allograft nephropathy and deteriorating allograft function, cyclosporine minimization and addition of mycofenolate mofetil achieve favorable effects in retarding the decline of graft function. Further prospective studies with larger cohorts are needed for validation.**

Key words: *Kidney transplant, Immunosuppressive agents, Outcome*

Chronic allograft nephropathy is the most common cause of late transplant failure. At 5 years after transplant, up to two-thirds of allografts show features of moderate to severe chronic allograft nephropathy and end-stage renal failure secondary to chronic allograft nephropathy; the condition accounts for 3% of all entrants to chronic dialysis programs (1). Because of the belief that the deterioration is due mostly to drug toxicity, initial attempts to halt the progressive deterioration of graft function frequently are directed at reducing or withdrawing calcineurine inhibitors. This hypothesis is supported by biopsy findings over a 10-year period showing that most patients with chronic allograft nephropathy had calcineurine inhibitor toxicity. However, the stability of allograft function seen in recent years contradicts this hypothesis (3, 4).

Another hypothesis posits that chronic allograft deterioration is due mainly to chronic rejection; instead of a reduction in immunosuppression, patients with chronic allograft deterioration may require treatments that are more potent. This hypothesis is supported by the findings of de novo, donor-specific, anti-HLA antibody production in serum samples and C4d tissue deposition in biopsy specimens of patients with a deteriorating allograft (2, 3).

Measures to control or prevent chronic allograft nephropathy would provide valuable health and economic benefits. There is evidence that

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mycofenolate mofetil in combination with a reduced dosage of cyclosporine is an effective regimen for treating established chronic allograft nephropathy (5-7). The reported studies did not include "control" patients, and the durations of patient follow-ups varied. The addition of mycofenolate mofetil without a concomitant cyclosporine dosage reduction or withdrawal has not been beneficial; however, the studies that examined this effect were limited by small patient numbers, variable durations of follow-up, and a lack of comparative control group data (8, 9). Pilot studies in which tacrolimus was substituted for cyclosporine in patients with chronic allograft nephropathy have been small and have not included control subjects (10-13). We examined 2 treatment regimens at our center that may be beneficial in cyclosporin-treated patients with chronic allograft nephropathy: mycofenolate mofetil with reduced-dosage cyclosporine and tacrolimus in place of cyclosporine with regard to renal function preservation in patients with chronic allograft nephropathy and progressive loss of graft function.

Patients and Methods

Patient Characteristics

The electronic records of renal transplant recipients receiving follow-up care at our center were examined to identify patients with progressive allograft dysfunction, defined by a gradual increase in the level of serum creatinine, proteinuria, and histo-pathological findings suggestive of chronic allograft nephropathy. The inclusion criteria for this retrospective study were as follows: age older than 18 years, cyclosporine-based immunosuppression, serum creatinine level of 300 μmol/L or less, and biopsy proven chronic allograft nephropathy of mild to moderate degree in accordance with the criteria of Banff Classification of 1997. Exclusion criteria included previous treatment with tacrolimus or mycofenolate mofetil; a serum creatinine level greater than 300 μmol/L; confirmed histo-pathological diagnosis of chronic calcineurine inhibitor toxicity, other indications for conversion including severe, acute, steroid-resistant rejection; hepatitis; and recurrent or de novo glomerulo-nephritis.

Treatment groups

Written, informed consent was obtained from each patient. The study protocol, which was approved by the ethics committee of the University of Mansoura before the study's onset, conformed to the ethical guidelines of the 1975 Helsinki Declaration. Patients were randomized into 2 groups. The 2 treatments groups were mycofenolate mofetil and reduced-dosage cyclosporine (group MMF/CsA) and azathioprine and reduced-dosage tacrolimus (group Aza/Tac). The protocol for each is summarized below:

Mycofenolate mofetil and reduced-dosage cyclosporine

(1) Mycofenolate mofetil 500 mg twice daily was initiated, and azathioprine was discontinued at once; (2) at the beginning of week 2, the dosage of mycofenolate mofetil was increased to 750 mg twice daily, and the cyclosporine dosage was reduced by 25%; and (3) at the beginning of week 3, the dosage of mycofenolate mofetil was increased to 1000 mg twice daily, and the dosage of cyclosporine was adjusted to achieve a trough blood level of 62.4 to 83.2 nmol/L (monoclonal assay; Abbott Diagnostics, Abbott Laboratories, Abbott Park, IL, USA). In cases of bone marrow suppression, the dosage of mycofenolate mofetil was reduced to 750 mg twice daily, and then to 500 mg twice daily if the white blood cell count did not return to the normal range and if neutropenia persisted, the mycofenolate mofetil was withdrawn.

