Real-Life Experience With mTOR Inhibitors Treatment After Liver Transplantation

O. Gilad[1], L. Rabinowich[2], N. Gotlieb[2], N. Lubezky[3], I. Nachmany[3], Y. Goichman[3] P. Katz[3], O. Shibolet[2], H. Katchman[2]

[1]Internal Medicine D, Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Tel-Aviv, Israel
[2]Liver unit, Department of Gastroenterology, Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Tel-Aviv, Israel
[3]Department of Surgery, Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Tel-Aviv, Israel

INTRODUCTION

Kidney injury is a common complication after liver transplantation (LT), with high incidence of chronic renal failure(CRF) and significant increase in mortality in CRF patients. The metabolic syndrome (MS), defined by a combination of hypertension, diabetes mellitus, dyslipidemia and obesity, is another common complication after LT and is associated with an increased risk of cardiovascular disease. Increased prevalence of the MS in post-LT patients compared to the pre-transplant period and the general population was demonstrated.
Immunosuppression with mammalian target of rapamycin inhibitors (mTORi) LT is widely used to minimize calcineurin inhibitors (CNI) related nephrotoxicity. Less data are available about metabolic effects of mTORi.

AIMS AND METHODS

Aim: To determine the renal and metabolic effects of Everolimus (EVR) and Sirolimus (SIR) treatment in real-life LT patients.

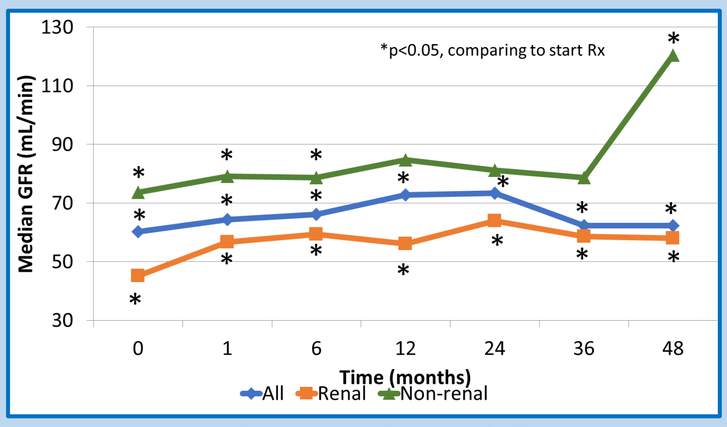
Methods: A retrospective cohort study of patients treated with mTORi after LT. Demographic, clinical data, glomerular filtration rate (GFR), Body mass index (BMI), blood glucose, lipid profile and blood pressure (BP) measurements were collected over a period of 6 years. Initiation of BP, diabetes and lipid medications was recorded.

RESULTS AND CONCLUSIONS

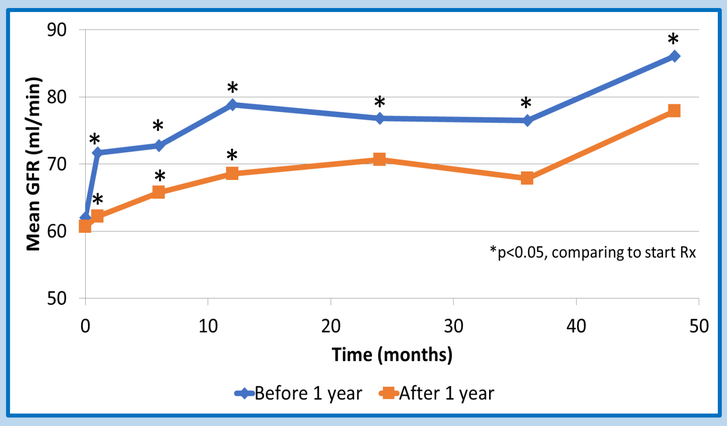
In 52 patients that underwent LT between the years 1998-2017, treatment with mTORi was started (Table1). Treatment protocol was CNI minimization in 33(63.4%) patients and CNI withdrawal in 19(36.5%) patients. GFR improved significantly after initiation of mTORi (2.5mL/min/1.73 m^2 per year±1.2, p=0.037) without significant difference between two groups. The improvement in GFR was more significant in the patients that started mTORi for renal impairment(picture 1) and in these who started mTORi in the first year after LT (picture2).

