

Inhibitors of the mammalian target of rapamycin in kidney transplantation: impact of conversion on allograft and patient survival

Inibidores da mTOR em transplantação renal: impacto da conversão na sobrevida do enxerto e do doente

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ABSTRACT

Background: Inhibitors of the mammalian target of rapamycin (mTOR) have demonstrated a similar outcome on allograft loss but its impact on patient survival has only recently been evaluated. In this outcome analysis all renal transplants performed at our unit since 1/1/2006 until 12/31/2011, were evaluated. Allograft failure and mortality were compared between patients who were converted to mTOR and those who remained on a calcineurin inhibitor (CNI). **Population and Methods:** We have evaluated 425 patients (mean age 46±13 years, 60.7% male, 10.1% diabetics, mean follow-up of 44 months). During this period, 123 patients were converted to mTOR: 8 included in a protocol study, 13 due to malignancy and 102 to evidence of chronic allograft dysfunction. The remaining patients were maintained on a CNI-based regimen. We compared patient and graft survival by Kaplan-Meier analysis and $p < 0.05$ was considered significant. **Results:** During the follow-up time, 10 patients died and 28 lost their graft. Baseline characteristics were similar, except for age (converted patients were older, $p = 0.012$), gender (higher male percentage in mTOR group, $p = 0.04$) and race (Caucasians were more prevalent in mTOR arm, $p = 0.012$). There was no difference between the 2 groups on either graft or patient survival, even after adjustment for age, gender, and presence of diabetes *mellitus* or immunological risk. Moreover, in the subgroup of patients with low immunological risk, the use of mTOR was associated with a trend towards improved renal allograft survival, although not statistically significant ($p = 0.06$). **Conclusion:** Despite worse prognosis conferred by the major indications for conversion to mTOR inhibitors (malignancy or chronic allograft dysfunction) and older age, we found no difference on allograft or patient survival between the 2 groups (mTOR versus CNI-based regimen). In patients with low immunological risk, mTOR group showed a trend towards better allograft survival.

Key words: Allograft failure, calcineurin inhibitor, inhibitors of the mammalian target of rapamycin, mortality.

■ RESUMO

Introdução: Os mTOR mostraram-se eficazes na imunossupressão de manutenção em relação à sobrevida do enxerto, mas o seu impacto na sobrevida do doente só recentemente foi avaliado. Neste estudo analisámos todos os doentes transplantados renais na nossa unidade desde 2006/01/01 até 2011/12/31 no que respeita à falência do enxerto e à mortalidade comparando os doentes que foram convertidos para mTOR com os que permaneceram sob inibidor da calcineurina (CNI). **População e métodos:** Foram avaliados 425 doentes (idade média de 46 ± 13 anos, 60,7% do sexo masculino, 10,1%, diabéticos com tempo médio de seguimento de 44 meses). Durante este período, 123 doentes foram convertidos para mTOR: 8, incluídos no protocolo de um estudo, 13 por neoplasia e 102 por evidência de disfunção crônica do enxerto. Os restantes doentes foram mantidos sob CNI. A sobrevida do enxerto e do doentes foram comparados por Kaplan-Meier e $p < 0,05$ foi considerado significativo. **Resultados:** Durante o tempo de seguimento, 10 doentes morreram e 28 perderam o enxerto. As características basais foram semelhantes para ambos os grupos, com excepção da idade (os doentes convertidos eram mais velhos, $p = 0,012$), sexo (masculino mais frequente no grupo mTOR grupo, $p = 0,04$) e raça (os caucasianos foram mais prevalentes no grupo mTOR, $p = 0,012$). Não houve diferença entre os dois grupos na sobrevida do enxerto ou do paciente, mesmo após ajuste para idade, sexo, presença de diabetes mellitus ou risco imunológico. Além disso, no subgrupo de doentes com baixo risco imunológico, o uso de mTOR foi associado a uma tendência para a melhoria da sobrevivência dos enxertos renais, embora não estatisticamente significativa ($p = 0,06$). **Conclusão:** Apesar do pior prognóstico conferido pelas principais indicações para a conversão de inibidores de mTOR (neoplasia ou disfunção crônica do enxerto) e da idade avançada, não foi encontrada diferença na sobrevida do enxerto ou do doente entre os dois grupos. Em doentes com baixo risco imunológico, o grupo mTOR mostrou uma tendência para melhor sobrevida do enxerto.

