

Observational Study

## Conversion from calcineurin inhibitors to mTOR inhibitors stabilizes diabetic and hypertensive nephropathy after liver transplant

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### Abstract

**AIM:** To investigate if conversion to the mammalian target of rapamycin inhibitors (mTORi) improves renal function in diabetic and/or hypertensive liver transplant patients immunosuppressed with tacrolimus or cyclosporine.

**METHODS:** The study included 86 liver graft recipients immunosuppressed with mTORi treatment after orthotopic liver transplantation (OLT), including all liver recipients with worsening renal function before conversion to mTORi ( $n = 55$  patients) and recipients with normal renal function who converted to mTORi for other reasons ( $n = 31$  patients). We identified patients with diabetes mellitus ( $n = 28$ ), arterial hypertension ( $n = 27$ ), proteinuria ( $n = 27$ ) and all three factors ( $n = 8$ ) (some patients have hypertension and diabetes and no proteinuria). The primary endpoint was evolution in renal function defined as the development in plasma creatinine as a function of diabetes mellitus (DM), hypertension (HT) or proteinuria. We required elevated serum creatinine for at least two weeks to define renal dysfunction.

**RESULTS:** Only patients that converted because of renal failure with plasma creatinine levels  $> 1.5$  mg/dL showed an improvement of renal function (2.14 to 1.77 mg/dL) ( $P = 0.02$ ). Patients with DM showed no improvement of serum creatinine levels (1.31 mg/dL to 1.37 mg/dL) compared with non DM patients (1.31 mg/dL to 1.15 mg/dL) ( $P = 0.01$ ), HT patients (1.48 mg/dL to 1.5 mg/dL) with non HT patients (1.21 mg/dL to 1.08 mg/dL) and patients with proteinuria (1.44 mg/dL to 1.41 mg/dL) and no proteinuria (1.31 mg/dL to 1.11 mg/dL).

**CONCLUSION:** In OLT recipients with diabetes or hypertensive nephropathy, conversion to mTORi does not improve renal function but stabilizes plasma levels

of creatinine. Proteinuria is not a contraindication to conversion to mTORi; it also stabilizes renal function. Conversion to mTORi should only be avoided in patients with diabetes, hypertension and proteinuria.

**Key words:** Mammalian target of rapamycin inhibitors; Liver transplant; Renal dysfunction; Hypertension; Diabetes

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**Core tip:** These results could be useful in choosing an immunosuppressant regimen in liver transplant recipients, especially in patients with diabetes mellitus and/or arterial hypertension with proteinuria and possibly renal dysfunction.

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## INTRODUCTION

Survival after orthotopic liver transplantation (OLT) is getting better because of improvement in surgical techniques and better management in immunosuppressant therapy. This important survival leads to more side effects from immunosuppression agents so it is very important to identify the best drug regimen for each patient to reduce toxicity<sup>[1]</sup>. Calcineurin inhibitors (CNI) tacrolimus and cyclosporine have a common (18%-25%) side effect of chronic renal dysfunction<sup>[2]</sup> and some of these patients will need hemodialysis with the possibility that this renal failure could be the cause of death<sup>[3]</sup>. Immunosuppressive therapies that reduce or eliminate CNI based treatment should preserve renal function after OLT.

mTOR inhibitors, sirolimus and everolimus (mTORi), block cell proliferation based on interleukin-2 pathway interacting kinases called the mammalian target of rapamycin<sup>[4]</sup>. CNI inhibit production of cytokines as interleukin-2 in the first phases of the lymphocyte cell cycle<sup>[5]</sup>. These days, mTORi is being studied more in renal transplant patients and less in liver transplant patients. There are some studies that show that elimination or reduction of CNI and inclusion of mTORi preserve renal function<sup>[6-12]</sup>. However, there are no controlled studies of the effect of mTORi exposure in liver transplant patients with well-known chronic renal insufficiency because of diabetes and/or hypertension associated with worsening urinary protein excretion and renal function. It is probable that improvement in renal function is reduced in patients with diabetes

mellitus (DM), hypertension (HT) and/or proteinuria.

