mTOR Inhibition and Cardiovascular Diseases: Cardiac Hypertrophy

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Abbreviations:
LVH, left ventricular hypertrophy
mTOR, mammalian target of rapamycin
KTR, kidney transplant recipient
CNI, calcineurin inhibitors
LVMi, left ventricular mass index
SRL, sirolimus

CsA, cyclosporine

EVR, everolimus

RAAS, renin angiotensin aldosterone system

CV, cardiovascular
Abstract

Left ventricular hypertrophy (LVH) is highly prevalent in kidney transplant recipients, and is associated with poor clinical outcome. Immunosuppressive agents might affect LVH behavior after kidney transplantation. This review is an appraisal of available data regarding LVH in renal transplantation and especially of studies that evaluated LVH response to treatment. In particular, the role of mammalian target of rapamycin inhibitors adopted as immunosuppressive agents in kidney transplantation is reviewed in the light of recent studies that have shown LVH regression induced by this class of medications in kidney transplant recipients with posttransplant cardiomyopathy. Larger randomized controlled trials are warranted in order to confirm these findings and to ascertain the impact of such LVH regression on hard endpoints in kidney transplant recipients with posttransplant cardiomyopathy.
**Introduction**

Left ventricular hypertrophy (LVH) is frequent in patients who received a successful renal transplant, and is associated with reduced long-term survival (1). In most cases, LVH is present in dialysis patients on the waiting list, and persists even after successful transplantation. The pathogenesis of LVH of renal patients is multifactorial, with both hemodynamic and nonhemodynamic mechanisms involved in its development. In the last few years great interest has been shown in the cellular mechanisms of cardiac growth and especially in the mTOR signalling pathway, which plays a major role in modulating structural and functional adaptation of the heart to both hemodynamic stress and nonhemodynamic factors (2).

In animal models mTOR inhibitor (mTORi) rapamycin proved to be effective in reducing cardiac hypertrophic response to aortic constriction (2), and the same was observed in spontaneously hypertensive rats and in mice in whom cardiac hypertrophy was the effect of surgically induced renal injury, 2 closer models to what we observe in our clinical practice in renal disease (3, 4). Furthermore, mTOR inhibitors proved to be effective in avoiding smooth-muscle cell proliferation, which is a mechanism involved in allograft vasculopathy of cardiac transplanted patients (5 Eisen NEJM 2009). This improvement in vascular function could also play a major role in affecting LVH, whose development is strongly associated with increased vascular stiffness.

Taken together these findings support the hypothesis that mTOR inhibition could be effective in reversing LVH in humans, and raise concerns about whether mTOR inhibition could be adopted in clinical practice for cardioprotection.

**LVH regression by mTOR inhibitors**

Available studies on the role of mTOR inhibitors on the LVH of transplanted patients are summarised in Table 1.
The hypothesis that mTOR inhibitors might lead to LVH regression was first tested in kidney transplant recipients (KTRs) in whom mTOR inhibitors are approved for administration as immunosuppressive medications, by echocardiographically evaluating the behaviour of left ventricular mass index (LVMi) in thirteen patients with biopsy-proven chronic allograft dysfunction who underwent conversion from calcineurin inhibitors (CNI) to the mTORi sirolimus (SRL), and twenty-six who continued a CNI-based immunosuppressive protocol as controls. After 1 year, significant LVH regression independent of BP changes was only observed in patients converted to mTORi (6). Another study in cardiac transplant recipients who were converted from CNI to SRL, showed that LV mass significantly decreased in patients who were administered the mTORi, whereas no changes were observed in those continuing CNI (7). Interestingly, conversion from CNI to mTORi was associated with reduction of pulse wave velocity as an expression of improvement in arterial stiffness which is a well-known predictor of the risk of LVH and adverse CV outcome, especially in renal patients.

However, both were interventional nonrandomized studies, and patients enrolled were highly selected since they had renal dysfunction. Moreover, in both studies full conversion from a CNI- to an mTORi-based regimen was made, while in clinical practice a combined therapy consisting of mTORi plus reduced exposure CNI is a more widely adopted immunosuppressive protocol.

A randomized controlled trial was therefore carried out in an effort to evaluate the impact of everolimus (EVR) plus reduced exposure cyclosporine (CsA) as compared to standard dose CsA in reversing the LVH of de novo KTRs (8). At the end of the 1 year follow-up period, significant LVH regression was only observed in the arm assigned to EVR, as an effect of reduction in the thickness of both the interventricular septum and the posterior wall of the left ventricle, whereas no changes were observed in left ventricle internal size. BP changes were similar in both groups. Multiple regression analysis showed that increased baseline LVMi, ie, LVH, and being allocated to receive EVR were the only significant predictors of 1-year LVMi changes, according to a model that accounted for half of the total LVMi variance.
Interestingly, these results were challenged by a posthoc analysis of the CENTRAL Study, that showed no changes in LV mass and function after conversion of de novo KTRs from a CsA to an EVR based immunosuppressive regimen (9), and this lack of cardiac effect was confirmed in a 3 year extension (10). However, some limitations must be recognized in both trials. First of all the CENTRAL study was not planned to evaluate the cardiac effect of mTORi. Secondly, only 44 out of 202 patients evaluated in the main Trial were evaluated by echocardiography, thus raising concerns about the possibility of a selection bias. Thirdly, and more importantly, baseline LVM was nearly normal in enrolled patients, thus making it quite difficult to appreciate any EVR LVM-lowering effect in subjects who did not suffer from LVH. By contrast the LVM-lowering efficacy of mTOR inhibitors was further confirmed in a clinical study that evaluated 30 KTRs converted from a CNI- to an mTOR inhibitor-based immunosuppressive regimen who were also administered renin-angiotensin aldosterone system (RAAS) blockers and whose LV diastolic function also resulted improved at the end of the observation (11).