Palavras chave: Falência do enxerto, inibidor da calcineurina, inibidor da mTOR, mortalidade.

■ INTRODUCTION

Inhibitors of the mammalian target of rapamycin (mTOR) have emerged from the need to develop less nephrotoxic regimens for immunosuppression in kidney transplantation with the objective to promote long-term graft function.

Mammalian target of rapamycin has been identified as the principal controller of cell growth and proliferation. Sirolimus or everolimus bind the immunophilin FKBP12 and form a complex that inhibits mTOR-mediated signal transduction pathways by blocking post-receptor immune responses to costimulatory signal 2 during G_0 to G_1 transition and to cytokine signalling during G_1 progression. They also inhibit IL-2- and IL-4-dependent proliferation of T and B cells, leading to suppression of new ribosomal protein synthesis and arrest of the G_1 -S phase of the cell cycle. These anti-proliferative effects lead to their beneficial use in malignancies, but have also

been associated to adverse effects like impaired wound healing, anaemia and proteinuria¹ (by impaired podocyte integrity).

The early studies that have been conducted to test efficacy of mTOR inhibitors in kidney transplantation have demonstrated a lower serum creatinine and a higher estimated glomerular filtration rate² compared with a calcineurin inhibitor (CNI)-based regimen, but have also found higher rates of biopsy-proven rejection, although this was not reflected by a worse allograft survival³ in short follow-up periods lesser than 2 years.

Cortazar *et al.* presented the first trial where the risk of mortality and allograft loss is studied. They found worse outcomes in patients who were converted to mTOR inhibitors from CNI-based regimens⁴.

The aim of this study was to evaluate in our kidney transplant population, the mid- to longterm impact of mTOR inhibitors on allograft and patient survival.

POPULATION AND METHODS

Study population

We have performed a retrospective study where we have analyzed all patients who underwent kidney transplantation, since January 1st 2006 until December 31st 2011, in our centre. We have collected information from the clinical records. Patients with incomplete information were excluded. The final sample included in 425 patients.

The following clinical data were collected: age, gender, race, aetiology of kidney failure, renal replacement therapy, modality before transplantation, donor type (living, deceased), presence of diabetes *mellitus*, occurrence of malignancy and recipient's immunological risk. High immunological risk was defined as a panel reactive antibody (PRA) > 60%, more than one kidney transplant or no HLA compatibility.

Induction therapy was performed on the basis of the Unit protocol, depending on the immunological risk. Low risk patients were given the interleukin-2 receptor inhibitor basiliximab and the remaining received thymoglobulin.

Standard maintenance immunosuppressive regimens at enrolment included low-dose prednisone plus cyclosporine A or tacrolimus, and mycophenolate-mofetil (MMF) or azathioprine.

Our practice was to convert kidney transplant recipients to mTOR inhibitors without performing an allograft biopsy if there was clinical evidence of CNJ toxicity or a history of malignancy.

Laboratory data collected included serum creatinine and 24-hour proteinuria measured at baseline and then in a biannual basis.

Conversion to mTOR inhibitors and Outcomes.

We divided patients in two groups: patients who were converted to mTOR inhibitors (either sirolimus or everolimus) and patients who remained in a CNI-based regimen (either cyclosporine or tacrolimus). Immunosuppressant levels were tested in every outpatient visit and doses were prescribed to reach low Co levels (sirolimus: 5-8ng/

ml, everolimus: 5-8ng/ml, tacrolimus: 5-8ng/ml, cyclosporine: 80-150 ng/ml).

We defined as primary outcomes all-cause mortality and allograft failure, defined as the need to return to dialysis. Secondary outcomes were the evolution of serum creatinine and proteinuria in each group.

Statistical analysis.

We compared baseline characteristics among users versus nonusers of mTOR inhibitors using two-sample t-tests, Wilcoxon rank-sum test, or χ^2 test, as appropriate. Survival analysis was performed with Kaplan-Meier analysis and multivariable adjusted analysis was performed using a Cox regression model. A $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics.

