Safety and Efficacy of Everolimus Rescue Treatment After Pediatric Living Donor Liver Transplantation

Abstract

Purpose

Everolimus (EVR) is a derivative of sirolimus with a similar mechanism of action. The safety and efficacy of EVR after pediatric living donor liver transplantation (LDLT) are currently unknown. The purpose of this study was to examine the safety and efficacy of EVR as rescue therapy after pediatric LDLT.

Methods

Patients younger than 19 years of age who received EVR after LDLT at our institution were included. EVR was administered as rescue treatment in addition to tacrolimus. In 21 patients, EVR dose, trough level, outcomes, and adverse effects were assessed.

Results

Original diseases of patients consisted of biliary atresia (n=11), Alagille syndrome (n=3), fulminant hepatitis (n=3), hepatoblastoma (n=2), and other (n=2). Mean age at transplant was 2.0 years (range, 0.6–6.2 years). Mean age at initial EVR administration was 8.0 years (range, 0.9–18.9 years). Indications for EVR use were graft fibrosis (n=8), refractory acute cellular rejection (n=5), renal sparing (n=4), hepatoblastoma (n=2), and chronic rejection (CR) (n=2). Mean duration of

administration was 17.1 months (range, 2.1–60.4 months). Mean dose was 0.5 mg/m^2 twice daily. Mean EVR trough level was 2.5 ng/mL (range, 1.5–5.0 ng/mL). Liver function improved and fibrosis did not progress in all patients with CR. However, 14 patients (67%) experienced adverse effects that required EVR dose reduction or discontinuation.

Conclusion

EVR is tolerable for pediatric patients after LDLT with dose adjustment. EVR had a certain effect on CR. Further follow-up is required.

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Introduction

Everolimus (EVR) is a derivative of sirolimus (SRL) and has a similar mechanism of action. EVR is an inhibitor of mammalian target of rapamycin (mTOR). SRL is a macrocyclic triene antibiotic initially found to have antifungal properties but also acts as a primary immunosuppressant or antitumor agent.

Chronic renal failure has been reported after pediatric liver transplantation [1]. Children also face longer exposure to calcineurin inhibitors (CNI) than adults, suggesting that they are at higher risk for long-term complications including diabetes [2], hypertension [3], and malignancy [4].

EVR can facilitate reduced use of CNIs in pediatric liver transplant patients. In a similar fashion to other mTOR inhibitors, EVR be renal sparing, have anti-cancer effects, and prevent fibrosis. In addition, mTOR inhibitors may prevent graft fibrosis, which may delay chronic rejection (CR) progression [5].

The safety and efficacy of EVR after pediatric living donor liver transplantation (LDLT) are currently unknown although adult use of EVR has been reported[6]. The purpose of this study was to examine the safety and efficacy of EVR as rescue therapy after pediatric LDLT.

Methods

Patients younger than 19 years of age who received EVR after LDLT at our institution were included. Prior to starting EVR, patients received standard tacrolimus (TAC)-based immunosuppression with a steroid taper at our institution. No patients were withdrawn from immunosuppressive therapy. EVR was administered to children as a rescue treatment in addition to TAC.

Oral EVR was started at 0.125 mg twice daily. The dose of EVR was increased until a target trough level of >3 ng/mL based on previous report [7]. EVR dose, trough level, outcomes, and adverse effects were assessed. Renal function was assessed based on serum cystatin C levels. Graft fibrosis was assessed using the METAVIR system with a per-protocol liver biopsy. METAVIR grade F2 or higher was considered graft fibrosis.

Data were analyzed using the JMP version 11 software package (SAS, Cary, NC, USA). Continuous variables are presented as medians with ranges and compared using Student's t-test. Linear regression was performed. A *P* value less than .05 was considered to be statistically significant.

Results

The study included 21 patients, consisting of 14 female patients and 7 male patients. Original diseases consisted of biliary atresia (n=11), Alagille syndrome (n=3), fulminant hepatitis (n=3),

hepatoblastoma (n=2), and other (n=2). Mean age at transplant was 2.0 years (range, 0.6–6.2 years). Mean body weight was 25 kg (range, 8.0–53 kg).

Indications for EVR were graft fibrosis (n=8), refractory acute cellular rejection (ACR) (n=5), renal sparing (n=4), hepatoblastoma (n=2), and CR (n=2). Mean EVR therapy duration was 17.1 months (range, 2.1–60.4 months). Mean age at initial EVR administration was 8.0 years (range, 0.9–18.9 years). Mean duration from LDLT to initial EVR administration was 53 months (range, 1.2–104 months). Immunosuppressive agents used concurrently with EVR were TAC (n=14), TAC and a steroid (n=6), and none (n=1). Target TAC trough levels were 0–2 ng/mL (n=3), 2–3 ng/mL (n=3), 3–5 ng/mL (n=9), and over 5 mg/mL (n=5).