Tacrolimus in place of cyclosporine

(1) Cyclosporine was discontinued, and tacrolimus was started at a dosage of 0.1 mg/kg/day, 12 hours after the last dose of cyclosporine or 24 hours after the last dose of cyclosporine if the trough level was more than 208 nmol/L. (2) A target whole blood trough level of 4.16 to 8.32 nmol/L (IMX tacrolimus II assay, Abbott Laboratories) was maintained throughout the study. Azathioprine was continued at the same dosage of 2 mg/kg/day to a maximum dosage of 125 mg/day.

The demographic, clinical, and laboratory data, and the various medical complications were documented chronologically on the patients' charts. Graft function was monitored using serum creatinine levels and calculated glomerular filtration rates using the Cockroft-Gault formula. All comorbidities after conversion were recorded; hypertension was accepted when the patient's systolic blood pressure was greater than 140 mm Hg and/or the diastolic

blood pressure was greater than 90 mm Hg and was graded according the number of antihypertensive medications taken. Diabetes mellitus was defined if the fasting blood glucose level was greater than 6.99 mmol/L. Bacterial, viral, or fungal infections were diagnosed by specific investigations and cultures as appropriate. Other complications including cardiovascular morbidities and malignancy were recorded.

Endpoints

The primary efficacy endpoints were the rate of a significant improvement in graft function defined as a stabilization or reduction in the serum creatininine level observed at 1 and 5 years after conversion. Secondary endpoints were graft and patient survival rates, incidence of acute rejection, blood pressure control, de novo posttransplant diabetes mellitus, and hyperlipidemia.

Statistical analyses

The SPSS statistics package (Statistical Product and Services Solutions, version 11.0, SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. For univariate analysis, the *t* test was used for continuous data, while noncontinuous data were compared using the Mann-Whitney *U* test. The chi-square test was used to compare categorical variables. Values for *P* less than .05 were considered statistically significant. Patient and graft survival rates were analyzed using Kaplan-Meier survival curves; the survival curves were compared with the log-rank test.

Results

Patients

Details of the patient characteristics are shown in Table 1. All participating subjects were ethnic Egyptians. Before study entry, the patients in groups MMF/CsA and Aza/Tac had 1.4 ± 1.0 and 1.3 ± 1.0 episodes of biopsy-proven acute rejection and 0.14 ± 0.3 and 0.11 ± 0.3 episodes of biopsy-proven acute cyclosporine toxicity, respectively ($P = .2$). In groups MMF/CsA and Aza/Tac, 4 and 5 patient had a grade 2 chronic allograft nephropathy score. The mean level of proteinuria at study entry in groups MMF/CsA and Aza/Tac was 0.85 ± 1.3 g/day and 0.73 ± 1.4 g/day ($P = .3$), and 2 patients in each group had proteinuria of more than 3 g/day. During the 12 months preceeding study entry, the mean increase of serum creatinine in groups MMF/CsA and Aza/Tac was from 158 ± 34 μmol/L to 185 ± 70 μmol/L and from 150 ± 44 μmol/L to 176 ± 79 μmol/L ($P < .05$).

