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Title	Everolimus Rescue Treatment for Chronic Rejection After Pediatric Living Donor Liver Transplantation: 2 Case Reports
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Abstract:

Everolimus rescue treatment for chronic rejection after pediatric living donor liver transplantation: Two case reports

Chronic rejection (CR) remains a challenging complication after liver transplantation. Everolimus, which is a mammalian target of rapamycin inhibitor, has an anti-fibrosis effect. We report here the effect of everolimus on CR. [Case 1] A 7-year-old girl underwent living donor liver transplantation (LDLT) shortly after developing fulminant hepatitis at 10 months of age. Liver function tests (LFTs) did not improve after transplantation despite treatment with tacrolimus + mycophenolate mofetil (MMF). Antithymoglobulin (ATG) and steroid pulse therapy were also ineffective. The patient was diagnosed with CR, and everolimus was started with a target trough level of about 5 ng/mL. LFTs improved and pathological examination showed no progression of hepatic fibrosis. [Case 2] A 10-year-old girl with Alagille syndrome underwent LDLT at 1 year of age. She had biopsy-proven acute cellular rejection with prolonged LFT abnormalities beginning 3 years after transplantation. She was treated with steroid pulse therapy, followed by MMF, tacrolimus, and prednisolone. Her condition did not improve, even after subsequent ATG administration. CR was suspected based on liver biopsy in the fourth postoperative year, and everolimus was introduced. The target trough level was around 5 ng/mL, but was reduced to 3 ng/mL due to stomatitis. Four

years have passed since the initiation of everolimus, and LFTs are stable with no progression of liver biopsy fibrosis. We describe two cases in which everolimus was administered for CR. In both cases, LFTs improved and fibrosis did not progress, suggesting that everolimus is an effective treatment for CR after LDLT.

Everolimus rescue treatment for chronic rejection after pediatric living donor liver transplantation: Two case reports

Introduction

Although the prognosis of pediatric living donor liver transplantation (LDLT) is relatively good, chronic rejection (CR) is still a challenging complication. Although acute cellular rejection (ACR) after LDLT is curable with high-dose steroid pulse therapy, there is no effective treatment against CR mediated by humoral immunity. Most patients with CR develop graft failure and subsequently require re-transplantation.

Tacrolimus-based protocols for CR have been used and tend to offer only minimal relief. Mycophenolate mofetil (MMF) combined with tacrolimus was previously used as a treatment for CR in patients with low serum bilirubin levels.[1] Immunosuppression for CR is currently under exploration.

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is a derivative of sirolimus with a similar mechanism of action, and both demonstrate an anti-fibrosis effect. Sirolimus is a macrocyclic triene antibiotic that was initially found to have antifungal properties but also may act as a primary immune suppressant or antitumor agent. It is currently used as an immunosuppressant to prevent rejection of renal and cardiac transplants in Japan.

The safety and benefit of mTOR inhibitors for CR are currently unknown. Calcineurin inhibitors (CNIs) are structurally similar to sirolimus but have different side-effect profiles and modes of action. Tacrolimus and cyclosporine, common immunosuppressive agents, inhibit calcium-dependent T-cell activation.[2] In contrast, mTOR inhibitors act on B cells independently of their effects on helper T cells, resulting in inhibition of antigen- and cytokine-driven B cell proliferation.[3]

Here we report the effect of everolimus as a rescue treatment for CR in pediatric LDLT.

Case reports

[Case 1] The patient is a 7-year-old girl who was healthy until the age of 10 months, when she developed jaundice, coagulopathy, and encephalopathy. She was diagnosed with fulminant hepatitis of unknown origin, and LDLT was performed 2 weeks later, with her mother serving as the donor. Immunosuppression was initiated with tacrolimus, prednisolone, and mizoribine. Frequent episodes of ACR occurred beginning at the fourth month after LDLT. Abnormal liver function tests (LFTs) and coagulopathy developed at 3 years after LDLT and liver biopsy confirmed ACR. Steroid pulse therapy with 20 mg/kg methylprednisolone was performed. However, LFTs did not improve and liver biopsy

confirmed refractory ACR. Rabbit anti-thymocyte globulin (rATG) administered at 1.5 mg/kg was followed by steroid pulse therapy for a total of 7 days. However, these treatments were ineffective, and the patient's total bilirubin (TB) level increased to 40 mg/dl. Liver biopsy showed complement component 4d (C4d) deposition on the vascular endothelium of the graft. Serum levels of donor-specific antibody (DSA) were elevated. The mean fluorescence intensity of DSA showed titers over 10000 for DQ 5, DQ6, DQ8, and DQ9. The patient was diagnosed with CR based on DSA and C4d positivity. Everolimus was therefore initiated in addition to tacrolimus and prednisolone, with a target trough level of about 5 ng/mL. The target tacrolimus trough level was around 5 ng/mL. Oral prednisolone was decreased to 1 mg/day. Although re-transplantation was considered at the time of everolimus introduction, the patient's LFTs gradually improved. Twenty-four months after the introduction of everolimus, alanine aminotransferase (ALT) levels decreased to 100 IU/L or less, TB to 2 mg/dl or less, and pathological examination showed no progression of hepatic fibrosis. The only adverse effect of everolimus was hyperlipidemia, with a total cholesterol level over 300 mg/dl. The patient required treatment with pravastatin, and the everolimus trough level was decreased to between 3 and 5 ng/mL. A summary of the patient's course is shown in Fig. 1. Liver biopsy findings are shown in Fig. 2.