Final mean EVR dose was 0.4 mg (range, 0.2–0.8 mg) twice daily. Final mean EVR trough level was 2.4 ng/mL (range, 1.5–4.7 ng/mL) during EVR therapy. The relationship between EVR dose and EVR trough level is plotted in **Fig 1.** The EVR dose for a target trough level of 3 ng/mL was 0.035 mg/kg or 0.8 mg/m^2 calculated from regression line.

Serum cystatin C levels improved from 1.19 mg/L before EVR administration to 1.12 mg/L after EVR administration (*P*=.031) in renal sparing patients without Alagille syndrome (n=4). Liver function improved and fibrosis remain stable in all patients with CR. Recurrent ACR was not observed in patients with a history of refractory ACR. Hepatitis did not recur in patients with a history of fulminant hepatitis. No progression of graft fibrosis occurred in patients with a history of

graft fibrosis.

However, 14 patients (67%) experienced adverse effects that required EVR dose reduction or discontinuation. In particular, oral ulceration (n=8) was common. Hyperlipidemia, enterocolitis, dermatitis, bacteremia, hand-foot syndrome, and Epstein–Barr virus infection were observed in one patient respectively. All adverse effects were disappeared after EVR was withdrawn.

Discussion

In 2006, Levy et al reported the safety and tolerability of EVR in adult patients [8]. However, few papers on the use of EVR in pediatric liver transplantation have been published. Studies in adult solid organ recipients showed that mTOR inhibitors act synergistically with CNIs, offering an opportunity to reduce CNI exposure and potentially prevent CNI-related toxicity [9]. Use of mTOR inhibitors as maintenance immunosuppression, which have antitumor effects, has been reported to be associated with a significantly lower risk of developing any posttransplant malignancy [10, 11]. They may also prevent graft fibrosis, which may delay CR progression [12, 13].

Posttransplant renal dysfunction is a frequent and important outcome for adults and children. Minimization of CNI exposure is considered a viable strategy for preserving renal function [1]. The literature on improvements in renal function with conversion to EVR in pediatric patients with liver transplants is sparse, but several studies have suggested improved renal

function in patients after pediatric renal transplantation. In a multicenter study, early introduction of EVR with reduced CNI use was associated with clinically relevant improvement in renal function [14]. Our data also showed improvement in renal function. In any liver transplant recipient with significant declines in renal function, we should consider conversion to EVR to help protect renal function.

EVR has proven efficacy against breast cancer, renal cell carcinoma, neuroendocrine tumors, and subependymal giant cell astrocytoma [15]. There are no data about the effect of EVR on de novo hepatocellular carcinoma (HCC). In a systematic review, liver transplant recipients taking mTOR inhibitors had lower rates of HCC recurrence [16].

SRL has been reported to have antiproliferative properties, specifically against hepatoblastoma both in vitro and in vivo [17]. Early conversion from TAC to EVR may have the same effect on tumors in pediatric liver transplant recipients. However, in our study the observation period was insufficient to evaluate for protection from recurrence. Most patients with hepatoblastoma have renal insufficiency because of previous chemotherapy containing cisplatin. Regarding renal sparing, EVR is beneficial in patients with hepatoblastoma.

Nielsen et al reported using EVR as rescue therapy in pediatric liver transplant recipients with chronic graft dysfunction; they reported that 4 of 12 patients with chronic graft dysfunction had completely normalized liver function tests after EVR therapy [5]. We reported 2 patients who

received EVR for CR. Since liver function was improved and fibrosis did not progress, EVR was considered effective against CR [18].

Graschow et al performed a multicenter, prospective study on EVR. In their study, adverse events suspected to be related to EVR were reported in 40 patients (71.4%). The most frequent adverse events were pyrexia (n=7), oral ulceration (n=7), Epstein-Barr viremia (n=6), pneumonia (n=5), and diarrhea (n=5) [14]. Nielsen et al reported that the typical side effects of EVR occurred in pediatric patients with liver transplants, namely severe and persistent ulcerative lesions in the mouth, leading to discontinuation of the drug after 12 weeks [5]. In our study, oral ulceration was the most common adverse effect, which resulted in the EVR trough level not being increased over 3 ng/mL. Our patients also experienced ulcerative lesions and hypercholesterolemia that resolved following reductions in EVR dose and administration of pravastatin.

Our study limitation was the small sample size. In addition, the timing of conversion from TAC to EVR therapy was variable in our group, ranging from 1.2 to 104 months after transplantation. Standardization of these treatments would improve the generalizability of these findings. An additional limitation is that there was only short‐term follow-up after conversion to EVR therapy. We plan to continue to follow these patients and evaluate outcomes such as graft fibrosis and hepatoblastoma recurrence; some patients are only a year out from transplantation.

Conclusions

EVR is tolerable for pediatric patients after LDLT with dose adjustment. EVR had a certain effect on CR. Further follow-up is required.

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