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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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## Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma

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### Abstract

The proportion of liver transplantation (LT) for hepatocellular carcinoma (HCC) has kept on increasing over the past years and account for 20%-40% of all LT. Post-transplant HCC recurrence is considered the most important factor affecting the long-term survival of patients. The use of different types of immunosuppressive agents after LT is closely associated with an increased risk for HCC recurrence. The most commonly used conventional immunosuppressive drugs include the calcineurin inhibitors tacrolimus (FK506) and mammalian target of rapamycin inhibitor rapamycin (RAPA). Compared with tacrolimus, RAPA may carry an advantage in survival benefit because of its anti-tumor effects. However, no sufficient evidence to date has proven that RAPA could increase long-term recurrence-free survival and its anti-tumor mechanism of combined therapy remains incompletely clear. In this review, we will focus on recent advances in clinical application experience and basic research results of RAPA in patients undergoing LT for HCC to further guide the clinical practice.

**Key Words:** Rapamycin; Hepatocellular carcinoma; Liver transplantation; Lenvatinib; Programmed death protein-1; Huaier granule

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**Core Tip:** Although liver transplantation (LT) is the radical method for patients with hepatocellular carcinoma (HCC), especially advanced HCC, by improving the survival benefits, the postoperative tumor recurrence seriously affects the survival of the graft and patients. The rapamycin (RAPA)-based immunosuppressive regimen has been

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recommended as a priority after LT due to its favorable survival benefits. In this paper, we describe the immune regulation and anti-tumor mechanism of RAPA, summarize the progress of RAPA transformation therapy after LT for HCC, further analyze the survival benefits of combined anticancer drugs and targeted drugs, and comb the prospect of immune checkpoint therapy such as programmed cell death protein 1, in order to provide a theoretical basis for RAPA transformation therapy after LT for HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer with a continuous increase in incidence over the past decades, and it is the third most common cause of cancer-related death worldwide and the second most prevalent cause of cancer-related death in men[1,2]. HCC has an insidious onset and rapid progression, and most patients with HCC have lost the chance of surgical resection at the time of diagnosis due to the accompanied severe liver cirrhosis and intrahepatic and extrahepatic metastasis. Liver transplantation (LT) is regarded as the most effective treatment for end-stage HCC that can completely remove the tumor and the "soil" of potentially inducing HCC such as liver cirrhosis and hepatitis B in comparison with liver resection and other treatment approaches[3]. According to data from multiple transplant centers worldwide[4], HCC is currently the main indication for LT and accounts for 20%-40% of all the LT cases, and this proportion continues to increase. Although the short-term prognosis of patients with HCC after LT is significantly improved, with a 5-year survival rate of more than 50%[5], the problem of HCC recurrence remains a serious challenge and it is associated with a dismal prognosis. Scientific selection of recipients in strict accordance with the standard of LT for HCC is an effective way to reduce the risk of HCC recurrence. Despite that physicians strictly adhere to Milan criteria and select recipients accurately, the 5-year recurrence rate of HCC after LT remains about 30%[6-8]. As known, there are several risk factors for post-LT recurrence. In addition to the primary tumor, calcineurin inhibitors (CNIs), a groups of routine immunosuppressive drugs, have been proved to be an independent risk factor for the recurrence of HCC[9]. The overuse of CNIs early after LT may block the recipient's immune system from detecting and killing residual HCC cells in the blood[10]. Therefore, it is a key issue to find an ideal treatment strategy that can inhibit rejection while minimizing the risk of HCC recurrence to improve the long-term survival of patients with HCC after LT.

To minimize the risk of post-LT recurrence caused by immunosuppressive drugs, mammalian target of rapamycin (mTOR) inhibitors have gradually attracted the attention of experts in the field of LT. mTOR inhibitor is a commonly used immunosuppressive drug with anti-tumor effects, which brings new choices to HCC transplant recipients and becomes a potential treatment strategy to solve the above issue[11]. Rapamycin (RAPA) is a first-generation mTOR inhibitor, which can not only prevent rejection, but also effectively inhibit the growth of tumor cells, and has less impact on renal function than CNIs. RAPA is presently employed as an immunosuppressant in recipients with abnormal renal function, intolerable adverse reactions of CNIs, and the high risk of post-LT recurrence, and it can provide sufficient immunosuppression while reducing the risk of recurrence, renal impairment, and infection[12]. Since 2011, our team has taken the lead in the application of RAPA conversion therapy in HCC transplant patients in China and recommended RAPA as the main immunosuppressive treatment strategy[13]. In recent years, the proportion of immunosuppressive regimens based on RAPA in HCC transplant patients has kept on increasing, but in the clinical treatment of such patients, there are still many controversies about the impact of RAPA on the survival benefits. In this review, we will focus on recent clinical and basic research on the application of RAPA in HCC

transplant patients, with the aim of summarizing existing evidence and areas for potential future study to guide the clinical application of RAPA more rationally and scientifically.

