

Early Conversion from Calcineurin Inhibitors to Sirolimus in Liver Transplant Patients with Renal Dysfunction: A Systemic and Splanchnic Hemodynamic Study

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ABSTRACT

AIMS: It has been demonstrated that sirolimus, a potent immunosuppressant agent, allowing a reduction of nephrotoxic effects of CNIs. We have evaluated whether conversion from a CNIs to sirolimus reduces nephrotoxicity in liver transplant recipients. We have also investigated whether this effect is accompanied to systemic, splanchnic and renal hemodynamic changes.

MATERIAL AND METHODS: Twelve patients with a suboptimal renal function, defined as an estimated glomerular filtration rate (GFR) of less than 50 ml/min, were included. Hemodynamic parameters were measured by doppler. Both measurements were performed in baseline (pre conversion to sirolimus) and 30 and 90 days after sirolimus.

RESULTS: The target range for whole blood sirolimus concentration was between 5 and 12 mg/ml. There was a significant difference in GFR at 30 (57 ± 20 ml/min) and 90 (58 ± 21 ml/min) days in patients switching to sirolimus compared to those observed during the administration of CNIs (39 ± 9 ml/min, $p < 0.05$). This effect on renal hemodynamic is accompanied by a significant reduction in mean arterial pressure. No significant changes were observed in the other

parameters studied.

CONCLUSION: Our results suggest that early withdrawal of CNIs is a safe option, which allows an improvement in renal hemodynamic in liver transplant recipients.

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Key words: Immunosuppression; Rapamycin; Tacrolimus; Nephrotoxicity; mTOR; Doppler measurements

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INTRODUCTION

Calcineurin inhibitors (CNIs) have been the mainstay of immunosuppressive regimens in liver transplantation. Although the use of cyclosporine and tacrolimus markedly improved liver graft and patient survival, both of these CNIs are nephrotoxic^[1,2]. At present, it is well known that the incidence of chronic renal dysfunction, defined as a glomerular filtration rate < 29 mL/min/m², has been estimated at 18.1 % at 5 years after liver transplantation^[3]. Moreover, development of renal failure has a negative impact on liver transplant patient survival, and is associated with a 4-fold increase in the relative risk of death^[2,3]. This has led to consider the CNIs minimization, besides the care of other risk factors like hypertension and diabetes, one of the most important approaches to preserve renal function after liver transplantation.

The renal dysfunction associated with CNIs treatment is initially manifested as a reversible damage caused by renal vasoconstriction with the subsequent alteration in renal blood flow^[4]. This injury

progresses to irreversible chronic renal failure. Therefore, it is important to evaluate new immunosuppressive regimens without deleterious effects on renal function. Sirolimus (SRL) has been shown to be effective as a novo therapy after renal transplantation^[5,6], and several studies also reported its use in liver transplantation^[7-11]. Unlike the CNIs, sirolimus is not associated with nephrotoxicity. The implication of these findings has been that sirolimus is a drug of choice both in patients with contraindications to the CNIs and in those with clacineurin-induced chronic renal insufficiency.

In the present study, we have evaluated whether early conversion from CNIs to sirolimus reduces nephrotoxicity in liver transplant patients. We have also investigated whether this effect is accompanied to systemic and hemodynamic changes.

MATERIAL AND METHODS

Patients

Twelve patients with cirrhosis undergoing liver transplantation with early renal dysfunction, defined as that which occurs during the first year after liver transplantation, were prospectively included. The cause of chronic liver disease was hepatitis C in 9 patients and cryptogenic in 3. Eight patients were male and 4 female, mean age was 48 years (range 23-58 years). None of the patients had impaired renal function at the time of transplantation. Glomerular filtration rate (GFR) was evaluated according to Modification of Diet in Renal Disease (MDRD) formula^[10]. Early renal dysfunction was defined as an estimated GFR of less than 50 mL/min. Liver recipients were stable and none of them had clinical or histological evidence of infection or rejection. Patients went to abrupt switch to sirolimus-based immunosuppression, receiving their last dose of CNIs the evening before conversion. Concomitant immunosuppression, such as prednisolone or mycophenolate was continued unchanged. Mean time from liver transplantation to inclusion in the study protocol was 16±2 months. The sirolimus dose consisted of a loading dose of 6 mg/day, followed by 4 mg/day for 2 days and then 2 mg/day. The target range for whole blood sirolimus concentration was between 5 and 12 ng/mL. At the time of conversion to sirolimus therapy, mean tacrolimus and cyclosporine levels were 6.8 and 130 ng/mL, respectively. None of the patients were taking any form of vasoactive drug for the treatment of arterial hypertension for at least 30 days prior to the hemodynamic evaluation. The study was approved by the local clinical research committee, and the patients gave written informed consent.