Immunosuppression

Data on drug dosages and blood concentrations at conversion are shown in Table 1. In group MMF/CsA, the cyclosporine dosage was reduced by a median of 44% [interquartile range, 24%-57%], giving a median 1-year cyclosporine trough blood level of 78 ng/mL (range, 70-113 ng/mL) (P = NS). The median maintenance dosage of mycofenolate

Table 1. Baseline demographics and clinical characteristics of the study subjects.

	group MMF/CsA (n=132)	group Aza/Tac (n=42)	*P* value
Age (years) at conversion	35.4 ± 8.7	32.9 ± 7.2	.1
Sex (M:F)	96:36	31:11	.5
Body mass index (kg/m^2)	23.4 ± 3.0	23.4 ± 4.1	.9
Time from transplant to conversion (months)	52.2 ± 31.1	47.9 ± 27.4	.6
Nature of transplants			
Related (%)	119 (91.2)	35 (83.3)	.6
Second (%)	5 (3.8)	3 (7.1)	.3
Mismatches on HLA-A and HLA-B≤1:≥2	42:90	9:33	.5
Mismatches on HLA-DR 0:1	16:116	1:41	.8
Causes of end-stage renal disease (%)			.08
Interstitial nephritis	21 (15.9)	6 (14.3)	
Glomerulonephritis	6 (4.5)	2 (4.8)	
Others	71 (53.8)	21 (50)	
Inapplicable	34 (25.8)	13 (31)	
Pre-emptive transplant (%)	15 (11.3)	4 (9.5)	.7
Acute tubular necrosis (%)	2 (1.5)	1 (2.4)	.6
Donor characteristics			
Age, y	35.6 ± 10.3	37.3 ± 10.7	.4
Sex (M:F)	62:60	25:17	.3
At the time of the conversion			
Prednisolone dose (mg/d)	7.5 ± 1.9	7.3 ± 1.8	.7
CsA dose (mg/kg/d)	2.7 ± 1.8	2.8 ± 1.7	.5
CsA trough level (ng/mL)	114.3 ± 41.2	117.1 ± 43.8	.8
Banff 97 score for CAN (%)			
Grade I	99 (75)	30 (71.4)	.1
Grade II	33 (25)	12 (28.6)	
History of previous acute rejection			
1 episode	49 (37.4)	13 (31)	
2 episodes	9 (6.9)	4 (9.5)	.5
≥ 3 episodes	7 (5.3)	1 (2.4)	
Treatment of rejection			
Methylprednisolone	81 (88.6)	18 (85.7)	.3
Anti-CD3	10 (11.4)	3 (14.3)	
Serum creatinine (μmol/L)			
Mean	194 ± 88	185 ± 96	.9
Range	132-300	141-300	
Creatinine clearance (mL/min)			
Mean	46.1 ± 13.9	45.6 ± 19.4	.3
Range	28.7-78.5	32.4-77	
Posttransplant comorbidities (%)			
Hypertension	123 (93.1)	39 (92.9)	.1
Diabetes mellitus	12 (9.1)	2 (4.8)	.5
Hyperlipidemia on statin	71 (53.8)	21 (50)	

Abbreviations: Aza, Azathioprine; CAN, chronic allograft nephropathy; CsA, cyclosporine; F, female; M, male; MMF, mycofenolate mofetil; Tac, tacrolimus

Table 2. Evolution of graft function after conversion in both groups.

	Serum creatinine (μmol/L)		Creatinine clearance (mL/min)	
Time (months)	Group MMF/CsA	Group Aza/Tac	Group MMF/CsA	Group Aza/Tac
0 (n^A=132, n^B=42)	158 ± 70	167 ± 62	46.1 ± 13.9	45.6 ± 19.4
6 (n^A=132, n^B=42)	141 ± 62	141 ± 62	53.1 ± 16.4	52.2 ± 17.4
12 (n^A=127, n^B=38)	150 ± 62	150 ± 44	55.1 ± 19.4	51.7 ± 18.2
24 (n^A=116, n^B=35)	158 ± 0.9	176 ± 62	50.2 ± 19.1	49.8 ± 20.0
36 (n^A=104, n^B=32)	158 ± 62[a]	194 ± 88[a,b]	49.9 ± 20.1[a]	40.8 ± 20.3[a,b]
60 (n^A=99, n^B=26)	167 ± 44[a]	211 ± 101[a,b]	47.2 ± 15.0[a]	40.2 ± 16.2[a,b]

[a]$P < .05$ comparing serum creatinine and creatinine clearance between both groups at different intervals (Unpaired samples *t* test).
[b]$P < .05$ comparing serum creatinine and creatinine clearance between the same group at conversion and at different intervals after conversion (paired samples *t* test).
n^A, number of group A; n^B, number of group B.

