Successful Conversion of Immunosuppressives from Cyclosporine to Tacrolimus in Chronic Rejection after Kidney Transplantation

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Graft 2002; 5; 128
DOI: 10.1177/1522162802005003002

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The persistence of chronic renal allograft nephropathy is an important cause of graft loss. Here the authors describe the 1st long-term results after switching from cyclosporin A (CyA) to tacrolimus in patients with chronic allograft nephropathy. Eighteen patients had chronic allograft nephropathy confirmed by biopsy. Mean observation period was 12.3 months. The mean rate of decline in glomerular filtration (1/serum creatinine × 100/year) was measured as a function of time before and after conversion therapy using linear regression analysis. The regression coefficients were compared using the Student *t*-test for paired samples. Conversion to tacrolimus significantly reduced the progression to kidney failure. Kidney function was stable in the observed time interval as the mean change of glomerular filtration rate decelerated significantly (1/creatinine per year × 100, $P < 0.029$). Lipids and blood pressure values were significantly lowered after conversion therapy. The authors' results suggest that switching from CyA to tacrolimus is adequate for treating chronic rejection in kidney allograft recipients.

ABBREVIATION

GFR Glomerular filtration rate

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Introduction

Several reports indicate that switching from cyclosporin A (CyA) to tacrolimus in patients with chronic allograft rejection increases the transplant survival rate, and thus delays the patients' return to dialysis therapy.[1-4] We now report on the long-term outcome of 18 recipients with biopsy-proven chronic rejection following conversion from CyA to tacrolimus. Evaluation of the clinical effect of conversion treatment was based on the determination of the mean rate of GFR (estimated according to Levin[5] as 1/serum creatinine × 100/year) as the parameter of the progression of renal function, as well as assessment of other factors contributing to renal transplant dysfunction, that is, dyslipoproteinemia and elevated blood pressure.

Patients and Methods

Between 1997 and 1999, we switched 18 patients with biopsy-proven chronic allograft rejection (Fig 1) from CyA to tacrolimus (Table 1). Concomitant immunosuppressive treatment (steroids between 5 and 10 mg daily in all patients and Mycophenolate Mofetil in 9 patients) was not changed after the switch from CyA to tacrolimus. The lipid-lowering therapy and the number of antihypertensive drugs affecting the renin-aldosterone system remained the same before and after switching. CyA through level amounted to 163 ± 29.6 ng/ml. Serum creatinine levels were documented every 2 weeks. Serum triglycerides and cholesterol, hemoglobin, antihypertensive drugs and blood pressure values were documented at least once a month. Data were document-

Table 1 | **Clinical Data of 18 Allograft Recipients**

Clinical Parameter	Patients with Chronic Rejection
Mean recipient age (± SD)	49.2 ± 10 years
Age ≥ 60 yr	3
Sex	
Male	12
Female	6
Mean time after transplantation (months) (±SD)	21.4 ± 26 months
Renal transplant	
Primary transplant	16
Retransplant	2
Patients with panel reactive antibody	3

Table 2 | **Mean Change of GFR* before and after Switching of Immunosuppressive Therapy from Cyclosporin A to Tacrolimus in Patients with Chronic Transplant Rejection****

Mean Change of GFR before Conversion 1/creatinine (mg/dl) per Year × 100 ± SD	Mean Change of GFR after Conversion 1/creatinine (mg/dl) per Year × 100 ± SD	Significance	Serum-Creatinine at Conversion Mean (mg/dl) ± SD	Serum-Creatinine after 1 Year Mean (mg/dl) ± SD	Significance
-7.92 ± 1.13	-0.04 ± 0.90	$P = 0.029$	3.36 ± 1.62	3.36 ± 1.63	ns

*glomerular filtration rate (1/serum-creatinine × 100 per year).
**serum-creatinine (mg/dl) at conversion and after 1 year ($n = 18$ ± SD), level of significance using the Student *t*-test.

ed for 3 months before the time of conversion and over a mean time of 12.3 months after conversion. To estimate the mean rate of decline in GFR,[5,6] the mean rate of GFR was computed as the trend of renal function (1/creatinine × 100) per year and equals the linear regression coefficient. The slopes of the GFR development before and after switching were compared by means of the Student *t*-test.

