



A Review on the Roles of mTOR Inhibitors in Pediatric Liver Transplant Recipients

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Background

- Immunosuppressive medications play a crucial role in determining both organ and patient survival following liver transplantation (LT).
- Inhibitors of mammalian target of rapamycin (mTOR) have demonstrated beneficial outcomes in adult LT recipients; However, their application in pediatric liver transplant recipients is a matter of debate due to uncertain efficacy and potential adverse effects.

Objectives:

• This review evaluates the potential roles of mTOR inhibitors in the context of pediatric LT patients.

Methods:

• This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Databases were searched until August 31, 2023. All clinical studies focusing on mTOR inhibitors in pediatric LT were included.

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Of 888 identified articles, 30 studies involving 386 children met the inclusion criteria.

Beneficial impacts of switching from CNI to mTOR inhibitor or adding mTOR inhibitor to CNI-reduced immunosuppression in LT pediatrics with impaired kidney function is controversial.

Results

It appears that enhancing the immunosuppression through the addition of an mTOR inhibitor to CNI is helpful for pediatric LT recipients who are experiencing refractory acute rejection or chronic rejection.

Implementary methods in the second second

The effectiveness of mTOR inhibitors in treating PTLD remains uncertain, however, in patients with PTLD who are at high risk of rejection, mTOR inhibitors may be administered.

Conversion to or adding mTOR inhibitors to maintenance immunosuppression seems to be suitable for pediatrics who are transplanted due to hepatic malignancies such as hepatoblastoma or hepatocellular carcinoma or for those with post-transplant primary or recurrent malignancies.

Switching to mTOR inhibitor may improve some CNI-related adverse effects such as gingival hyperplasia, neurotoxicity, nephropathy, hypertrophic cardiomyopathy, or thrombotic microangiopathy.

Results

Conclusion

Two algorithms are presented to guide converting from CNIs to mTOR inhibitors (Fig 1) or adding mTOR inhibitor to a CNI-minimization immunosuppressive regimen (Fig 2) for pediatrics that may benefit this class of drugs.

Figure 1.

Conversion from CNI to mTOR inhibitor

This intervention is likely to benefit the following patients:

- CNI-induced nephrotoxicity

- Pre-existing malignancies or PTLD

- Intolerable side-effects with CNI

-Start a mTOR inhibitor (EVL or SRL):

- EVL: 0.8-2 mg/m²/dose twice a day (maximum 1.5 mg per dose). Patients receiving Tac may require higher doses, while patients receiving CsA may require lower doses of EVL based on body surface area
- SRL: 1 mg/m²/day in one or two divided doses. If used simultaneously with CsA, administer SRL 4 hours after taking CsA

- 25% reduction of CNI dose

- Check the blood trough level of SRL 5-7 days and EVL 4-5 days after commencing or adjusting the dose

- Once the target blood level of mTOR inhibitor is achieved, discontinue CNI

mTOR inhibitor target trough level:

- 2nd and 3rd month: 8-10 ng/mL
- 4th to 12th month: 6-8 ng/mL
- > 12 months: 4-6 ng/mL

• It is not recommended to initiate mTOR inhibitor for the patient within the first month after transplantation.

- Tacrolimus target blood levels may var depending on individual center protocol, the patient's immunologic status, and the time elapsed since transplantation.
- · Depending on the patient's condition, mycophenolate can be continued if the patient is using it.
- The decision to use corticosteroids should be based on the time elapsed after transplantation, underlying disease led to transplantation, or the occurrence of rejection episodes, as per the center's standard protocol.

CNI: Calcineurin inhibitor CsA: Cyclosporin EVL: Everolimus PTLD: Post transplant lymphoproliferative disorder SRL: Sirolimus Tac: Tacrolimus



- It is not recommended to initiate mTOR inhibitor for the patient within the first month after transplantation. When initiating mTOR inhibitor, it is advisable to discontinue mycophenolate for the patient. The decision to use corticosteroids should be based on the time elapsed after transplant, underlying disease
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 For patients with a history of malignancies or post-transplant malignancies, it is recommended to maintain the trough level of mTOR inhibitor and CNI close to the lower limit of target levels. CNI: Calcineurin inhibitor CsA: Cyclosporin EVL: Everolimus PTLD: Post transplant lymphoproliferative disorder SRL: Sirolimus Tac: Tacrolimus

Limitations

 This review mainly consisted of retrospective studies with inadequate sample sizes and lack of control group.

Future Research

• Clinical trials with suitable sample sizes are necessary to determine the exact effects of mTOR inhibitors in pediatric LT recipients.

Publication:

 This research has been accepted for publication in: Pediatric Drugs; 2024. 10.1007/s40272-024-00648-4