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Echocardiographic Changes after Conversion from a Calcineurin Inhibitor to an Anti-Mammalian Target of Rapamycin Drug in Nondiabetic Kidney Transplant Recipients

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Abstract

The conversion from a calcineurin inhibitor to an anti-mammalian target of rapamycin drug in 30 nondiabetic kidney transplant recipients was associated with left ventricular hypertrophy reduction, independently of the blood pressure and the posttransplant time. **(Trends in Transplant. 2013;7:89-91)**

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Key words

Renal transplantation. Left ventricular hypertrophy. Anti-mTOR drug. Calcineurin inhibitor.

Introduction

Cardiovascular disease is the main cause of death after kidney transplantation[1] and left ventricular hypertrophy (LVH) is very prevalent in this population[2]. Morphological and functional changes inherent to LVH may contribute to the high degree of morbidity and mortality.

Multiple risk factors have been associated with the development of this entity, including the use of calcineurin inhibitors (CNI)[3]. Animal models, and more recently renal transplant patients[4], have shown that anti-mammalian target of rapamycin (anti-mTOR, sirolimus and everolimus) can lead LVH to regress. The aim of this study was to assess the morphological and functional changes in nondiabetic kidney transplant recipients who were converted from a CNI to an anti-mTOR drug in accordance with clinical practice.

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Material and methods

This prospective, longitudinal cohort study involved 30 nondiabetic kidney transplant patients. Inclusion criteria were: (i) clinical indication for conversion from a CNI (tacrolimus or cyclosporine) to an anti-mTOR drug (sirolimus or everolimus); (ii) stable renal function (serum creatinine < 2.5 mg/dl); (iii) 24-hour urinary protein excretion < 500 mg/day; (iv) informed written consent signed. Exclusion criteria were: (i) previous lung disease; (ii) previous cardiac disease; (iii) impaired renal function (serum creatinine > 2.6 mg/dl); and (iv) proteinuria > 500 mg/day.

Table 1. Echocardiographic parameters and Doppler echocardiographic measurements at baseline and 12 months after conversion

	Baseline	12 months	P value
LVESD (mm)	26.07 ± 5.59	26.13 ± 5.86	0.937
LVEDD (mm)	48.23 ± 5.47	48.23 ± 5.57	0.693
LAD (mm)	38.31 ± 5.56	37.55 ± 5.16	0.472
PWT (mm)	12.27 ± 2.23	11.33 ± 2.09	0.001
IVST (mm)	12.67 ± 2.43	12.03 ± 2.76	0.002
LVSF (%)	45.82 ± 8.57	45.89 ± 7.71	0.966
LVEF (%)	66.67 ± 5.52	64.33 ± 5.29	0.140
LVM (g)	242.34 ± 104.26	217.29 ± 93.34	0.004
LVMI (g/m^2)	61.96 ± 22.10	55.70 ± 20.08	0.003
Peak E cm/s	0.81 ± 0.22	0.91 ± 0.22	0.034
Peak A cm/s	0.92 ± 0.28	0.97 ± 0.21	0.359
E/A ratio	0.90 ± 0.30	0.98 ± 0.31	0.207
LVIRT (ms)	99.03 ± 23.60	104.40 ± 21.50	0.382

LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter; LAD: left atrial diameter; PWT: posterior wall thickness; IVST: interventricular septal thickness; LVSF: left ventricular shortening fraction; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; LVMI: left ventricular mass index; Peak E: peak early diastolic flow velocity; Peak A: peak late diastolic flow velocity; E/A ratio: ratio of early to late diastolic flow; LVIRT: left ventricular isovolumetric relaxation time.

All patients received renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers).

Echocardiographic technique

M-mode, two-dimensional color flow Doppler echocardiograms were performed by the same examiner at baseline and after 12 months.

Statistical analysis

Results of quantitative variables are expressed as mean ± standard deviations and qualitative variables as relative percentages. We used the T test and Fisher exact probability test for quantitative and qualitative variables, respectively. We examined the changes in left ventricular mass over time by adjusting a linear mixed effects model. A value of $p < 0.05$ was considered significant.

Results

The mean age was 58 ± 14 years and 70% were men. The main cause of chronic kidney disease was glomerular (30%). The mean posttransplant follow-up period was 77 ± 72 months. A total of 26 (86.7%) patients had previously received tacrolimus, whereas the rest received cyclosporine.

The main reasons for conversion were cancer (50%), chronic allograft nephropathy (23.3%), and CNI nephrotoxicity (10%). After switching, 19 (63.3%) patients received sirolimus. The other patients received everolimus to maintain blood levels between 4-7 ng/ml.

Significantly higher Hb1Ac (5.8 ± 0.7 vs. 6.2 ± 0.9; $p = 0.005$) and cholesterol (181 ± 30 vs. 202 ± 47; $p = 0.015$) levels were observed after conversion. In addition, a significantly decreased hemoglobin level (13.2 ± 1.5 vs. 12.2 ± 1.4; $p = 0.0001$) was also observed after switching. There were no significant changes

in other parameters such as systolic and diastolic blood pressure, serum creatinine, triglycerides, proteinuria, or body mass index.

Echocardiographic data are summarized in table 1. A significant decrease in the left ventricular mass index as well as an increased peak E was observed after 12 months. Consequently, the percentage of patients with LVH fell significantly (77 vs. 57%; p = 0.001) at the end of study.

Discussion

The main finding of this study was that anti-mTOR drugs lead LVH to regress in nondiabetic kidney transplant patients during the first 12 months of follow-up. This reduction was achieved mainly by reducing the ventricular wall thickness and intraventricular septum. In addition, regression of LVH was independent of blood pressure and the posttransplant time. Previous reports have documented similar results[5-9]. However, no patients previously received RAS blockers. The m-TOR inhibitors attenuate the angiotensin II-induced increase in protein synthesis by blocking phosphorylation of the S6 protein, which is involved in cardiac growth[10-13]. Therefore, our results suggest that, in nondiabetic renal transplant recipients, a more pronounced effect of m-TOR drugs on left ventricular mass might be expected in the presence of RAS blockers. The fact that the LVH reduction is accompanied by an improvement in passive ventricular filling, as evidenced by a higher peak E after 12 months, supports this view. Further longitudinal studies are needed to confirm these findings.

We conclude that conversion from a CNI to an anti-mTOR drug may contribute to changes in cardiac remodeling and distensibility, independently of the blood pressure and the posttransplant time.

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