The potential side effects of mTORi, such as hyperlipidemia, hepatic artery thrombosis and a bad wound cicatrization, have been investigated in these patients<sup>[13]</sup>. No controlled studies have examined these potential effects in the OLT population.

This study attempts to compare outcomes of renal function in cohorts treated with mTORi with diabetes mellitus, hypertension or/and proteinuria.

## MATERIALS AND METHODS

### Study cohorts

We studied 86 liver recipients immunosuppressed with mTORi treatment after OLT at our center from March 2007 to June 2013. Renal dysfunction was defined as serum creatinine  $\geq 1.2$  mg/dL for at least two weeks (whenever it occurred at least two months after OLT). We included all liver recipients who were diagnosed with renal dysfunction before conversion to mTORi ( $n = 55$  patients) as well as patients with normal renal function who converted to mTORi for other reasons ( $n = 31$  patients). We identified patients with diabetes mellitus ( $n = 28$ ), arterial hypertension ( $n = 27$ ), proteinuria ( $n = 27$ ), and all three factors ( $n = 8$ ) (some patients had hypertension and diabetes and no proteinuria).

### Definition of variables

Baseline creatinine was determined as plasma creatinine level at the moment of switching to mTORi, then at 6, 12 and 18 mo, and actual creatinine (last drawn serum creatinine) when collected.

DM patients were defined by the American Diabetes Association criteria [*Diabetes Care* 2005; 28 (suppl 19): 37-42]. HT patients were catalogued as patients with systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg. Proteinuria was defined as the appearance of proteins in urine. There was no difference in severity.

### Endpoint

The main endpoint was evolution of renal function, determined by serum creatinine and according to the presence of DM, HT and/or proteinuria. Renal dysfunction was defined by elevated serum creatinine for at least two weeks.

### Administration of immunosuppression

The immunosuppressant regimen after OLT was administered inside a wide protocol at our center. Induction drugs at time of OLT were given in cases of well-known renal dysfunction before transplant. Post OLT, tacrolimus was given to obtain serum levels between 7 and 10 ng/mL for 180 d after OLT and levels between 5 and 8 ng/mL for the next 180 d. Cyclosporine was only used in cases of neurotoxicity because of tacrolimus. If cyclosporine was used, the serum level was between

**Table 1** Features of patients converted to mammalian target of rapamycin inhibitors

Variable	DM (28)	HT (27)	Prot (27)	DM + HT + prot (8)	P-value
Age (yr)	54.3	55.1	54.8	55.2	0.61
Male	21	23	22	7	0.43
DM prior to OLT	28	8	8	8	0.52
Hypertension prior to OLT	5	19	5	5	0.34
Proteinuria prior to OLT	7	6	19	6	0.42
Etiology of liver disease					
Hepatitis C	11	11	10	3	0.32
Alcohol	14	13	13	4	0.67
Other	3	3	4	1	0.56
Hepatocellular carcinoma	6	5	5	1	0.48
Initial creatinine	1.31	1.48	1.44	1.35	0.23

DM: Diabetes mellitus; HT: Hypertension; Prot: Proteinuria; OLT: Orthotopic liver transplant.

250-350 lg/L after OLT with a maintenance cyclosporine level of 50-100 lg/L. Prednisone was administered after OLT and generally stopped within the first two months, except in autoimmune, primary biliary and primary sclerosing cholangitis cirrhosis. Mycophenolate mofetil was used in all patients, one gram/day, except in CMV infection.

mTORi has been used in liver grafts recipients with renal dysfunction, patients with tacrolimus and cyclosporine neurotoxicity, in high risk hepatocellular carcinoma (HCC) liver transplant patients to avoid its recurrence, and in patients with "de novo" neoplasia after OLT, adjusting the dosage to obtain levels between 5 and 8 ng/mL. After two to four weeks of double immunosuppressant treatment with tacrolimus, this is usually discontinued. mTORi use is stopped for an elective surgical procedure.