Abbreviations: Aza, azathioprine; CsA, cyclosporine; MMF, mycofenolate mofetil; Tac, tacrolimus

mofetil was 1.5 g/day (interquartile range, 1.5-2 g/day), and owing to gastrointestinal adverse effects, there were only 8 patients who took an average dose less than the target amount. In group Aza/Tac, the median 1-year tacrolimus trough blood level was 7 ng/mL (interquartile range, 5-9 ng/mL), and the final stable dosage of tacrolimus was in the range of 0.066 to 0.08 mg/kg/day. Owing to leucopenia, azathioprine dosages were reduced in 2 patients.

Graft Function and Survival

Two distinctive patterns of response emerged: The first was a continuing deterioration in renal function with no apparent benefit over the trend of the glomerular filtration rate (GFR). This pattern was seen in 69 patients (45 patients in group MMF/CsA and 24 patients in group Aza/Tac). Forty-two patients lost their grafts during the observation period (29 patients in group MMF/CsA and 13 patients in group Aza/Tac). Nine patients started dialysis treatment during the 12 months after conversion, 5 from group MMF/CsA and 4 from group Aza/Tac. Analysis of the GFR data also showed a trend toward a treatment advantage for patients in group MMF/CsA ($P < .05$). The mean decrease in GFR in group MMF/CsA was 1.0 mL/min compared with a mean decrease of 5.11.7 mL/min in the group Aza/Tac (Table 2).

Of 174 patients with chronic allograft nephropathy, mild chronic allograft scores were observed in 74.1% of patients (grade 1, 99/30), while 25.9% (grade 2, 33/12) showed moderate chronic allograft scores. Compared with patients showing grade 1 chronic allograft scores, those with grade 2 had significantly longer posttransplant follow-ups at the time of conversion ($P < .01$). Moreover, there were significant differences observed in the mean creatinine values at the time of conversion (mean serum creatinine was 114 ± 44 μmol/L and 141 ± 97 μmol/L for those with grade 1 and grade 2 scores, respectively) ($P = .04$). The most significant benefit was observed among patients showing grade 1 chronic allograft nephropathy (mean serum creatinine levels after the first year were 132 ± 53 μmol/L and 158 ± 62 μmol/L in patients with grade 1 and grade 2 chronic allograft nephropathy, respectively) ($P < .05$). There was no significant difference in the proportion between group MMF/CsA and group Aza /Tac (48% vs 35%) ($P = .1$). There were significant graft losses among moderate-degree chronic allograft scores in the 2 groups (25 [76%] in group MMF/CsA and 10 [83%] in group Aza/Tac) ($P = .02$). After conversion, 10 patients developed an acute rejection (7 in group MMF/CsA after a mean of 4.9 ± 1.1 months and 3 patients in group Aza/Tac after a mean of 4.5 ± 1.0 months) ($P = .08$). Rejections were less severe in patients in group MMF/CsA, but this result was not statistically significant ($P = 0.1$). Three patients, 2 of whom were in group MMF/CsA, required treatment with antithymocyte globulin within 12 months of the conversion. There was no relation between the frequency and the severity of acute rejection before conversion and acute rejection after conversion ($P = .4$ and $P = .3$, respectively). Graft survival at 5 and 10 years was 75% and 38% in group MMF/CsA; 62% and 19% in group AzaF/Tac ($P = .05$ and $P = .04$, respectively) (Figure 1). Recurrence of original kidney disease occurred in 3 patients (1 focal segmental glomerulosclerosis in each group, and 1 membranous nephropathy in group MMF/CsA) (Table 3). Figure 2 shows that there were no between-group differences regarding