There were 425 patients enrolled in this study with a mean age of 46±13 years, 60.7% were male and 10.1% were diabetics. Twenty-four patients were excluded because of incomplete information. Seventy-eight (18.4%) patients were considered to have a high immunological risk. These patients received thymoglobulin as induction therapy. Table I shows the baseline characteristics of the studied population.

During a mean follow-up time of 44±21 months, 123 patients were converted to an mTOR inhibitor: eight included in a clinical trial, 13 with a history of malignancy and 102 because of chronic allograft

Table I

Baseline characteristics

	mTORi	CNI	p
Mean age (years)	48.5 ± 13.1	45.0 ± 13.1	0.012
Male gender (%)	68.3	57.6	0.04
Afro-portuguese (%)	9.8	19.8	0.012
Previous therapy	HD: 85.4% PD: 8.4% Pre-emp: 5.7%	HD: 83.8% PD: 12.6% Pre-emp: 3.6%	NS
Diabetes <i>mellitus</i> (%)	7.3	11.3	NS
High immunologic risk (%)	13.8	20.2	NS

dysfunction, mainly defined in the clinical setting as a progressive and slowly growing serum creatinine. Patients were converted in a median period of 10 (1-67) months after transplantation.

Most patients were on a sirolimus based regimen (86 pts, 70%) and the remaining were on everolimus (34 pts, 30%).

■ **Outcomes.**

During the follow-up period, 10 patients died (table II) and 28 lost their allografts (table III). There was no statistical difference in the primary outcomes, defined as graft loss or patient’s mortality, in the two groups as stated in figure 1.

By Cox proportional hazards model, after adjustment for baseline characteristics (age, gender, race and diabetes), there was also no difference on patient and allograft survival.

In a subgroup analysis, a trend towards a better outcome on allograft survival was seen within the 106 low immunological risk patients that were converted to mTOR inhibitor, although not statistically significant ($p = 0.06$), as shown in figure 2.

In secondary outcomes, we have observed that renal function, expressed by serum creatinine, was significantly worse in mTOR inhibitor group at the

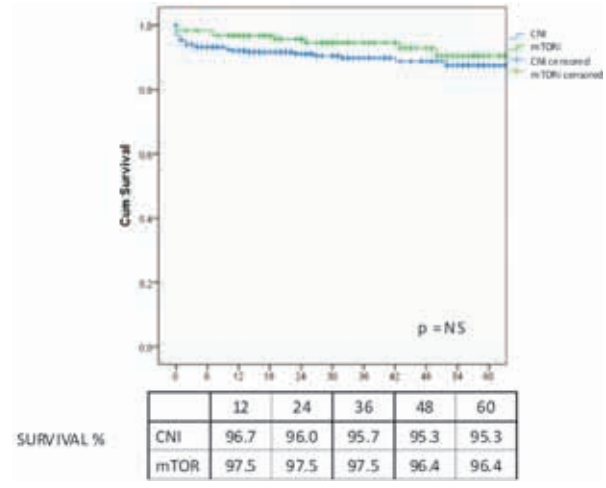


Figure 1
Survival rates comparing the two groups CNI and mTOR.

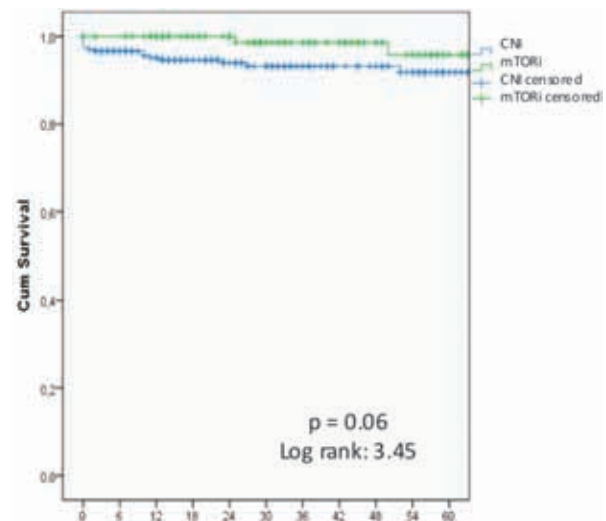


Figure 2
Survival rates comparing the two groups CNI and mTOR in low immunologic risk patients.

