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## Lower Homocysteine Levels in Renal Transplant Recipients Treated With Everolimus: A Possible Link With A Decreased Cardiovascular Risk?

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### ABSTRACT

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in renal transplant recipients. The incidence of CVD in this setting is approximately 5-fold greater than in age- and gender-matched subjects. This excess cardiovascular risk is not completely explained by traditional cardiac risk factors. It has been well documented that these patients show greatly increased prevalence of both fasting and postmethionine-loading hyperhomocysteinemia (hHcy) compared with the general population. An immunosuppressive therapy based on everolimus has been demonstrated to reduce the incidence major adverse coronary events at 4 years compared with azathioprine among heart transplant recipients. In contrast, scarce data are available on the impact of everolimus on emerging risk factors, such as homocysteine (Hcy), in renal transplant recipients. The aim of this study was to evaluate the possible impact of everolimus compared with other immunosuppressive regimes among 132 stable recipients, including 91 men and 41 women who were at least 1 year after transplant with stable renal function and no clinical evidence of acute or chronic renal graft rejections. We compared 31 subjects on everolimus immunosuppressive therapy (group A) versus 101 on immunosuppressive therapy based on cyclosporine, steroids, and mycophenolate. The Hcy levels were significantly lower among group A patients compared with group B:  $16.5 \pm 5 \mu\text{mol/L}$  vs  $21.2 \pm 11 \mu\text{mol/L}$ ;  $P < .005$ . Hyper-Hcy, defined as Hcy levels  $>15 \mu\text{mol/L}$ , was diagnosed in 18 out of 31 patients (51%) of group A and in 82 out of 101 patients (81%) of group B. This preliminary study demonstrates a favorable impact of everolimus on a marker of atherothrombosis which is associated with a worse vascular prognosis.

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in renal transplant recipients (RTRs).<sup>1</sup> Indeed, the incidence of CVD in RTRs is approximately 5-fold greater than in age- and gender-matched subjects. This excess cardiovascular risk is not completely explained by the number of traditional cardiac risk factors to which RTRs are exposed. The greatly increased prevalence of both fasting and postmethionine loading hyperhomocysteinemia (hHcy) in RTRs compared with the general population has been well documented.<sup>2-4</sup> An immunosuppressive therapy based on everolimus has been demonstrated to reduce the incidence of 4-year major adverse coronary events compared with azathioprine in heart transplantation.<sup>5</sup> On the other hand, no data are available on the impact of everolimus on emerging risk

factors, such as Hcy, in RTRs. The aim of the present study was to evaluate the possible impact of everolimus compared with other immunosuppressive regimes on Hcy levels.

### PATIENTS AND METHODS

We investigated 229 stable RTRs (150 male, 79 female) at least 1 year after transplant with stable renal function and no clinical evidence of acute or chronic renal graft rejection episodes. Thirty-nine RTRs were on immunosuppressive therapy based on everoli-

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mus (group A), and 190 were on immunosuppressive therapy based on triple therapy (cyclosporine, steroids, micophenolate; group B).

Statistical analysis was performed by means of the SPSS package. Data are reported as mean  $\pm$  SD. The comparison between different groups was performed by a Mann-Whitney *U* test. All probability values were 2 tailed, with values of  $<.05$  considered to be statistically significant.

## RESULTS

No significant differences were documented between the 2 groups in the dialysis age, graft duration, or creatinine levels. Hcy levels were significantly lower in patients of group A compared with group B:  $16.5 \pm 5 \mu\text{mol/L}$  vs  $21.2 \pm 11 \mu\text{mol/L}$ ;  $P < .005$ . Hyper-Hcy, defined as hHcy levels  $>15 \mu\text{mol/L}$ , was diagnosed in 23 out of 39 patients (58.9%) of group A and in 144 out of 190 patients (75.8%) of group B. No significant differences were found in vitamin B6 levels:  $5.0 \pm 3.5 \mu\text{gram/L}$  vs  $4.4 \pm 3.4 \mu\text{gram/L}$ .

## DISCUSSION

Several studies have found increased levels of Hcy both in patients with end-stage renal disease and in RTRs with a recovered renal function.<sup>2-4</sup> We previously demonstrated, in the same clinical setting of the present study, that vitamin supplementation reduces the carotid artery intima-media thickness in renal transplant recipients with hHcy.<sup>6</sup> In the present paper, we confirmed the high prevalence of mild hHcy in RTRs. Notably, this preliminary study demonstrates a favorable impact of everolimus on this marker of atherothrombosis which is associated with a worse vascular prognosis. The proliferation-signal inhibitor (PSI)/mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus have shown considerable promise in reducing acute rejection episodes in renal transplant recipients. Although PSIs are associated with an increase in hyperlipidemia, which is a major risk factor for atherosclerosis and associated cardiovascular disease, recent studies with sirolimus have demonstrated protection from atheroma progression in hyperlipidemic apolipoprotein E-deficient mice. Sirolimus and everolimus inhibit the mTOR signaling pathway, inducing inhibition of gene transcription, reduced cell growth and proliferation, reduced vascular endothelial

growth factor production. In the endothelial cell, the effect of PSIs is reduced cell growth and proliferation. Furthermore, there may also be alterations in endothelial nitric oxide synthase expression, changes in the ratio of matrix metalloproteinases (MMP) to tissue inhibitors of metalloproteinases, MMP-2 and MMP-9 activation, reduced expression of the positive cell-cycle regulator cyclin-dependent kinase 2, proliferating-cell nuclear antigen, and proinflammatory cytokines, and diminished expression of monocyte chemoattractant protein 1, which is associated with the attenuation of monocyte chemotaxis and reduced neointimal macrophage counts in sirolimus-fed mice.

The potential protective role of mTOR inhibitors, particularly everolimus, in the processes that lead to atherosclerosis and cardiovascular events seems to be confirmed by the results of this preliminary study. Hcy levels, which represent an independent risk factor for cardiovascular disease, are significantly reduced in renal transplant patients treated with everolimus compared with patients treated with other immunosuppressive regimens. Larger prospective studies are needed to clarify the impact that the use of everolimus may have on methionine metabolism and on morbidity and mortality from cardiovascular causes in RTRs.

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