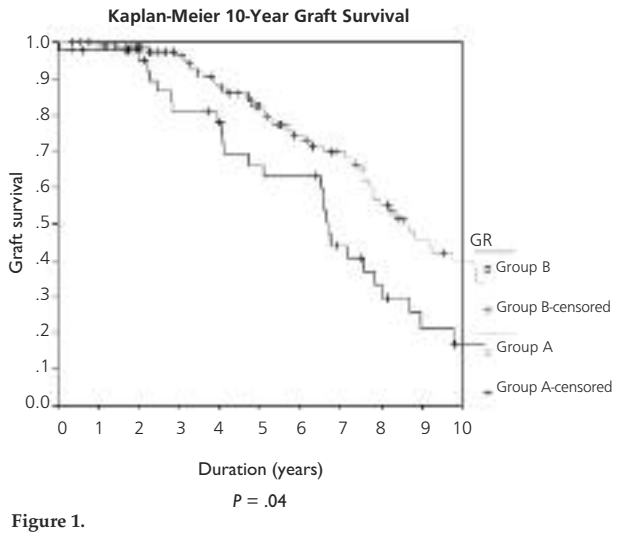

Figure 1.

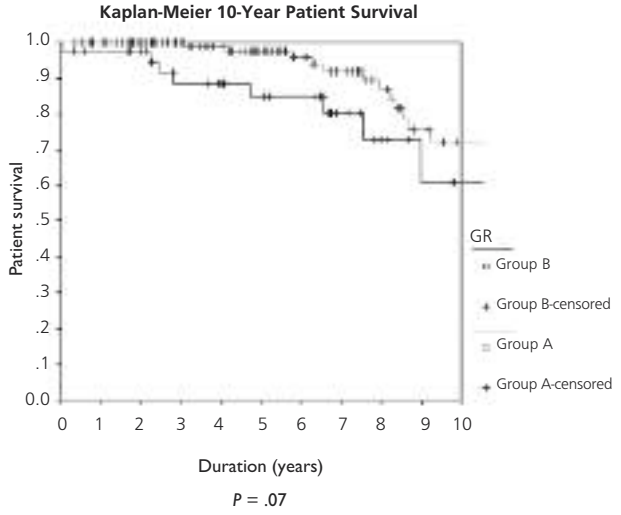

Figure 2.

5- and 10-year actuarial patient survival rates ($P = .5$ and $P = .07$, respectively).

Safety

Changes in the salient clinical variables are listed in Table 3. Both treatment groups showed a sustained, though nonsignificant, reduction in systolic blood pressure compared with baseline values within the first 6 months. Twenty-five patients in group MMF/CsA and 9 patients in group AzaMMF/Tac stopped taking antihypertensive medications ($P = .06$). The number of antihypertensive medications taken per patient, however, decreased significantly, in group MMF/CsA (2.99 ± 1.1 to 1.75 ± 0.8) compared with group Aza/Tac (2.1 ± 1.0 to 1.87 ± 1.1) ($P = .04$). Proteinuria did not change significantly and remained similar between the groups. None of the subjects developed de novo diabetes mellitus in

Table 3. Safety parameters after conversion in both groups

	Group MMF/CsA (n= 132)	Group Aza/Tac (n=42)	*P* value
Acute rejection episodes			.5
1 episode	6 (4.6)	3 (7.1)	
2 episodes	1 (1.5)	1 (2.4)	
Banff 97 of acute rejection episodes		0.2	
Borderline	4 (3.1)	2 (4.8)	
IA/IB	2 (1.5)/2 (1.5)	1 (2.4)/1 (2.4)	
Metabolic complications			
Diabetes mellitus		6 (14.3)	.003
Hyperlipidemia	10 (7.6)	2 (4.8)	.05
Hypertension (%)			.9
No. of patients	98 (74.2)	30 (71.4)	
No. of antihypertensive drugs ≤2 / ≥3	83/15	25/5	
Infections (%)			
Bacterial	42 (31.8)	18 (42.9)	.08
Viral	3 (2.3)	-	.06
Fungal	3 (2.3)	1 (2.4)	1.0
Mycobacterium Tuberculosis	2 (1.5)	1 (2.4)	.1
Malignancy (%)	3 (2.3)	2 (4.8)	.1
Symptoms and signs (%)			
Gastrointestinal	12 (9.1)	2 (4.8)	.5
Gum hyperplasia	2 (4.5)	-	.6
Neurotoxicity	1 (0.8)	1 (2.4)	.09
Hypertichosis	2 (1.5)	-	.4
Graft loss (%)			
CAN	29 (22)	13 (31)	.04
Recurrence	2 (1.5)	1 (2.4)	
Death with function	4 (2.3)	2 (4.8)	
Causes of death with function			.4
Cardiovascular	1	1	
Infections	2	-	
Malignancy	-	1	
Hepatitis	1	-	

