Role of Everolimus on Cardiac Functions in Kidney Transplant Recipients

U. Cakir[a,*], G. Alis[a], T. Erturk[a], A.H. Karayagiz[a], U. Karabulut[b], and I. Berber[a]

[a]Transplant Center, Acibadem International Hospital, Acibadem University, Istanbul, Turkey; and [b]Cardiology Department, Acibadem Healthcare Group, Istanbul, Turkey

ABSTRACT

Background. Kidney transplantation is known to increase the survival of dialysis patients by ameloriating cardiac status, including both systolic and diastolic functions. We aimed to evaluate the role of immunosuppressive drug regimens on cardiac functions of kidney transplant recipients (KTRs).

Methods. We prospectively evaluated 120 KTRs immediately before and 1 year after the kidney transplantation, using tissue Doppler echocardiography. A triple immunosuppressive therapy including tacrolimus, mycophenoloic acid (MPA), and prednisolone was started for all patients. After 3 to 6 months, the tacrolimus dose was lowered to achieve target serum levels of 5 to 8 ng/mL in both groups. MPA was switched to everolimus, with target levels of 4 to 6 ng/mL, in group 1 (n = 58), whereas group 2 (n = 62) continued with MPA.

Results. No differences in age, sex, or dialysis duration existed between the groups. The prevalence of diabetic or hypertensive nephropathy as the etiology of chronic kidney disease was similar. Blood pressure was strictly controlled. The number of acute rejection episodes was not different in both groups, and no graft loss was observed in either group. Improvement in cardiac parameters including ejection fraction, left ventricular diastolic diameter, posterior wall thickness, and left ventricular hypertrophy was significantly better before and 1 year after transplantation. Interestingly, when compared with group 2, amelioration of all of the parameters mentioned above was even better in group 1 patients ($P = .02$, $P = .03$, $P = .04$, and $P = .04$, respectively). Multivariate analysis of the significant variables determined by univariate analysis identified albumin (relative risk [RR] = 1.05, $P = .02$) and everolimus (RR = 1.07, $P = .01$) as two independent factors of improving cardiovascular function.

Conclusions. Better amelioration of cardiovascular functions with everolimus may favor the choice of this drug in KTRs.

CARDIAC disorders are very common in individuals with chronic kidney disease and are associated with high morbidity and mortality rates. The HEMO study showed that 80% of all patients enrolled in the study were found to have some form of heart disease, with nearly 40% having ischemic heart disease. It has also been estimated that only 27% of patients about to enter a dialysis regimen have a normal echocardiogram, whereas 19% already have severe left ventricular hypertrophy. Long-term dialysis patients have severe cardiovascular problems. Kidney transplantation is known to be associated with regression of cardiovascular disease regarding mainly decreased uremic milieu and more stable hemodynamics. However, death caused by cardiac disorders even with a

*Address correspondence to Ulkem Cakir, Acibadem University, Acibadem International Hospital, Istanbul Cd 82 Yesilkoy, 34149 Istanbul, Turkey. E-mail: ulkem.cakir@internationalhospital.com.tr

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Table 1. Demographic and Clinical Features of Kidney Transplant Patients

Patient Data	Group 1 (n = 58)	Group 2 (n = 62)
Age (years)	39.6 ± 11.2	40.1 ± 10.2
Sex (male/female)	26/24	27/23
Preemptive	4/58 (6%)	5/62 (8%)
Dialysis duration (months)	37.5 ± 16.1	38.2 ± 18.4
Hemodialysis/peritoneal dialysis	52/2	54/3
Diabetes mellitus	15/58 (26%)	16/62 (26%)
Hypertension	36/58 (62%)	36/62 (58%)
Coronary artery disease	18/58 (31%)	19/62 (30%)
Congestive heart failure (NYHA class I–II)	34/58 (58%)	35/62 (56%)

Abbreviation: NYHA, New York Heart Association.

functioning graft is still an important issue in kidney transplant patients [1–3].

In this study, we aimed to evaluate the role of immunosuppressive drug regimens on cardiac functions of kidney transplant recipients (KTRs).

