Real-world experience of mTOR inhibitors in liver transplant recipients in a region where living donation is predominant

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1 Introduction

Mammalian target of rapamycin (mTOR) inhibitors, such as everolimus and sirolimus, may be efficacious in preserving renal function in liver transplantation (LT) recipients while preventing hepatocellular carcinoma (HCC) recurrence.

2 Aim

To evaluate the safety, efficacy, and reno-protective effects of mTOR inhibitors in liver transplant recipients with HCC in a real-world setting

3 Method

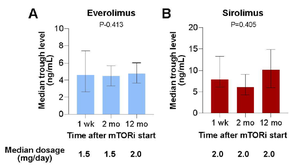
This retrospective observational study initially screened 500 patients who underwent LT at Seoul St. Mary's Hospital between November 2012 and October 2020. And 84 patients received everolimus or sirolimus as immunosuppressants. Median observational period was 1,016 days. Among these, 62 LT recipients had HCC before LT.

4 Results

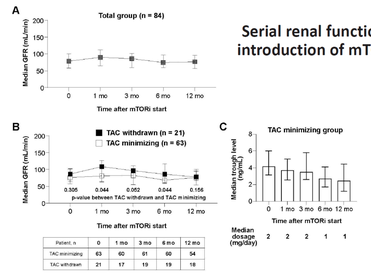
Variables	All patients n = 84	Everolimus group n = 71
Male gender	70 (83.3)	59 (83.1)
Age, years	55.7 ± 8.6	55.5 ± 8.8
Underlying liver disease		
HBV	54 (64.3)	43 (60.6)
HCV	6 (7.1)	4 (5.6)
Alcohol	15 (17.9)	15 (21.1)
Others	9 (10.7)	9 (12.7)
HCC at explant liver	62 (73.8)	49 (69.0)
LDLT	72 (85.7)	60 (84.5)
ABO incompatible LT	14 (16.7)	12 (16.9)
Laboratory findings at the time of LT		
Creatinine, mg/dL	0.8 (0.7-1.0)	0.9 (0.7-1.0)
GFR, mL/min	90.9 (77.8-104.0)	90.0 (70.5-103.0)
Total bilirubin, mg/dL	1.5 (0.7-4.0)	1.8 (0.7-4.5)
INR	1.3 (1.2-1.7)	1.3 (1.2-1.8)
MELD	9.4 (4.3-16.7)	10.1 (5.0-17.3)
Basiliximab induction	72 (85.7)	61 (85.9)
Types of immunosuppressants 6 month after LT		
Tacrolimus	78 (92.9)	69 (97.2)
mTOR inhibitor	23 (27.4)	18 (25.4)
Steroids	8 (9.5)	8 (11.3)
MMF	35 (41.7)	29 (40.8)
Time to conversion to mTOR inhibitor, months		
0-3 (early), median	10 (11.9)	9 (12.7)
4-12 (mid), median	40 (47.6)	31 (43.7)
>12 (late), median	34 (40.5)	31 (43.7)
Duration of mTOR inhibitor maintenance, days	344 0 (146.5-528.5)	449 (162.5-549.5)
Reason for mTOR inhibitor start		
Impaired renal function	17 (20.2)	16 (22.5)
Non-hepatic de novo cancers	7 (8.3)	7 (9.9)
Prevention of HCC recurrence	22 (26.2)	22 (31.0)
Presence of HCC recurrence	23 (27.4)	11 (15.5)
Intolerance to other immunosuppressants	10 (11.9)	10 (14.1)
Others	5 (6.0)	5 (7.0)
Types of mTOR inhibitor		
Everolimus	71 (84.5)	71 (100.0)
Sirolimus	13 (15.5)	0 (0)
CKD		
Stage 1, 2	61 (72.6)	48 (67.6)
Stage 3	16 (19.0)	16 (22.5)
Stage 4	5 (6.0)	5 (7.0)
Stage 5	2 (2.4)	2 (2.8)
Concomitant immunosuppressants with mTOR inhibitor		
Tacrolimus	63 (75.0)	60 (84.5)
Steroids	6 (7.1)	6 (8.5)
MMF	17 (20.2)	13 (18.3)
Adverse events by mTOR inhibitor use (within 2 months)		
Anemia	3 (3.0)	2 (2.8)
Leukopenia	5 (6.0)	5 (7.0)
Thrombocytopenia	6 (7.1)	5 (7.0)
Aminotransferase elevation	7 (8.3)	5 (7.0)
Proteinuria	10 (11.9)	8 (11.3)
Mouth ulceration	5 (6.0)	3 (4.2)
GI trouble	8 (6.5)	5 (7.0)
BPCR after mTOoR inhibitor	8 (6.5)	7 (9.9)
Death	22 (26.2)	15 (21.1)
Cause of death		
HCC recurrence	11 (55.0)	6 (40.0)
Liver failure	4 (20.0)	4 (26.7)
Infection	4 (20.0)	4 (26.7)
Other	1 (5.0)	1 (6.7)

Data are given as n (%) or median (IQR). HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; LT, liver transplantation; GFR, glomerular filtration rate; INR, international normalized ratio; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; CKD, chronic kidney disease; GI, gastrointestinal; BPCR, biopsy-proven cellular rejection; HCC, hepatocellular carcinoma.

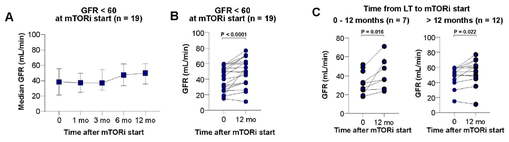
Trough levels after the introduction of everolimus (A) and sirolimus (B)



Serial renal functions after the introduction of mTOR inhibitors



Serial renal functions in CKD patients after the introduction of mTOR inhibitors



5 Conclusions

- This study demonstrated the safety, efficacy, and reno-protective effects of mTOR inhibitors in LT recipients with HCC.
- This is the first real-world report of mTOR inhibitor application in Korea, where HBV infection is the principal cause of HCC and LDLT is predominant.
- The rejection rate in our cohort was low because 75% of patients maintained a low dose of TAC after mTOR inhibitor initiation and 20% of patients maintained a low dose of MMF.
- Many patients received mTOR inhibitors 3 months after transplantation (88%), and 40% of the patients started mTOR inhibitors over 12 months after transplantation in our study.
- Renal function was analyzed according to the presence or absence of CKD at the time of mTOR inhibitor initiation, and a significant improvement in renal function was noted in the CKD group after 12 months of mTOR inhibitor use.
- Future prospective studies comprising patients with or without mTOR inhibitors will elucidate the blood levels and the role of mTOR inhibitors in rescuing renal function and prolonging recurrence-free survival and overall survival in LT patients.

6 Acknowledgements

This research was supported by the Research Fund of Seoul St. Mary's Hospital.

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