Abbreviations: Aza, Azathioprine; CAN, chronic allograft nephropathy; CsA, cyclosporine; MMF, mycofenolate mofetil; Tac, tacrolimus

group MMF/CsA, and there was no change in the number of lipid-lowering medications. After conversion to tacrolimus in group MMF/Tac, the statin was stopped in 3 patients. In group Aza/Tac, 6 patients (14.3%) developed de novo diabetes mellitus after receiving tacrolimus; in 1 of them, the blood sugar was not controlled and the steroid dosages had to be reduced. In 5 patients who had diabetes mellitus before conversion, the dosage of antidiabetic medication had to be increased; 2 patients were started on insulin. In group MMF/CsA, gastrointestinal disturbances occurred in 12 patients. This generally improved with a mycofenolate mofetil dosage reduction in 8 patients and improved spontaneously in the others with medications. The dosage of mycofenolate mofetil was reduced in 1 patient because of progressive anemia. There was apparently an increased incidence of viral infection in patients in group MMF/CsA and in bacterial infections in patients in group Aza/Tac; however,

this difference was not statistically significant ($P = .08$ and $P = .06$, respectively). Twenty patients developed infectious complications that required hospitalization after conversion (11 patients in group MMF/CsA: 3 with cytomegalovirus and 8 patients with bacterial pneumonia; and 9 patients in group Aza/Tac, all with bacterial pneumonia).

Discussion

Our study provides evidence of a treatment advantage for mycofenolate mofetil/reduced dosage cyclosporine as compared with substituting tacrolimus for cyclosporine in patients with established chronic allograft nephropathy, in the short and the long term. There is some evidence that use of mycofenolate mofetil in place of azathioprine produces clinical benefit in terms of a reduced incidence of chronic renal allograft failure (14). Our results confirm the observations of 2 earlier studies that suggested beneficial effects of a mycofenolate mofetil and cyclosporine dosage reduction in renal transplant recipients with late allograft dysfunction (6, 7).

In our series, renal function stabilized and even improved in approximately 75% of the patients, and few episodes of acute rejection were observed despite the great reduction in cyclosporine dosage. It is important to note that the addition of mycofenolate mofetil alone may not be sufficient to improve renal function in patients with established chronic allograft nephropathy (9). We would like to suggest that, in patients with chronic allograft dysfunction, the major beneficial action of mycofenolate mofetil is to allow a safe reduction of cyclosporine, thereby improving renal hemodynamics and function without exposing patients to an increased risk of acute rejection. In the "cyclosporine-steroids-azathioprine era," cyclosporine dosage reduction was associated with a significant risk of acute rejection, and most transplant programs, including ours, were reluctant to decrease cyclosporine dosages below an average of 4 mg/kg/day to avoid chronic immunological injury. Given the vasoconstrictive and profibrogenic properties of cyclosporine, use of new agents (eg, mycofenolate mofetil) that will allow for a cyclosporine dosage reduction might provide not only adequate immunosuppression, but might also be the ideal approach for treating chronic allograft nephropathy and preventing further chronic allograft injury (15, 16).

The Creeping Creatinine Study (17) examined the effect of introducing mycofenolate mofetil followed by complete withdrawal of cyclosporine and was unique because it had a control group. Renal function stabilized in 58% of patients receiving mycofenolate mofetil in place of cyclosporine as compared with 28% of controls. The incidence of acute rejection in the 2 groups was similar. Thus, while the safety of complete calcineurine inhibitor withdrawal is debatable, a minimization approach may be an alternative that alters the course of chronic allograft nephropathy without compromising safety. Our results also demonstrate that this therapeutic maneuver results in stabilization of renal function in these patients without risk of acute allograft rejection. Moreover, this therapeutic change facilitates control of dyslipidemia and may lead to better blood pressure control—both of which may play a role in improving graft function.