METHODS

Selection and Description of Participants

Since we started our transplant program in October 2010, a total of 850 end-stage renal disease patients underwent a successful kidney transplantation at Acibadem International Hospital, Istanbul, Turkey. All of the patients in our program were advised to have their cardiac evaluation at the end of the first year. In this prospective study, we included 120 patients with low immunological risk and transplanted from a living donor.

Immunosuppression

A triple immunosuppressive therapy including tacrolimus, mycophenoloic acid (MPA), and prednisolone was started for all KTRs. At the end of the 6th month, they were divided into two groups; in group 1 (n = 58) MPA was switched to everolimus, with target levels of 4 to 6 ng/mL, whereas in group 2 (n = 62), patients continued with MPA. The tacrolimus dose was lowered to achieve target serum levels of 5 to 8 ng/mL in both groups.

Cardiac Evaluation

Doppler echocardiography was performed before kidney transplantation, at the time of the immunosuppressive drug switch (6 months after transplant), and at the end of the first year for all KTRs. Cardiac parameters including ejection fraction (EF), left ventricular diastolic diameter (LVDD), posterior wall thickness (LVPW), left atrium (LA), pulmonary artery systolic pressure (PASP), and left ventricular hypertrophy (LVH) were evaluated, and the results were compared between the two groups.

Data Collection and Statistical Analysis

The demographical and clinical data were obtained from charts and records. The results were analyzed by use of the Statistical Package for the Social Sciences, version 22 (SPSS, Chicago, Ill, United States). Values displaying a normal distribution are expressed as mean ± standard deviation (SD). Differences between numeric variables were tested with the use of the independent-samples Student t test or Mann-Whitney U test, whichever was appropriate. Ratios for categorical variables were compared by use of χ^2 tests and Fisher tests. Comparison of the two paired groups was analyzed by use of Wilcoxon rank sum and McNemar tests. The relative risk of cardiovascular morbidity after transplantation for various risk factors including glomerular filtration rate (GFR), body mass index (BMI), levels of hemoglobin (Hb) and albumin, and use of everolimus were first analyzed by means of univariate analysis. Variables shown by univariate analysis to be significantly associated with EF were entered into a Cox proportional hazards regression model for multivariate analysis. A value was considered statistically significant at $P < .05$.

RESULTS

Data regarding KTR demographic and baseline clinical characteristics such as age (years), sex (male, female), dialysis duration (months) and modality (hemodialysis, peritoneal dialysis), diagnosis of diabetes mellitus, hypertension, coronary artery disease, and congestive heart failure are presented in Table 1.

No differences in age, sex, dialysis duration, or modality existed between the groups. The prevalence of diabetic or hypertensive nephropathy as the etiology of chronic kidney disease and co-existing cardiac disorders in each group was similar. The number of acute rejection episodes was not different in both groups, and no graft loss was observed in either group. Blood pressure was strictly controlled in both groups.

During the follow-up, ameloriation of hemoglobin and albumin levels was observed among all patients after transplantation, and hyperlipidemia was a concomittant finding at the end of the first year, even with higher levels in group 2 ($P = .02$) (Table 2).

Evaluation of the pre-transplant and post-transplant periods showed that improvement in cardiac parameters

Table 2. Clinical Features of Patients Before and After Transplantation

	Pre-transplant Period		Post-Transplant Month 12	
Parameters	Group 1 (n = 58)	Group 2 (n = 62)	Group 1 (n = 58)	Group 2 (n = 62)
GFR (mL/min)	<15	<15	64 ± 12	62 ± 11
BMI (kg/m^2)	20.4 ± 3.7	21.1 ± 3.1	23.3 ± 2.1	23.4 ± 1.1
Hb (g/dL)	9.7 ± 1.6	9.9 ± 0.6	11.4 ± 3.1	11.7 ± 3.3
Albumin (g/L)	3.1 ± 0.7	3.2 ± 0.4	3.6 ± 0.8	3.5 ± 0.7
Hyperlipidemia*	15/50 (30%)	14/50 (28%)	29/50 (58%)	18/50 (36%)
Hypertension	36/50 (72%)	34/50 (68%)	28/50 (56%)	31/50 (62%)

*$P = .02$.