mTOR Inhibitors in Liver Transplantation

Kwang-Woong Lee

The m-TOR is an evolutionarily conserved PI3-kinase family member that plays a key role in integrating different biochemical and growth factor signals, including amino acids, glucose, ATP, and insulin. There are two types of m-TOR inhibitors (m-TORi), Rapamycin (Sirolimus, SRL) and Everolimus (EVRL) in clinical setting. m-TORi continue to be explored as immunosuppressive drugs in allogeneic transplantation and as novel anticancer agents.

It has several potential advantages in liver transplantation (LT), especially in HCC. It has also rationale for selective use in other situations in LT, e.g. HCV or renal dysfunction (1).

In this review, the impact of m-TORi in LTx will be introduced.

Mammalian target of rapamycin (m-TOR) inhibitors and the effect on immunity

m-TOR is a key signaling kinase that affects broad aspects of cellular functions, including metabolism, growth, survival, aging, synaptic plasticity, and memory. Rapamycin engages FK506-binding protein 1A, 12 kDa (FKBP12); the complex engages and inhibits TOR but not calcineurin, thereby blocking cell cycle progression at the G1 to S phase, causing inhibition of T cell.

In addition to the regulating effects of m-TOR in dividing cells, it has been recently demonstrated that m-TOR affects the innate immunity system. Inhibition of innate immunity by m-TORi affects adaptive immunity via co-stimulatory molecules and cytokine production.

Potential clinical advantages of m-TORi

1) Reduce CNI related nephrotoxicity

m-TORi may have a role in minimizing post-transplant chronic kidney disease related with CNI. It can be used in De novo fashion with low CNI or conversion fashion. The course of renal function in *de novo* liver transplantation recipients with EVRL therapy has been evaluated in an open-label, randomized multicenter phase III study (Clinical Trials.gov Identifier NCT00378014), although results are not yet available. Morard switched 48 patients to SRL a median of 19.4 months after LTx for reasons of renal impairment (78%), CNI-neurotoxicity (13%), or post-transplant cancer (9%) (2). Nineteen percent presented severe (cGFR 20–40 ml/min) and 45% moderate (40–70 ml/min) renal impairment at switch. Mean cGFR improved from 33 to 48 ml/min in patients

with severe and from 56 to 74 ml/min in patients with moderate renal impairment. Patients with a cGFR >70 ml/min did not benefit. Acute rejection occurred in 8 patients (17%) with a mean delay of 4 months; 5 out of 8 patients improved after increasing SRL trough levels to 10–15 μg/L. The authors concluded that conversion from CNI to SRL is safe and is associated with significant renal function (cGFR) improvement, but warned that SRL may worsen nephropathy (some developed severe albuminuria >500 mg/L) if patients have severe hypertension and pre-existing albuminuria.

2) Beneficial effect on recurrent HCV

SRL inhibits the m-TOR/p70S6K pathway and may reduce *in vivo* phosphorylation of NS5A phosphopeptides and therefore viral replication. This effect, however, may be dose dependent. Studies of non genotype-1 virus in cell culture which used higher doses of rapamycin (100 nM) have shown that m-TORi may increase the production of HCV core protein by inhibiting, the suppressor of cytokine signalling 3 (SOCS3) (3). However, The published evidence is mixed in respect to the impact of m-TORi on HCV.

3) Beneficial anti-cancer effect in LT for HCC

The antitumor role of m-TORi has been observed, and it ranges from stopping cellular transformation to proliferation and metastasis development. The most impressive aspect is the effect in diminish of angiogenesis because it lowers the production of VEGF which is a stimulating agent of endothelium cells. Long termed observation shows diminish in the incidence of PTLD and skin tumors and in renal transplant patients due to Kaposi tumors that receive sirolimus. According to the previous information, it appears to be that sirolimus is the best option for immunosuppressor in transplant patients due to HCC, but more complete and specifically designed long-term clinical studies are needed to come to more firm conclusions.

References

1. Kawahara T, Asthana S, Kneteman NM. m-TOR inhibitors: what role in liver transplantation? *J Hepatol* 2011; 55 (6): 1441.
2. Morard I, Dumortier J, Spahr L, et al. Conversion to sirolimus-based immunosuppression in maintenance liver transplantation patients. *Liver Transpl* 2007; 13 (5): 658.
3. Shao RX, Zhang L, Peng LF, et al. Suppressor of cytokine signaling 3 suppresses hepatitis C virus replication in an mTOR-dependent manner. *J Virol* 2010; 84 (12): 6060.