Table II

Causes of death in the two groups

	mTORi	CNI
Malignancy	2	0
Infection	1	3
Cardiovascular disease	1	3

Table III

Causes of allograft loss in the two groups

	mTORi	CNI
Primary allograft dysfunction	1	4
Acute rejection	1	8
Chronic rejection	2	7
Infection	1	2
Urological problem	0	2

time of the conversion and, not surprisingly, serum creatinine remained stable but higher in this group of patients (figure 3). Proteinuria, at baseline was slightly, but not significantly, lower in the group of patients converted to mTOR, and as expected, there was a significant increase after conversion. In opposition, proteinuria remained stable in the CNI group

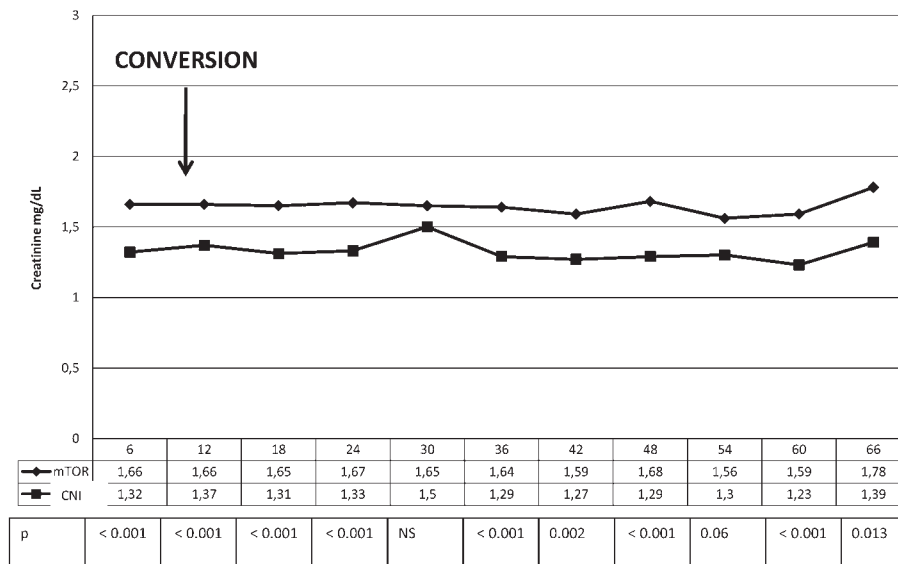


Figure 3
Creatinine evolution between the two groups CNI and mTOR.

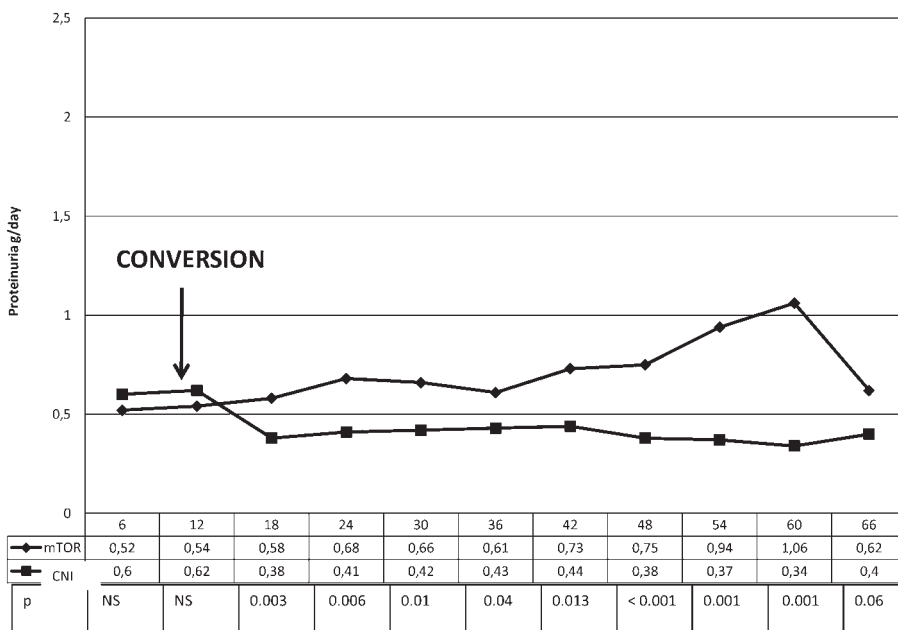


Figure 4
Proteinuria evolution between the two groups CNI and mTOR.