After hospital discharge, patients are visited and blood samples taken every week and after three/four months, patients are visited monthly for laboratory testing. One hundred and eighty days after OLT, visits were every 60 d.

Elevation in serum creatinine, blood pressure and blood sugar or the appearance of proteinuria were registered.

**Data collection**

Patient information is prospectively registered in an SPSS electronic register on all OLT patients at our center. The database is available only for clinical studies. For this study, data were extracted on mTORi treated patients from this clinical register. Clinical and demographic information contained sex, age, donor age, cause of liver cirrhosis, graft quality, existence of HCC, OLT date, complications, cause of CNI treatment being converted to mTORi, retransplantation and presence of diabetes mellitus and/or hypertension before OLT. Biochemistry and hematological data included baseline plasma creatinine levels (just to conversion to mTORi), at 6, 12, 18 mo, and the last serum creatinine level while taking mTORi treatment. One independent investigator audited 10% of the

results and found > 99% data congruity.

**Statistical analysis**

This analysis used means for parametric data and medians for non-parametric data. We used Fisher's exact tests for comparisons of categorical variables. We analyzed non-normally distributed variables with Mann-Whitney U-tests and two-sided t-tests were used to compare normally distributed variables.

Linear regression was applied to examine the effect of mTORi exposure on the last serum creatinine at the end of follow-up. MTORi exposure was examined as a continuous and a dichotomous variable.

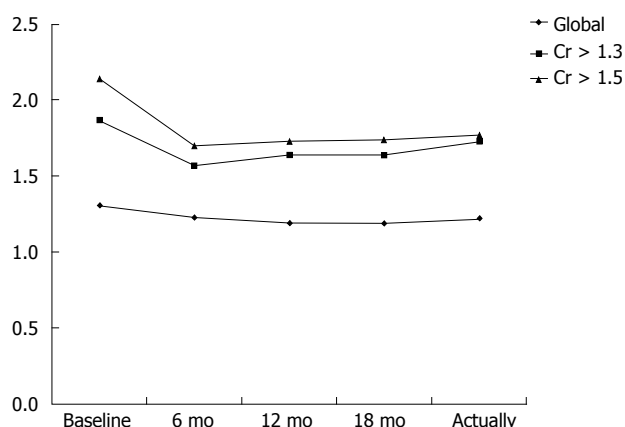
We applied only confounders which influenced the point estimate by ≥ 10% for adjusted models (19). We considered P value < 0.05 as significant; two-sided tests were used.

**RESULTS**

mTORi was started at a median 48 mo (DT: 56.8, range = 0-241) after OLT. Recipients were followed on mTORi for a median of 40.6 mo (DT: 18.0, range = 18-76). Reasons for switching to mTORi were avoiding HCC recurrence (n = 27), neurotoxicity because of tacrolimus (limb tremors, headaches, paresthesia) (n = 3), prevention of renal insufficiency (n = 28), acute rejection with tacrolimus/cyclosporine (n = 6), and "de novo" neoplasia (n = 22).

No mTORi patient developed serious adverse effects and there was no hepatic artery thrombosis. The clinical characteristics of the patients converted to mTORi are described in Table 1.

Initial plasma creatinine levels of patients at the moment of initiating mTORi treatment (median 48 mo after OLT) were 1.31 mg/dL. Creatinine was (mg/dL) 1.19, 1.19, 1.22 at 6, 12 and 18 mo and 1.23 mg/dL at the follow-up after the mTORi switch. There was an improvement between the initial and final creatinine levels while taking mTORi, but without statistical significance: 1.31 mg/dL and 1.22 mg/dL (P = 0.92), although this is a global analysis in all patients,



**Figure 1** Improvement of serum creatinine (mg/dL) after conversion to mammalian target of rapamycin inhibitors. Cr: Serum creatinine mg/dL; Baseline: Serum creatinine just before conversion.

converting because of renal dysfunction or for other reasons. We can observe the same low difference when we analyze converted patients with plasma creatinine levels > 1.3 mg/dL (1.87 mg/dL and 1.73 mg/dL,  $P = 0.78$ ). Only patients converted because of renal dysfunction with plasma creatinine levels > 1.5 mg/dL show a statistically significant improvement of renal function, with initial levels of 2.14 and final ones of 1.77 mg/dL ( $P = 0.02$ ) (Figure 1).

