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Opinion

Safety of Everolimus in Living Donor Liver Transplant Recipients: Busting the Myth of Hepatic Artery Thrombosis with mTOR Inhibitor Use

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In our previously published study, we concluded the safety of everolimus (EVR) in early stage after living donor liver transplantation (LDLT) [1]. In this large scale study, we have analysed the long term effects of EVR and tacrolimus (TAC) combined primary immunosuppression on graft functions, renal functions and hepatocellular carcinoma recurrence (HCC). In our earlier study, none of the studied recipients developed hepatic arterial thrombosis (HAT).

From January 2012 till October 2014, 215 recipients that underwent LDLT received TAC-EVR based primary immunosuppression within 1st month of transplantation (4th to 20th day after transplant) with minimum 2 months of follow up were included in study cohort. A subgroup HCC patients (n = 30) with follow up of 2 years or more was also studied for the recurrence of HCC. The mean age of cohort (n = 215, M:F, 166:49) was 54.01 ± 10.17 (range, 2 - 73 years). The average EVR dose was 1.09 ± 0.20 mg with a trough level 3.47 ± 1.53 ng/ml (range, 1.5 - 11.2) at the end of 3 months. None of the patients suffered from hepatic artery thrombosis and/or wound dehiscence. Acute rejection episodes based on laboratory data and clinical suspicion needing steroid administration occurred in 5 recipients. The mean serum creatinine at 1 month, 6 months and 1 year was 1.26 ± 0.81 mg/dl, 1.40 ± 1.08 mg/dl and 1.42 ± 1.01 mg/dl, respectively. Renal dysfunction was present in 35 patients before transplantation. In recipients without end-stage-renal disease (n = 8), renal functions improved in 48.18% (n = 13) of patients while remained stable in 25.92% of patients (n = 7). However, 7 patients showed further deterioration of their renal functions. New onset renal dysfunction occurred in 6.97% (15/215) of the recipients during the follow up. In HCC cohort (n = 30), at median 30 months of follow up, the HCC recurrence was 16.66% (3/18) for patients within UCSF criteria while for beyond UCSF, it was found to be 50% (6/12).

Although, earlier studied shows correlation of the mammalian target of rapamycin (mTOR) inhibitor use and HAT in liver transplant recipients, we did not find any such association. In this large-scale study of 215 sequential recipients, we did not encounter HAT and incisional hernia. Hence, we state that the occurrence of HAT is more related to surgical technique of HA reconstruction than secondary to any drug treatment. The occurrence of wound infection was same as that of non-EVR group. Recent studies have demonstrated the efficacy of EVR in de novo and maintenance liver transplant recipients [2,3]. Although, few studies showed increased incidence of incisional hernia when EVR was introduced within 10 days, the difference of wound infection and incisional hernia were not significant in EVR and non-EVR group [4]. The recent reports regarding EVR related complications in liver transplant recipients are overall observation in a particular time period. To associate EVR as a causative factor, the incidence of incisional hernia or HAT in pre-EVR era should be investigated. As HAT is often due to intimal dissection, multiple attempts of HA anastomosis or poor caliber of HA secondary to pre-transplant transarterial chemoembolization, mere EVR administration should not be considered as a risk factor. In our large scale study, the early usage of EVR in LDLT was safe without risk of hepatic arterial thrombosis with stable graft functions and has positive impact on renal function improvement. Overall, the incidence of HAT at our institute is 1.36% [9/659 (unpublished data)].

The effect of EVR-reduced TAC combination on the renal functions has been reported in our earlier study [1]. In this study the renal functions improved in 48% of the recipients with prior renal failure. Fischer., *et al.* demonstrated that an early conversion from a CNI-based to an EVR-based regimen can be achieved safely, with beneficial effects on renal function [5]. However, proteinuria can be significant adverse effect that may lead to discontinuation of the EVR. Although, the incidence of significant proteinuria is low overall, it was higher in the EVR plus reduced TAC group than in the standard TAC group (3.7% vs 0.8%, respectively; P = 0.063) and proteinuria was the leading cause of study drug discontinuation (eight vs one patient). However, in our study significant proteinuria was nil.

The important finding of our study was the impact of EVR based primary immunosuppression in reducing the recurrence of the HCC. In this ongoing retrospective and prospective study, the subgroup of HCC patients is being investigated for the HCC recurrence in EVR and non-EVR group. For the recipients within UCSF criteria in HCC subgroup of this study, at median follow up of 30 months the recurrence of HCC was significantly reduced. As TAC has a minimal effect on EVR blood levels, TAC and EVR combination as primary immunosuppression has potential beneficial effect on the patients with pre-transplant renal dysfunction as well as reducing TAC with EVR may have impact on the HCC recurrence reduction in post-transplant period.

1.	Age	Was 54.01 ± 10.17 (range, 2-73 years)
2.	M:F	166:49
3.	EVR dose	1.00 ± 025 mg/day
4.	EVR trough level at 3 months	3.47 ± 1.53 ng/m1 (range, 1.5-11.2)
5.	Tacrolimus trough levels	6.97 ± 3.98 ng/ml (range, 2.50 to 11.28 ng/ml)
6.	Liver functions AST ALT Total Bilirubin	 48.62 ± 62.96 IU/ml 48.23 ± 61.08 IU/ml 0.75 ± 0.65 mg/d1
7.	HCC cohort excluding the patients with major portal vein tumour thrombus Overall survival at mean follow-up of 28 months (25 months-33 months) Within UCSF criteria Beyond UCSF criteria	n = 24 (6 recipients were excluded from the cohort of 30) 87.50% (21/24) 93.33% (15/16) 75.00% (6/8)

Table 1: *Recipient characteristics, drug levels and HCC recurrence statistics*

In conclusion, the early conversion to EVR based immunosuppression was safe in LDLT recipients with a significant role in renal function improvement. There was no HAT occurrence in sequential 215 recipients proves the safety of EVR even in early phase after LDLT. The possible positive impact of EVR on HCC recurrence in post-transplant period is continued to be investigated in our ongoing study.

Conflicts of Interest

No conflicts of interest.

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