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LETTER TO THE EDITOR

# Decrease in sirolimus-induced proteinuria after switch to everolimus in a liver transplant recipient with diabetic nephropathy

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Mammalian Target of rapamycine (mTOR) inhibitors are effective in preventing acute rejection in renal as also cardiac transplantations, causing less nephrotoxicity than calcineurin inhibitors (CNI) and benefit in prevention of post-transplant malignancies [1,2]. However, proteinuria and worsening of renal function have been reported after switchover from CNI to sirolimus in renal transplantation [3]. There are few data on renal function evaluation with everolimus. We report a case of decrease in proteinuria after switching over from sirolimus to everolimus in a liver transplant recipient with diabetic nephropathy.

A 63-year-old male with type 2 diabetes underwent a liver transplantation (LT) for alcoholic cirrhosis in 1996. Immunosuppressive treatment combined initially tacrolimus and corticosteroids. Steroids were stopped 3 years post-LT. Because of diabetes, proteinuria was monitored annually. Until December 2005, there was a mild renal dysfunction and microalbuminuria (Fig. 1).

In 2000, a spinocellular carcinoma of the scalp in this patient was treated by surgical resection. Spinocellular carcinoma recurrences were then observed, requiring surgical treatments, external radiotherapy and autologous cutaneous graft. Sirolimus was introduced in June 2006 and tacrolimus was stopped. At sirolimus initiation, creatininemia was 127 $\mu$mol/l, Cockcroft-Gault-calculated creatininemia clearance 51 ml/min/1.73 m$^2$, and microalbuminuria 0.15 g/day. Liver function, hepatic and renal echographies were normal. In February 2007, edema of the face and of the legs appeared. Laboratory data showed anemia, proteinuria over 3 g/day without hypoprotidemia [62 g/l (normal values 60–75 g/l)] or hypoalbuminemia [36 g/l (normal values 32–52 g/l)], and mild increase of creatininemia to 150 $\mu$mol/l. Sirolimus trough levels were between 3.8 and 8 ng/ml. Sirolimus dosage was then decreased. The other treatments consisted of insulin, pravastatin, allopurinol, nicardipine and candesartan cilexetil, unchanged for more than 1 year. One month later, edema disappeared without biologic improvement. A renal biopsy was performed, revealing diabetic nephropathy without sign of sirolimus toxicity. However, sirolimus

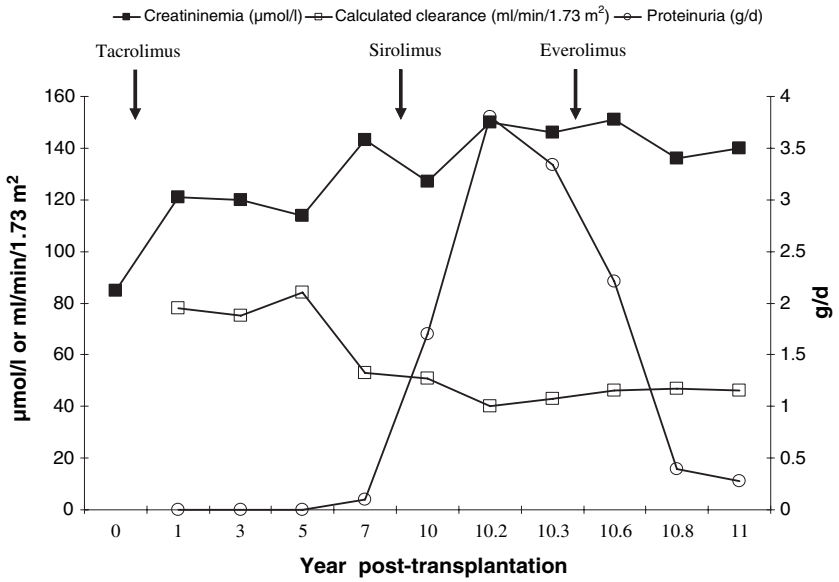


**Figure 1** Evaluation of creatininemia and proteinuria before and after everolimus introduction.

was stopped and there was switchover to everolimus administration in June 2007. Six months later, clinical examination was normal. Renal function was stable and proteinuria decreased to 0.39 and 0.28 g/day. Everolimus trough levels were 3.4–11 ng/ml. Liver function remained normal and no spinocellular carcinoma recurrence was observed.

