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# Conversion From Calcineurin Inhibitors to Everolimus With Low-Dose Cyclosporine in Renal Transplant Recipients With Squamous Cell Carcinoma of the Skin

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## ABSTRACT

Squamous cell carcinoma of the skin (SCC) is the most frequent cancer in renal transplant recipients. Conversion to mammalian target of rapamycin inhibitors after diagnosis of SCC may reduce the incidence of recurrence of skin cancer. This retrospective study evaluated the outcome of renal transplant recipients followed by the Renal Unit with posttransplant diagnosis of SCC treated with conversion from calcineurin inhibitors (CNIs) to Everolimus (EVR) associated with low-dose cyclosporine. Eleven patients developed SCC at a median time from renal transplantation of 107 months (range 36–264). Five patients with creatinine clearance (CCI) below 40 mL/min before conversion developed end stage renal disease (two cases) or further deterioration of renal function (two cases); only one patient in this group maintained a stable renal function. The remaining six patients with a CCI greater than 40 mL/min and proteinuria below 0.8 g/24 hours maintained a stable renal function after conversion to EVR at a median follow-up of 22 months (range 15–75). Conversion from CNIs to EVR has been proven safe, effective, and associated with low recurrence of SCC in patients with a CCI >40 mL/min. In the case of preexisting deterioration of renal function or significant proteinuria, conversion to EVR should be carefully evaluated.

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**T**HE INCIDENCE OF nonmelanoma skin cancers (NMSC) increases with time after transplantation and varies from 5% to 60% among different geographic areas and according to the time after transplantation. Mammalian target of rapamycin (m-TOR) signaling has an important role in development of cancer and is a critical pathway for several growth factors.<sup>1</sup> Many clinical trials demonstrated that m-TOR inhibitors (m-TORi) have been associated with a reduced incidence of SCC particularly in patients converted from a calcineurin inhibitors (CNI) immunosuppressive regimen.

## METHODS

We performed a retrospective study of patients who underwent renal transplantation from 1995 to 2009 and who developed a squamous cell carcinoma of the skin (SCC) in the posttransplant period treated with conversion of the immunosuppressive regimen to m-TORi with low dose of cyclosporine (CYA). The admission history, medications administered, and laboratory data were reviewed from the medical records. Patients were stratified in two

groups (Table 1) according to renal function and proteinuria at the time of conversion to Everolimus (EVR).

## RESULTS

Eleven patients developed SCC at a median time from renal transplantation of 107 months (range 36–264). There were 10 males and one female patient; the overall median age at diagnosis of SCC was 60 years (range 51–70). The histological diagnosis of SCC was performed after surgical excision of the lesions. The immunosuppressive regimen at diagnosis was CYA, mycophenolate mofetil (MMF), and corticosteroids in all cases. In all patients, conversion to EVR associated with low-dose CYA was performed after

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**Table 1. Number of Patients With Any Squamous Cell Carcinoma Stratified for Renal Function and Proteinuria at the Time of Conversion to Everolimus**

	Group A	Group B
Number of patients	6	5
GFR (mL/min)	>40	<40
Proteinuria (g/24 h)	<0.8	>0.4 <3.5
Median follow-up after conversion to everolimus (mo)	23 (range 15–75)	10 (range 2–26)
SCC recurrence after conversion to Everolimus	2	0

GFR, glomerular filtration rate; SCC, squamous cell carcinoma of the skin.

minimization or withdrawal of MMF. Median follow-up after conversion to EVR was 22 months (range 2–75). Six patients at the time of conversion had a creatinine clearance greater than 40 mL/min and proteinuria below 0.8 g/24 hours (group A). Five of these maintained a stable renal function and proteinuria after conversion to EVR at a median follow-up of 23 months (range 15–75). Only one patient in this group presented a deterioration of renal function due to acute kidney injury. Five patients at the time of conversion to EVR had a creatinine clearance below 40 mL/min and a proteinuria ranging from 0.4 to 3.5 g/24 hours (group B). Three developed end stage renal disease due to chronic allograft nephropathy at a median follow-up of 10 months (range 2–26) after conversion; one of them also developed a significant increase of proteinuria from baseline. Only two cases of recurrence of SCC was observed in group A, and no recurrence was observed in group B.

## DISCUSSION

Use of m-TOR<sub>i</sub> in renal transplant recipients who develop SCC allows reduction or elimination of CNI-based immunosuppression. This study confirms that conversion to EVR with minimization of CYA in patients with creatinine clearance greater than 40 mL/min and low-grade proteinuria (<0.8 g/24 hours) is safe and effective and is associated with low recurrence of SCC (only two cases of recurrence in a cohort of patients with recognized aggressive SCC). In fact this cohort of patients benefits from the antiproliferative and antiangiogenic actions of m-TOR<sub>i</sub> with low risk of deterioration of renal function as demonstrated in other observational studies.<sup>2</sup> Conversely, conversion to EVR in patients with glomerular filtration ratio below 40 mL/min or high-grade proteinuria may lead to further deterioration of renal function. In such patients, the risk-benefit profile of conversion to EVR should be carefully evaluated on a case-by-case basis. A recent study demonstrated that a particular immune phenotype characterized by greater than 35 peripheral FOXP3 regulatory T cells/ $\mu$ L is significantly associated with increased risk for new SCC development.<sup>3</sup> This could be a new useful parameter to decide which patients submit to conversion to EVR-based immunosuppressive treatment.

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