Results

We investigated the effect of conversion from CyA to tacrolimus in 18 patients with chronic transplant rejection after transplantation (clinical data in Table 1). Renal transplant function amounted 3.36 ± 1.62 mg/dl at the time of conversion from CyA to tacrolimus (Table 2). Switching from CyA to tacrolimus led to a significant improvement in transplant function (Table 2, Fig 1). The mean rate of decline in GFR per year clearly decelerated compared with the 3 months prior to conversion ($P < 0.029$). Serum creatinine after conversion from CyA to tacrolimus stabilized at 3.36 ± 1.63 mg/dl after a time interval of 1 year. Obviously, tacrolimus prevented further transplant function loss due to chronic rejection in the long term. Serum values of cholesterol and triglycerides were significantly lowered after conversion therapy (Table 3). In contrast, hemoglobin values remained stable. Blood pressure values were slightly lowered, and the antihypertensive regimen could be reduced significantly from 4 to 3 antihypertensive drugs after switching to tacrolimus (Table 4).

Discussion

The aim of the study was to evaluate the effect of tacrolimus conversion therapy in 18 patients with persistent chronic rejection under cyclosporine, as described in single case reports.[7] The deterioration of transplant function, as expressed by a declining mean change of GFR per year, continued after switching to tacrolimus, but the velocity of the decline was significantly lower. Tacrolimus could not reverse the transplant function loss due to chronic rejection, but it was able to slow down the deterioration of graft function. Elevated levels of both blood pressure and blood lipids accelerate the pro-

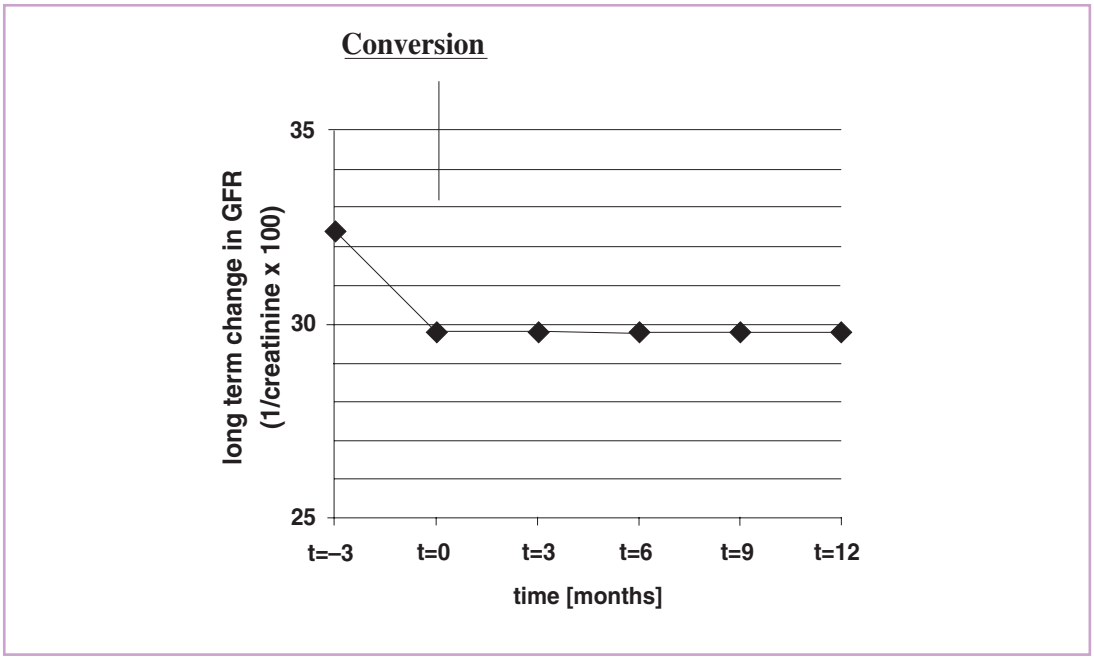

Figure 1. Graphic presentation of the long-term change in renal function (represented by the mean rate of glomerular filtration rate, 1/serum creatinine) in patients with biopsy proven chronic graft rejection in the observed time interval 12.3 months after time of conversion treatment at $t = 0$ months (mean of $n = 18$).

gression of chronic rejection. Treatment of chronic transplant rejection therefore always includes optimizing those factors. After conversion of CyA to tacrolimus, we saw a significant decline of serum cholesterol and serum triglycerides, whereas hemoglobin values remained stable. Whether or not the stabilization of renal function after conversion, and the decline in serum lipids, is due to a withdrawal of CyA[7,8] or is directly caused by tacrolimus,[9] cannot be determined on the basis of these data.

Blood pressure in the observed patients was better controlled under therapy with tacrolimus. This observation is compatible with results from Taylor and others in patients after heart transplantation, and by the U.S. Multicenter study group.[10,11] In conclusion, we demonstrate that in patients with chronic allograft rejection, tacrolimus significantly reduced the progression toward graft failure. Kidney function was stable during a mean observation period of 12.3 months. Based on our results, we would recommend that in patients with chronic allograft rejection, one should convert the therapy from CyA to tacrolimus.