Sirolimus-induced proteinuria is a well-known adverse event. In recipients with chronic renal allograft dysfunction treated by sirolimus, increase of proteinuria has been reported in 25–50% of the renal allograft recipients [4–6]. In cardiac transplantation, the incidence was 15%, mainly in cardiac recipients with the previous altered renal function or diabetic nephropathy [7]. However, it seems uncommon in liver transplant recipients [8]. Proteinuria over 300 mg/day has also been described in 39% of renal transplants treated with everolimus [9]. Currently, there was no data on the capacity of everolimus to induce proteinuria in heart or liver transplant recipients [10,11]. mTOR inhibitors could be less nephrotoxic for native kidney than for renal allograft. Moreover, despite common mechanisms of action, everolimus and sirolimus have different molecular structure and pharmacologic properties and could have also different side-effects. We report a case of rapid decrease of proteinuria after switching from sirolimus to everolimus in a liver transplant recipient; others have described a favorable outcome of interstitial pneumonia after switching from sirolimus to everolimus [12]. To sum up, some patients may benefit from a switching over to mTOR inhibitor, and some sirolimus-side effects could be improved by switching over to everolimus. Further studies are necessary to confirm this observation.

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## References

1. Kreis H, Oberbauer R, Campistol JM, *et al.* Rapamune maintenance regimen trial. Long-term benefits with sirolimus-based therapy after early cyclosporine withdrawal. *J Am Soc Nephrol* 2004; **15**: 809.
2. Raichlin E, Khalpey Z, Kremers W, *et al.* Replacement of calcineurin-inhibitors with sirolimus as primary immunosuppression in stable cardiac transplant recipients. *Transplantation* 2007; **84**: 467.
3. Saurina A, Campistol JM, Piera C, *et al.* Conversion from calcineurin inhibitors to sirolimus in chronic allograft dysfunction: changes in glomerular haemodynamics and proteinuria. *Nephrol Dial Transplant* 2006; **21**: 488.
4. Letavernier E, Bruneval P, Mandet C, *et al.* High sirolimus levels may induce focal segmental glomerulosclerosis de novo. *Clin J Am Soc Nephrol* 2007; **2**: 326.
5. Ruiz JC, Campistol JM, Sanchez-Fructuoso A, *et al.* Increase of proteinuria after conversion from calcineurin inhibitor to sirolimus-based treatment in kidney transplant patients with chronic allograft dysfunction. *Neprol Dial Transplant* 2006; **21**: 3252.
6. Letavernier E, Pe'raldi MN, Pariente A, Morelon E, Legendre C. Proteinuria following a switch from calcineurin inhibitors to sirolimus. *Transplantation* 2005; **80**: 1198.
7. Aliabadi AZ, Pohanka E, Seebacher G, *et al.* Development of proteinuria after switch to sirolimus-based immunosuppression in long-term cardiac transplant patients. *Am J Transplant* 2008; **8**: 1.
8. Dervaux T, Caillard S, Meyer B, *et al.* Is sirolimus responsible for proteinuria? *Transplant Proc* 2005; **37**: 2828.
9. Lorber MI, Mulgaonkar S, Butt KM, *et al.* Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation* 2005; **80**: 244.
10. Zuckermann A, Manito N, Epailly E, *et al.* Multidisciplinary insights on clinical guidance for the use of proliferation signal inhibitors in heart transplantation. *J Heart Lung Transplant* 2008; **27**: 141.
11. Levy G, Schmidli H, Punch J, *et al.* Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; **12**: 1640.
12. De Simone P, Petruccelli S, Precisi A, *et al.* Switch to everolimus for sirolimus-induced pneumonitis in a liver transplant recipient-not all proliferation signal inhibitors are the same: a case report. *Transplant Proc* 2007; **39**: 3500.

 