We next investigated whether the mTORi effect is less in recipients with diabetes mellitus and/or high blood pressure (HT) (Figure 2). Subgroup analysis of only those mTORi patients with DM shows no improvement of serum creatinine levels (1.31 mg/dL to 1.37 mg/dL) compared with non DM patients (1.31 mg/dL to 1.15 mg/dL) ( $P = 0.01$ ) and it is the same when comparing HT patients (1.48 mg/dL to 1.5 mg/dL) with non HT patients (1.21 mg/dL to 1.08 mg/dL) and patients with proteinuria (1.44 mg/dL to 1.41 mg/dL) and no proteinuria (1.31 mg/dL to 1.11 mg/dL).

Finally, we considered patients with DM, HT and proteinuria (Figure 3). Although converting to mTORi, these patients have worsening renal function (1.35 mg/dL to 2.07 mg/dL) compared with patients when only one of these factors is present ( $P = 0.04$ ).

## DISCUSSION

Our study shows retrospectively that mTORi conversion resulted in an improvement in renal function in patients with plasma creatinine levels above 1.5 mg/dL. In patients with better renal function, conversion therapy involves no improvement. This improvement has been described in several published studies but none have shown that the worse the renal function, the greater the improvement after conversion<sup>[9,10,14-17]</sup>.

mTORi was started a median of eight months after OLT for a variety of reasons. Plasma levels of creatinine at the start of the study were comparable in both mTORi and CNI cohorts. A personal history

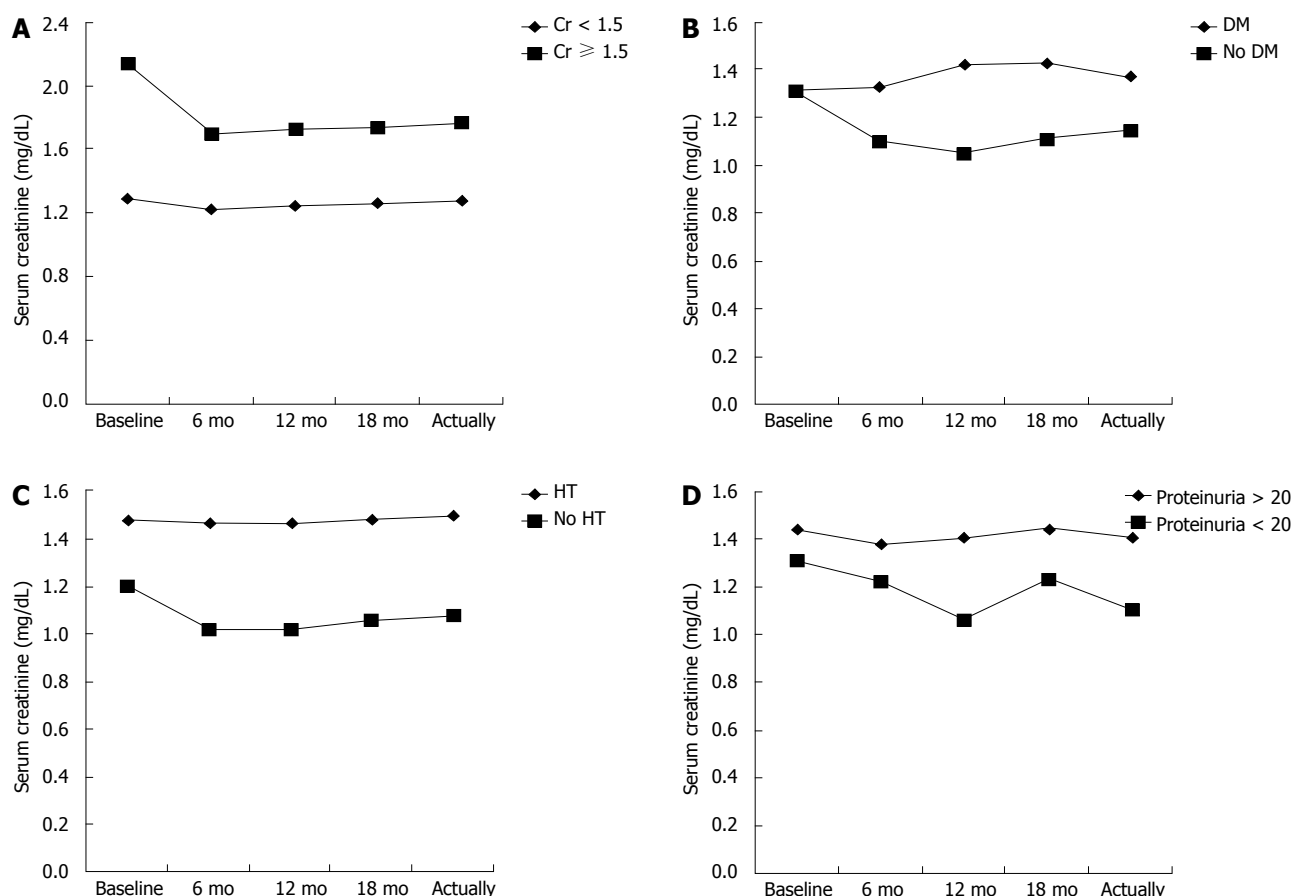
of risk factors for renal damage, such as diabetes mellitus and arterial hypertension, was comparable in both mTORi and CNI cohorts and considered in a multivariate model. Patients with hepatocellular carcinoma were adjusted in the mTORi cohort because treatment with chemotherapy may have affected serum creatinine. Despite this, it could be possible that some confounders are distributed unevenly in both groups. Further randomized trials may be necessary to avoid this problem.