Methods

Hepatic hemodynamic parameters measured using a Toshiba SSA 270 A (Tokyo, Japan) duplex scanner, consisting of a real-time, two dimensional ultrasonic device and an attached 3.5- MHz pulsed Doppler flowmeter. After a sampling marker had been set in the middle of the lumen of the portal vein along the beam axis, a second marker was positioned parallel to the direction of blood flow. Care was taken to maintain the angle 0 (the angle formed by the ultrasonic beam and the direction of blood flow) below 60, since the accuracy of the measurements decreases at increasing angles. Measurements were carried out during expiration, for this can be easily standardized and allows a better visualization of the portal vein for Doppler, as the angle 0 is reduced to a minimum^[13,14].

Blood flow was obtained by multiplying the blood velocity by the cross sectional area of the vessel, calculated on the basis of the inner diameter and assuming circular geometry. Doppler assessment of the left ventricular ejection velocity was obtained by positioning of the

sample marker in the aorta just distal to the aortic valve on a B-mode, four chamber image plus aorta image with the transducer placed on the apical zone. This position makes the angle between the ultrasound beam and the direction of blood stream near zero. The pulsatility index of the renal artery [calculated as (peak systolic frequency shift - minimum diastolic frequency shift)/peak systolic frequency shift] was determined manually by using calipers, and an average of two to three waveforms were seen in each scan. Doppler evaluation was always carried out by the same specialized examiner (DA).

Arterial pressure was measured with a sphygmomanometer and expressed as mean arterial pressure according to the formula: (systolic pressure+diastolic pressure × 2)/3. Peripheral vascular resistance was calculated as: mean arterial pressure /cardiac output × 80.

After an overnight fast, subjects were transferred to the hemodynamic Lab, where eco Doppler measurements were performed. Glomerular filtration rate and hemodynamic parameters were evaluated in basal conditions (pre conversion to sirolimus) and 30 and 90 days after sirolimus administration.

Results are expressed as mean±SD. Hemodynamic variations were compared using Student's paired *t* test. Differences were considered significant when *p* was less than 0.05.

The conversion from CNIs to sirolimus was well tolerated. Biochemistry liver tests and graft function were stable throughout the study. Rejection was not detected in any case. Minimal adverse effects were observed in relation to sirolimus, in none of the cases required discontinuation of therapy.

As shown in figure 1, there was a modest but a significant difference in GFR at 30 and 90 days in patients switching to sirolimus. This beneficial effect was observed in each the patients studied. The increase in GFR was observed at 30 days of conversion to sirolimus and remained at 90 days. The estimated GFR increased at 30 and 90 days after conversion to sirolimus were not associated with changes in renal pulsatility index (Table 1).

Systemic and splanchnic hemodynamic parameters are shown in table 1. Mean arterial pressure declined in each of the patients studied as early as 30 days after the switch from CNIs to sirolimus. This difference was statistically significant at 90 days. A moderate degree of splanchnic vasodilation was observed in patients who were converted to sirolimus. Portal blood flow was higher at 30 and 90 days after the switch from CNIs to sirolimus

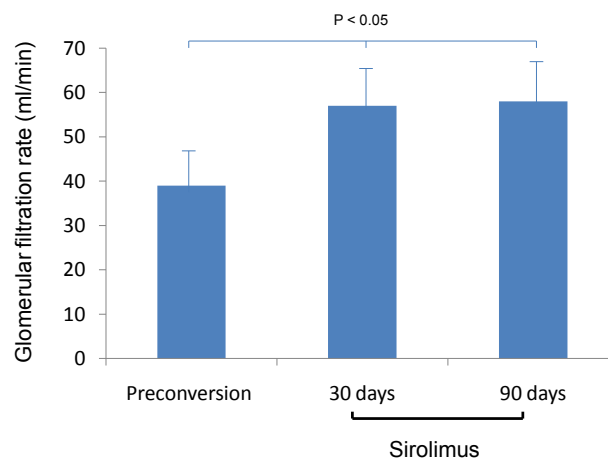


Figure 1 Glomerular filtration rate in liver transplantation recipients converted to sirolimus.