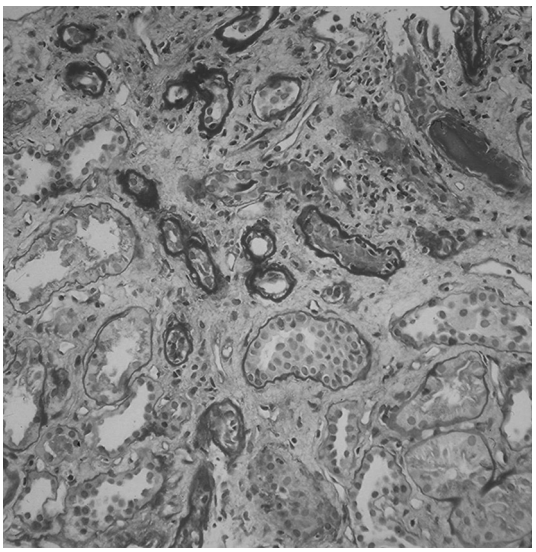

Figure 2. Light microscopic appearance of an exemplary biopsy specimen in renal transplant recipients: chronic, focally floride interstitial rejection with lymphocytes in atrophic and better maintained epithelial cell formations. Periodic acid-Schiff, original magnification × 360. GFR = glomerular filtration rate.

Table 3 | **Lipids and Hemoglobin of All Patients before and after Therapy Conversion from Cyclosporin A to Tacrolimus***

	Before Conversion	After Conversion	Significance
Serum-cholesterol (mg/dl) mean ± SEM	255.52 ± 8.08	223.57 ± 6.01	$P < 0.001$
Serum-triglycerides (mg/dl) mean ± SEM	225.65 ± 13.61	180.78 ± 10.41	$P < 0.001$
Hemoglobin (g/d) mean ± SEM	12.32 ± 0.31	12.31 ± 0.22	ns

*N = 18 ± SD, level of significance using the Student tailed t-test for paired samples.

Table 4 | **Blood Pressure Levels before and after Switching to Tacrolimus as Observed in the Renal Allograft Recipients and Number of Antihypertensive Drugs Given before and after Switching to Tacrolimus (N = 18 ± SD)**

	Before Conversion	After Conversion	Significance
Blood pressure mean ± SD (mm Hg)	146 ± 17/84 ± 7	141 ± 18/82 ± 4	$P < 0.001$
Antihypertensive drugs (total)	3.4 ± 1.1	2.8 ± 1.2	$P < 0.001$
ACE-inhibitors, AT-II antagonists mean ± SD	1.8 ± 0.5	1.9 ± 0.9	ns

References

1. van Hooff JP, Christiaans MH. Use of tacrolimus in renal transplantation. **Transpl Proc 1999;31:3298-9**.
2. Hauser IA, Neumayer HN. Tacrolimus and cyclosporine efficacy in high-risk kidney transplantation. European Multicentre tacrolimus (FK 506) Renal Study Group. **Transpl Int 1998;11:73-7**.
3. Henry, ML. Cyclosporine and tacrolimus (FK 506): a comparison of efficacy and safety profiles. **Clin Transplant 1999;13:209-20**.
4. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, et al. Multicenter randomised trial comparing tacrolimus (FK 506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. **Transplantation 1997;15(64):436-43**.
5. Levin, LM. The elderly patient with advanced renal failure. **Hosp Pract 1989;30:35-44**.
6. Nishioka T, Imanishi M, Akiyama T, Kurita T, Kokado Y, Takahara S, et al. Is tacrolimus effective for persistent renal allograft rejection? **Hinyokoka Kiyo 1998;4:369-72**.
7. Hilbrands LB, Demacker PN, Hoitsma AJ, Stalenhoef AF, Koene RA. The effects of cyclosporine and prednisone on serumlipid and (apo)lipoprotein levels in renal transplant recipients. **J Am Soc Nephrol 1995;5:2073-81**.
8. Hricik DE, Mayes JT, Schulak JA. Independent effects of cyclosporine and prednisone on posttransplantant hypercholesterinemia**. Am J Kidney Dis 1991;18:353-8.**
9. McCune TR, Thacker LR, Peters TG, Molloy L, Rohr MS, Adams PE, et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation: a Southeastern Organ Procurement Found multicenter clinical study. **Transplantation 1998;15:87-92**.
10. Taylor DO, Barr ML, Radovancevic B, Renlund DG, Mentzer RM Jr, Smart FW, et al. A randomized multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. **J Heart Lung Transplant 1999;18:336**.
11. U.S. Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation**. N Engl J Med 1994;331:1110**.