The results of this study of a relatively small group of patients with initially impaired renal function (mean creatinine level, 167.96 μmol/L at 47 months after transplant) showed that late conversion from cyclosporine to tacrolimus might be of little benefit. Our data show that in 60% of the patients, conversion to tacrolimus for deteriorating renal function was followed by stabilization but ultimately, deterioration of renal function over the course of 5 years' follow-up. The rate of change of the GFR was reduced in some patients receiving tacrolimus, but the treatment response in patients in the tacrolimus group, as a whole, did not prevent chronic allograft dysfunction. Tacrolimus previously has been shown to salvage refractory allograft rejection in 60% to 80% of recipients on baseline cyclosporine therapy who have failed either high-dose corticosteroid therapy and/or antilymphocyte therapy in short-term follow-up (11). Contrary to those findings, there is a little information about tacrolimus rescue for patients with chronic rejection. From our results, tacrolimus seems not to be useful, even in patients with chronic rejection of a mild degree, because tacrolimus could not improve or even stabilize renal function in the majority of patients after 5 years of follow-up. However, the dramatic improvement in renal function after tacrolimus conversion observed in the first 6 months was not sustained in most patients. These results are comparable with those of earlier reports (18). Our results show that the average serum creatinine levels of successfully rescued patients

were significantly lower than those of patients who could not be rescued. From our results, tacrolimus conversion seems to be much more effective when applied in the early phase of chronic allograft nephropathy than when it is applied in the late phase. Some studies have shown beneficial effects of late conversion from cyclosporine to tacrolimus on renal function, an effect that was not observed in our study.

Unfortunately, postswitch biopsy specimens were not systematically taken because this had not initially been planned for at the time of conversion. However, in the absence of a control group (ie, patients continuing on cyclosporine immunosuppression), what would have happened to renal function for patients undergoing a cyclosporine regimen is not known. Continuing cyclosporine treatment in some of these patients was considered ethically unjustified. Apart from cyclosporine minimization or conversion to tacrolimus or mycofenolate mofetil, there is an emerging trend to combine calcineurine inhibitor minimization or withdrawal, with a mammalian target of rapamycin inhibitors such as sirolimus (19). An absence of nephrotoxicity is a distinct advantage of a mammalian target of rapamycin inhibitors, but they were not available at the inception of this study. In a recent report of 43 patients with chronic allograft nephropathy, conversion from a calcineurine inhibitor to sirolimus was associated with improved renal function, yet up to a third of the subjects developed overt proteinuria. Moreover, patients with an initial creatinine clearance of less than 30 mL/minute or with a basal 24-hour protein loss of more than 500 mg who were converted to sirolimus did worse after conversion. The long-term safety and efficacy of this approach requires further validation. Timely intervention depends on early detection of chronic allograft nephropathy. This is probably best achieved by protocol transplant biopsy, because currently there are no validated noninvasive tests of renal allograft injury.

One of the limitations of this study was the inability to monitor the therapeutic drug level of mycophenolic acid in our patients. Several studies regarding the relation between mycophenolic acid pharmacokinetics and clinical outcomes have been done in renal transplant patients. The results of the these studies clearly demonstrate a pharmaco-kinetics/pharmcaodynamics relation between mycophenolic acid concentration and adverse effects or acute rejection at a fixed dosage of 2 g/day. A low mycophenolic acid area under the curve (AUC0-12 hours) was associated with a high risk of rejection. These low values were obtained after a reduction in the oral dosage in patients who had experienced mycofenolate mofetil-related adverse effects (20).

In summary, we conclude that conversion to mycofenolate mofetil with a reduction in cyclosporine dosage may be an effective therapeutic approach for patients with chronic renal allograft dysfunction due to chronic allograft nephropathy. However, prospective, controlled trials with suitable control groups are needed to determine whether it is the addition of mycofenolate mofetil or the cyclosporine dosage reduction that accounts for the improvement in renal function.

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