Table 1 Systemic and splanchnic hemodynamic parameters in liver transplant recipients.

	Pre conversion	Sirolimus (30 days)	Sirolimus (90 days)
Mean arterial pressure(mmHg)	107±7	99±8	95±4 *
Cardiac output (L/min)	4.7±0.3	4.7±0.4	4.8±0.3
Peripheral vascular resistance (dyn.s.cm-5)	1540±190	1503±140	1450±145
Renal pulsatility index	0.8±0.1	0.7±0.2	0.8±0.2
Portal blood flow (mL/min)	1450±450	1590±478	1680±780

Mean ± SD, * $p < 0.05$.

DISCUSSION

Calcineurin inhibitors are the basis of the liver transplant immunosuppressive regimen in the vast majority of patients. However, it is becoming clear that the inhibition of calcineurin may be linked with nephrotoxicity, hypertension, hyperlipidemia and new-onset diabetes mellitus, side effects that may lead to late hepatic allograft loss^[14,15]. It is well known that the CNIs cause both acute functional nephrotoxicity and chronic structural nephrotoxicity. The acute nephrotoxicity associated with CNIs is due to vasoconstriction of the renal microcirculation with the consequent alteration in renal blood flow^[16]. This process is completely reversible with stopping administration of cyclosporine or tacrolimus^[17,18]. Chronic nephrotoxicity, unlike what was observed with the acute damage, leads to structural renal damage via obliterative arteriopathy, tubular atrophy, interstitial fibrosis and glomerular fibrosis^[19,20]. These changes produce a definitive deterioration of renal function^[19,20]. These findings has led to long-term maintenance of renal function has become a challenge in liver transplantation recipients.

Our results demonstrated that early conversion, within one year after transplantation, to sirolimus improves renal function impairment associated with CNIs in liver transplant patients. The change in GFR from baseline (pre-conversion) to 90 days was approximately

17 mL/min. Moreover, patients with the shortest time post transplant showed the greatest benefit after conversion to sirolimus, with GFR increasing by 22 mL/min. This time dependency of renal function is not unexpected, because CNI - related arteriolar lesions have been shown to increase progressively after renal transplantation and are generally irreversible once established despite CNI dose reduction or suspension^[21]. Our results suggest that early introduction of sirolimus after transplantation may be the best approach, acting preemptively before extensive, irreversible CNI-related renal damage has occurred. Finally, and despite being a small number of patients, we found that HCV positive patients have a greater increase in GFR after conversion to sirolimus (+39% vs 19 %). Recent studies suggest that HCV may be an independent risk factor for the development of renal failure in liver and in other non-renal transplant patients^[3,22].

Vascular complications associated with the CNIs are a frequent complication of patient who undergoes liver transplantation. Endothelial dysfunction is thought to be the initial event in this pathologic condition. A variety of insults including nitric oxide (NO) synthesis are involved in this process, leading to endothelial damage attendant loss of homeostatic regulatory properties of the vascular wall. In this sense, another relevant finding of our study was that patients administered sirolimus have a moderate but significant reduction in mean arterial pressure.

In the last years, one of the main questions has been the potential risk of acute rejection after conversion to sirolimus. There was evidence that conversion could impair immunosuppressive efficacy. In this regard, clinical studies have shown that the rate of acute

rejection following conversion to sirolimus varies from 10 to 30% in liver transplant recipients^[23,24]. In our study, and although in some patients the conversion to sirolimus was made early, there have been no evidence of acute rejection in any of them. In our experience, all patients continued to receive sirolimus after the hemodynamic study was completed. During this time, the presence of adverse effects, particularly anemia and leucopenia was minimal, and was no necessary to use growth factors in any of the evaluated patients.

In summary, we report here that early conversion to sirolimus after liver transplantation is associated with an improvement in renal function. Also, has not been an increase in the number of rejections and the presence of significant adverse effects after this conversion. However, the benefit of this strategy, the conversion from CNIs to sirolimus, should be confirmed in the long term.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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