Parameter	Data
Sex – male (%)	31 (59.6%)
Age at transplantation, years, median (IQR)	59.9 (55.7-65.2)
Type of transplantation	
OLT	46 (88.4%)
Living	2 (3.8%)
Split	4 (7.7%)
Indication for LT	
HCC	28 (53.8%)
Cholangio	3 (5.7%)
HCV	27 (51.9%)
HBV	7 (13.4%)
NASH	9 (17.3%)
Cryptogenic	1 (1.9%)
Fulminant	3 (5.7%)
PBC	2 (3.8%)
ALD	4 (7.7%)
Time from LT to mTORi initiation, months, median (IQR)	10.9 (4.4-19.6)

Table 1. Patient's characteristics

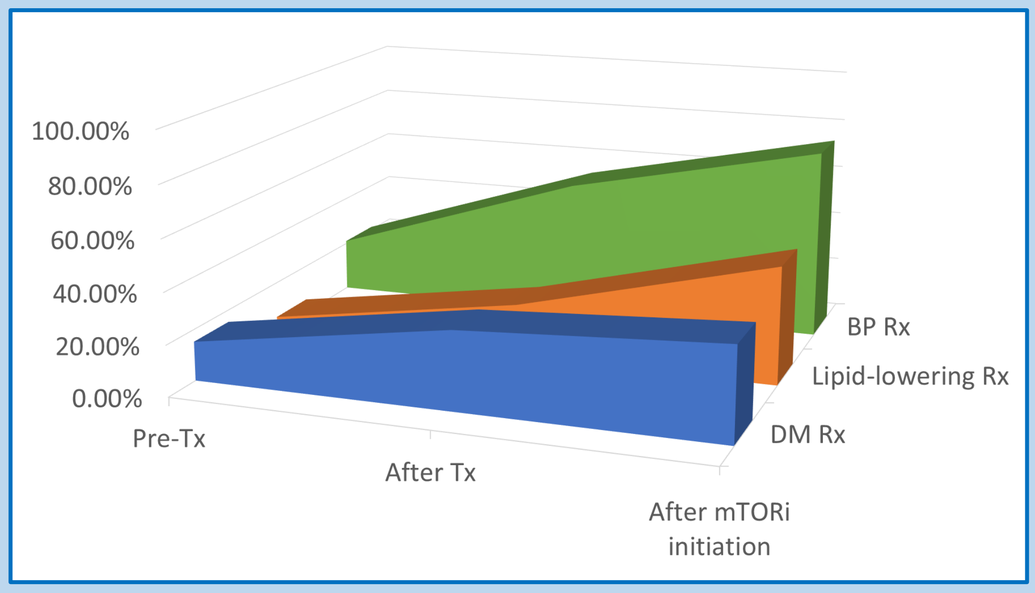


Picture 1. Median GFR during follow-up, according to indication for mTORi initiation



Picture 2. Median GFR during follow-up, according too timing of mTORi initiation

Most common side effects were aphthae (30.7%) and edema (15.3%). Treatment was discontinued due to side effects in 17(32.6%) of patients with clear advantage to SIR based regiment (16 on EVR and 1 on SIR, p=0.029).
Before undergoing LT, only 3 patients (5.7%) were on lipid lowering drugs. Post-transplant this number riszed to 11 patients(21.1%). After mTORi initiation, additional 13 patients (25%) were started on lipid lowering medications. Pre-transplant, 11 patients (21.1%) were on BP medications. Post-transplant this number rises to 28 patients (53.8%). After initiation of mTORi 7 additional patients (13%) started BP medications. Before undergoing LT, 8 patients (15.3%) were on DM medications. Post-transplant this number is doubled – 16 patients (30.7%). After mTORI initiation only 3 patients (5.7%) started DM medications.
Median time from start of mTORi therapy to initiation of lipid lowering drugs, BP and diabetes medications was 11.9, 23.9 and 13.08 months respectively.
No difference was observed between CNI protocol, type of mTORi or indication for mTORi therapy .
Patients on CNI minimization with SIR gained more weight compared to their counterparts (6.8kg ±3.3, p=0.042; 7.05kg ±3.4, p=0.041; respectively).
In conclusion, mTOR inhibitors are a viable option as an immunosuppressive drug for LT patients, demonstrating acceptable adverse events profile (with advantage to SIR), a significant improvement in renal function in general but particularly in patients with kidney dysfunction. Although we did note an increase in dyslipidemia and hypertension, these metabolic abnormalities were well controlled with proper medical treatment. Following prospective data collection will help us to define a preferable treatment protocol.



Picture 3: Initiation of treatment for metabolic complications.

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