The cardiac effect of mTOR inhibitors was further assessed in a recent multicentre RCT that evaluated 24-month changes in LVMi of KTRs undergoing full conversion to EVR plus mycophenolic acid as compared to controls who continued a tacrolimus-based regimen (12). Even though LVMi similarly decreased in both groups after 24 months, however the proportion of KTRs who were administered RAAS blockers was greater in the tacrolimus group than in the EVR group, suggesting a hemodynamic mechanism in LVMi reduction in controls. Furthermore, disappearance of concentric LVH in the EVR group which emerged from the study is consistent with our findings of a reduction in left ventricular parietal thickening by EVR, and highlights the possibility of an anti-remodeling action of mTOR inhibitors probably related to their antifibrotic action which has been previously reported in animal studies (13).

Interestingly, LVH regression in KTRs was reportedly associated with improvement in both general and CV outcome according to a recent extension study of 2 previous RCTs – the first evaluating ACE inhibitors, the second EVR – aimed at ascertaining the clinical effect of active intervention in
reversing LVH in the renal transplant setting (14). This finding suggests that immunosuppressive therapy adopting mTOR inhibitors could play a major role in ameliorating CV outcome of KTRs also by regression of cardiac hypertrophy, even though the impact of CNI minimization in reversing LVH cannot be ruled out.

**Conclusion**

mTOR inhibitors seem to be effective in regressing the LVH of KTRs. This result is independent of BP lowering, and is mainly accounted for by a reduction of LV parietal thickness, which seems to be the result of the anti-proliferative effect of mTOR inhibitors. Moreover, LVH regression is associated with improvement in vascular stiffness, which is one of the mechanisms involved in LVH development, and with amelioration of diastolic function, which early worsens in subjects with proven LVH. Larger randomized controlled trials are warranted in order to confirm these findings, as well as to assess whether mTOR inhibitors *per se* or CNI minimization or avoidance play a major role in regressing LVH, and to ascertain the impact of such LVH regression on the clinical outcome of KTRs with posttransplant cardiomyopathy.
References


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three year serial echocardiographic substudy of the randomized controlled CENTRAL trial. 

*Clin Transplant* 2015; 29: 678-684


Table 1. Studies that evaluated the effects of mTOR inhibitors on the behaviour of LVH in transplanted patients

<table>
<thead>
<tr>
<th>Author, year, ref</th>
<th>Study, sample size</th>
<th>Setting, f-up</th>
<th>LVMi at baseline</th>
<th>LVMi change (P)</th>
<th>mTORi vs controls, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paoletti, 2008 (6)</td>
<td>Longitudinal, controlled 39 KTRs</td>
<td>13 KTRs on SRL vs 26 on CNI, 1 year</td>
<td>54.5 g/m² in SRL; 52.1 g/m² in CNI</td>
<td>-8.5 g/m² in SRL (P=0.002) vs +0.2 (ns) in CNI</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reichlin, 2008 (7)</td>
<td>Longitudinal, controlled 70 HTRs</td>
<td>70 HTRs undergoing full conversion from CNI to SRL, 1 year</td>
<td>98.9 g/m² in SRL; 94.2 g/m² in CNI</td>
<td>-4.9 g/m² (P=0.05) in SRL vs +4.7 g/m² (P=0.03) in CNI</td>
<td>0.011</td>
</tr>
<tr>
<td>Paoletti, 2012 (8)</td>
<td>RCT, 30 KTRs</td>
<td>10 KTRs on EVR plus reduced CsA vs 20 on standard CsA (controls), 1 year</td>
<td>54.7 g/m² in EVR; 55.2 g/m² in controls</td>
<td>-8.9 g/m² (P=0.0016) in EVR vs +0.2 (ns) in CNI</td>
<td>0.005</td>
</tr>
<tr>
<td>Muerbrach, 2014 (9)</td>
<td>RCT, 63 KTRs</td>
<td>17 on EVR vs 27 on CsA, 1 year</td>
<td>115 g/m² in CsA; 115 g/m² in EVR</td>
<td>-4 g/m² (ns) in EVR vs -3 g/m² (ns) in CsA</td>
<td>0.98</td>
</tr>
<tr>
<td>Muerbrach, 2015 (10)</td>
<td>RCT, 34 KTRs</td>
<td>17 on EVR vs 27 on CsA, 3 years</td>
<td>115 g/m² in CsA; 115 g/m² in EVR</td>
<td>-12 g/m² (ns) in EVR vs -11 g/m² (ns) in CsA</td>
<td>0.7</td>
</tr>
<tr>
<td>Hernandez, 2014 (11)</td>
<td>Longitudinal, controlled 88 KTRs</td>
<td>30 on mTORi (19 on SRL; 11 on EVR) vs 58 controls on CNI, 1 year</td>
<td>62 g/m² in mTORi; 65 g/m² in CNI</td>
<td>-8.4 g/m² (P=0.003) in mTORi vs -3.8 (P=0.052) in CNI</td>
<td>0.25</td>
</tr>
<tr>
<td>Cruzado, 2016 (12)</td>
<td>RCT, 60 KTRs</td>
<td>32 KTRs on TAC vs 28 KTRs on EVR, 2 years</td>
<td>54 g/m² in TAC vs 53.4 g/m² in EVR</td>
<td>-5.8 g/m² (ns) in TAC vs -4 g/m² (ns) in EVR</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations: KTRs, kidney transplant recipients; SRL, sirolimus; CNI, calcineurin inhibitors; LVMi, left ventricular mass index; HTRs, heart transplant recipients; CsA, cyclosporine; TAC, tacrolimus