(figure 4). Because of increasing nephrotic range proteinuria, oedema or severe dyslipidaemia, 18 patients have been reconverted to CNI.

■ DISCUSSION

In our historical cohort study with up to 6 years of longitudinal follow-up, we have found no difference on patient or allograft survival, despite the mTOR inhibitor group patients having presented worse prognostic factors, such as older age or indications for mTOR conversion (malignancy or chronic allograft dysfunction).

This is consistent with the results of other large cohort studies, which found no difference in patients who were converted from a CNI to a mTOR inhibitor. In 2006, Webster *et al.*² found no difference in acute rejection, chronic allograft nephropathy, and patient or allograft survival in a meta-analysis that included 750 patients from 8 randomized controlled trials (RCT). In 2009, Schena *et al.* in the Convert Trial performed a RCT with 830 patients who were converted from CNI to sirolimus in a broad post transplantation period (from 6 to 120 months). The primary end-points (graft loss or death) at 12 months were identical⁵.

In 2011, in the ORION study, Flechner *et al.* reported similar graft and patient survival in an RCT enrolling 469 patients for a 2-year follow-up period⁶. In the same year, Weir *et al.* reported a trend to a better graft and patient survival in an RCT with 299 patients, the Spare-the Nephron trial⁷.

Recently, in 2012, Budde *et al.* in the Zeus study randomized 300 patients to continue on cyclosporine or to be converted to everolimus at 4.5 months post-transplantation. At 12 months of follow-up, there was no difference in patient or graft survival⁸.

There are some limitations that may explain different results in different studies. The first difference stands in the time of conversion. Because of impaired healing, mTOR inhibitors have been avoided in the immediate post-transplantation period^{2,9}. Studies where mTOR inhibitors have been introduced soon after transplant have reported worse outcomes compared to CNI¹⁰. In our study, although there has been a great dispersion in the time of mTOR conversion,

it occurred in a mean period of 10 months. Second, therapeutic drug levels are important to draw conclusions. We have used low dose regimens, perhaps limiting dose-related side effects like dyslipidaemia and anaemia associated to worse cardiovascular outcomes that would influence patient survival. Finally, induction and concomitant therapy may also influence results. All our patients underwent induction therapy and most were maintained on MMF as anti-metabolite.

In our study, we cannot infer conclusions about mTOR inhibitors benefits in Glomerular Filtration Rate (GFR) because the main indication to switch was chronic allograft dysfunction. However, we may state that serum creatinine remained stable in the follow-up period. Proteinuria is also an independent factor for worse outcome. After an initial significant increase in proteinuria at the time of conversion, it remained stable thereafter and outcomes were not different.

In the subgroup analysis, the only difference we found was in the low immunological group, who presented a trend to a better allograft survival in comparison with the patients who remained in CNI¹¹.

Our study presents several limitations. It is a retrospective study, with a limited number of patients. From another point of view, this study included all transplant recipients at our unit, a “real life” situation that may be different from many clinical trials. It is a single centre study, so results cannot be extrapolated to other populations. Another important limitation is that the main conversions were made in the setting of chronic allograft failure but biopsies have not been obtained systematically. The number of events is also small, a fact that may influence results, but the follow-up time, up to 72 months, is rather significant, since the literature has limited data in long follow-up periods.

■ CONCLUSION

We believe our results may be helpful in the decision analysis of mTOR inhibitor conversion. Until more studies are conducted, we cannot recommend or discourage conversion to mTOR inhibitors but its use seems a reasonable alternative with appropriate indications.

Conflicts of interest statement. None declared

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