Furthermore, we have segregated groups of patients with DM, hypertension and proteinuria and patients with all three diseases. We have seen how renal function does not improve after conversion to mTORi in these patients but it stops the progressive deterioration secondary to calcineurin inhibitors. However, in patients with DM, hypertension and proteinuria, renal function worsens despite conversion to mTORi.

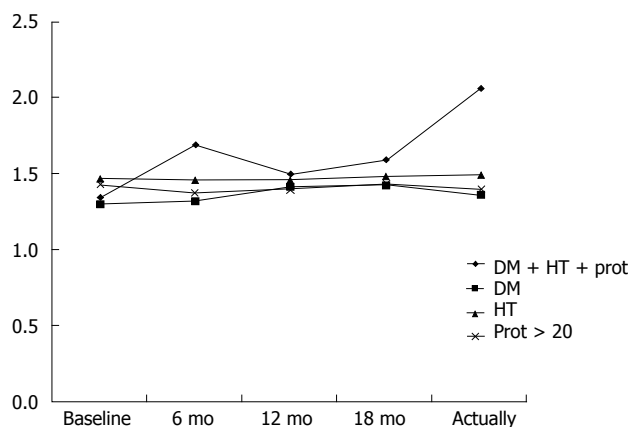
Nephropathy is a major complication of type 1 and type 2 diabetes mellitus, along with CNI toxicity, end-stage renal dysfunction and hemodialysis<sup>[18]</sup>. Chronic nephropathy is also worsened by arterial hypertension. Diabetic nephropathy is first characterized by microalbuminuria and later by glomerular sclerosis. Podocytes play an important role in preventing proteinuria. Podocyte damage and reduction in the number of these cells contribute to the development of diabetic nephropathy<sup>[19]</sup>. mTOR plays a very important role in podocyte growth and size control. This molecule forms two different functional complexes, mTORC1 and mTORC2. Sirolimus and everolimus selectively inhibit mTORC1 but not mTORC2. In the first stages of diabetic damage in the kidney, an increased mTORC1 activity and podocyte hypertrophy can be observed. Moreover, there are some studies that report mTORi treatment to prevent diabetic nephropathy in animal models. Paradoxically, sirolimus and everolimus cause proteinuria and glomerular sclerosis in some patients<sup>[19,20]</sup>. In our study, we observed that these experimental findings are corroborated clinically in liver transplant patients with diabetic nephropathy.