[Case 2] The patient is a 10-year-old girl who underwent LDLT at 1 year of age for

severe pruritus associated with Alagille syndrome. Her mother served as the donor. She developed biopsy-proven ACR with prolonged LFT abnormalities beginning 3 years after LDLT. Steroid pulse therapy was performed with 20 mg/kg of methylprednisolone, and subsequently MMF was administered along with tacrolimus and prednisolone. The patient then received ATG at 1.5 mg/kg/day for 7 days, but none of these treatments improved her LFTs or liver biopsy findings. In the fourth postoperative year, CR was suspected because of ductopenia on liver biopsy. Everolimus was therefore introduced and the patient continued receiving tacrolimus and prednisolone. The target trough level of everolimus was around 5 ng/mL, but it was reduced to 3 ng/mL due to stomatitis. Four years have passed since the initiation of everolimus, and ALT levels have remained below 60 IU/L. There has been no progression of fibrosis and restoration of bile ducts has been observed on liver biopsy. A summary of the patient's course is shown in Fig. 3. Liver biopsy findings are shown in Fig. 4.

Discussion

The prevalence of CR in liver transplant recipients is less than about 5%, however the pathogenesis of CR is poorly understood. Current strategies for CR treatment following liver transplantation come from experience with renal transplants.[4] Current treatments are specifically aimed at suppressing immune system-mediated damage to hepatocytes and

bile ducts in order to preserve bile ducts and prevent graft fibrosis. Achieving therapeutic levels of CNIs may theoretically stabilize bile duct damage and prevent further progression of fibrosis. However, immunosuppressive therapies based on CNIs are usually ineffective for CR.[4]

In 2006, Levy et al. reported the safety and tolerability of everolimus in adult patients.[5] However, few papers have been published on the use of everolimus in pediatric liver transplantation. Studies in adult recipients of solid organ grafts showed that mTOR inhibitors act synergistically with CNIs, offering an opportunity to lower CNI exposure and potentially prevent CNI-related toxicity.[6] mTOR inhibitors have antitumor effects, and their use for maintenance immunosuppression has been reported to be associated with a significantly reduced risk of developing any posttransplant malignancy.[7, 8] mTOR inhibitors may also prevent graft fibrosis, which may delay CR progression.[9, 10]

Everolimus is a hydroxyethyl derivative of sirolimus that is more hydrophilic than the parent drug and therefore has greater oral absorption. Everolimus is rapidly absorbed and reaches a peak blood level after about 2 h. Its half-life is shorter than that of sirolimus, and oral dosing is adjusted to target a blood level between 3 and 12 ng/mL.

Nielsen et al. reported using everolimus as rescue therapy in pediatric liver transplant recipients with chronic graft dysfunction, suspected CNI toxicity, hepatoblastoma,

and recurrence of primary sclerosing cholangitis. Four out of 12 patients with chronic graft dysfunction demonstrated completely normalized LFTs following everolimus therapy, while six patients exhibited partial improvement and two showed no response. One patient with CNI-induced nephropathy showed slightly improved renal function. The first study evaluating the use of everolimus in pediatric liver transplant recipients showed promising results in cases of chronic graft failure when standard immunosuppression had failed.[11]

Sinke et. al. added sirolimus at a dose of 1.0 mg/d to a cyclosporine-based regimen in CR pediatric LDLT patients. LFTs, including TB, were successfully decreased. They concluded that sirolimus in combination with cyclosporine may be an effective treatment for CR after liver transplantation.[12] The current study showed that everolimus used with a tacrolimus-based regimen may be similarly effective in pediatric LDLT patients with CR.

Nielsen et al. reported that the typical side effects of everolimus occurred in pediatric LDLT patients, namely severe and persistent ulcerative lesions in the mouth, leading to discontinuation of the drug after 12 weeks. No viral inclusions or positive viral serologies were identified. Two patients developed hypercholesterolemia and an increase in serum triglycerides. However, it remains unclear if chronic graft failure or everolimus was responsible for these findings. Our patients also experienced ulcerative lesions and hypercholesterolemia, which resolved following reductions in everolimus levels and

administration of pravastatin. However, other published side effects must be taken into account when administering everolimus to children and adolescents, namely nausea and diarrhea, hematologic changes, and impaired fertility.[5, 6]

The lowest effective everolimus level is still undetermined. Sinke et al. set the target trough levels of sirolimus and cyclosporine to around 15 ng/mL and 180 ng/mL, respectively.[12] Nielsen et al. aimed for everolimus target trough levels of between 4 and 6 ng/mL, in combination with reduced tacrolimus trough levels of between 4 and 6 ng/mL.[11] In our experience, everolimus trough levels over 5 ng/mL cause adverse effects. We therefore targeted everolimus trough levels of 3 to 5 ng/mL combined with tacrolimus trough levels of around 5 ng/mL. Dosing of everolimus and CNI was based on data from de novo renal trials, and additional studies in children are required to determine appropriate dosing regimens.

Further studies are needed to assess the role of everolimus in preventing graft failure when the drug is included in immunosuppressive protocols for pediatric liver transplant recipients suffering from CR.

Conclusions

We report two patients who received everolimus for CR. Since LFTs improved and fibrosis did not progress, it was concluded that everolimus was effective against CR.

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