There are no studies linking mTORi effectiveness in patients with hypertensive nephropathy. In our series, we showed how renal function, although not improved after conversion to mTORi, stabilizes after this change in immunosuppression regimen.

Proteinuria is a frequent side effect after switching from CNI to mTORi treatment in another solid transplant patient as a kidney graft recipient<sup>[21-26]</sup>. Wade *et al.*<sup>[21]</sup> shows that patients who developed massive proteinuria had a 3.3-fold increased risk of further renal insufficiency after mTORi conversion and proteinuria less than 1000 mg/d do not present with this association. This author indicates that a higher mTORi level after OLT diabetes and a lower eGFR at time of mTORi switching were observed with the appearance of very important urinary protein excretion after mTORi treatment. This study is in concordance with other articles that show a dose-dependent effect of mTORi on proteinuria and



**Figure 2** Improvement of serum creatinine (mg/dL) after conversion to mammalian target of rapamycin inhibitors in different groups. Baseline: Serum creatinine just before conversion; Cr: Serum creatinine mg/dL; DM: Diabetes mellitus; HT: Hypertension.



**Figure 3** Improvement of serum creatinine (mg/dL) after conversion to mammalian target of rapamycin inhibitors in different groups. Baseline: Serum creatinine just before conversion; DM: Diabetes mellitus; HT: Hypertension; Prot: Proteinuria.

podocyte protein expression<sup>[12,27-31]</sup>. Higher proteinuria before mTORi treatment has also been correlated with massive proteinuria after switching.

Our results do not support these studies as we have shown that in patients with proteinuria, mTORi conversion leads to a stabilization of this proteinuria as well as serum levels of creatinine.

We recognize some limitations in this study. We do not routinely measure eGFR levels with Modification of Diet in Renal Disease or Cockcroft-Gault equations because this measurement is not very precise and not validated in OLT recipients.

In conclusion, we observed that, after OLT, switching from a CNI-based immunosuppression regimen to mTORi-based treatment improves renal function, when compared with recipients who did not switch, when creatinine levels are  $\geq 1.5$  mg/dL. In patients with diabetes or hypertensive nephropathy, conversion to mTORi does not improve renal function but stabilizes plasma levels of creatinine. Proteinuria is not a contraindication to conversion to mTORi, it also stabilizes renal function. Only patients with diabetes, hypertension and proteinuria should avoid conversion to mTORi because it worsens. Complete understanding of the effects of mTORi in liver transplant recipients derived from randomized, controlled trials will help better use of this immunosuppression regimen after OLT.

## COMMENTS

### Background

This study shows how mammalian target of rapamycin inhibitors (mTORi) based immunosuppression therapy in liver transplant recipients with diabetic

and/or hypertensive renal dysfunction, even in patients with proteinuria, preserves renal function and plasma levels of creatinine.

### Research frontiers

mTORi based immunosuppression therapy in liver transplant patients and renal chronic disease.

### Innovations and breakthroughs

Observational study in diabetic and hypertensive liver transplant patients and those with proteinuria.

### Applications

This study helps to choose immunosuppression treatment in patients with renal dysfunction after liver transplant.

### Terminology

mTORi (mTOR inhibitors like sirolimus and everolimus, immunosuppression drugs for transplanted patients).

### Peer-review

The manuscript observed the effect of mTORi-based immunosuppression therapy on diabetes mellitus, arterial hypertension and proteinuria for analysis of the potency of mTORi to renal function. This may be useful for clinical therapy.

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