## MECHANISM AND APPLICATION OF RAPA

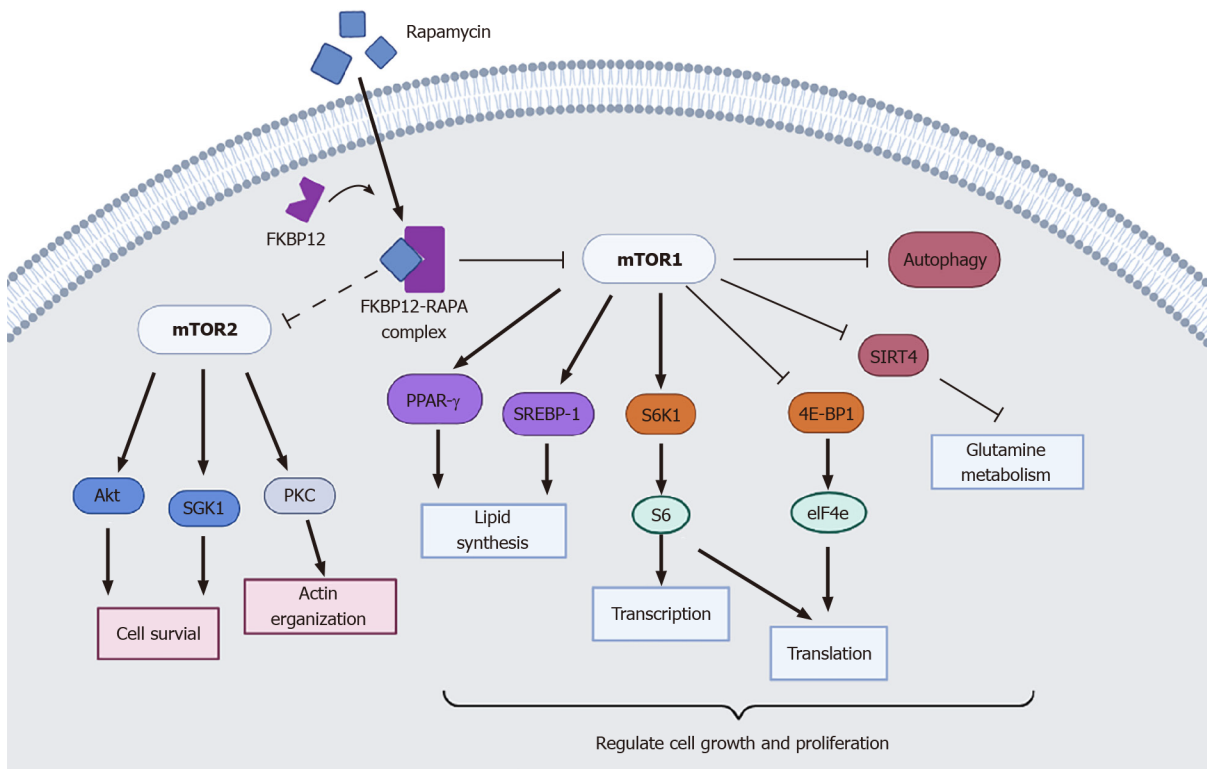
### **Development and application trends of RAPA**

RAPA is also known as sirolimus. In 1964, Canadian Wyeth Ayrest Research Institute identified an antifungal metabolite produced by *Streptomyces hygroscopicus* AYB-944 from plant and soil samples from Rapa Nui (Easter Island) in the Pacific Ocean and named it rapamycin after Rapa Nui[14]. RAPA was initially widely used as a low-toxic and powerful antifungal agent in anti-inflammatory therapy. With the in-depth study of the pharmacological properties and molecular mechanism of RAPA, it was found that RAPA is a triene macrolide immunosuppressive drug that can exert an immunosuppressive effect by inhibiting cellular immune response[15]. In 1989, Meiser *et al*[16] began to try to use RAPA as a new immunosuppressant for the treatment of rejection after organ transplantation and now RAPA has been widely used in clinical treatment. In recent years, it has been found that RAPA has anti-tumor effects, which open up a new direction for the prevention of tumor recurrence and metastasis after organ transplantation.

RAPA exerts its immunomodulatory effect mainly by inhibiting the mTOR signal pathway, and mTOR is the target of RAPA in mammals. The essence of mTOR is a serine/threonine protease that belongs to the phosphoinositide 3-kinase (PI3K) related kinase family. It plays an important role in immune homeostasis by integrating different response signals of the microenvironment in the body. The main function of mTOR is to regulate multiple key pathways associated with cell cycle development and progression, including cell growth, proliferation, and metabolism[17]. At present, it is known that mTOR mainly exists in two structurally and functionally distinct protein complexes, mTOR complex 1 (mTORC1) and mTORC2[18]. mTORC1 is sensitive to RAPA and the activation of the mTORC1 pathway promotes a variety of pathways related to cell metabolism, such as glucose metabolism, protein synthesis, and lipid synthesis, and then regulates cell metabolic growth and proliferation activation[19]. mTORC2 is comparatively insensitive to RAPA compared with mTORC1, and it needs long-term exposure to the drug[20]. Currently, it is generally believed that most of the effects of RAPA *in vivo* are mediated by mTORC1, and P70 ribosomal protein S6 kinase (p70S6K)/protein S6 (RPS6) and eukaryotic translation initiation factor 4e binding protein 1 (4EBP1)/eukaryotic translation initiation factor 4e (eIF4E) are the main downstream targets of mTORC1 (Figure 1). RAPA can specifically block p70S6K/RPS6, but does not affect the response of 4EBP1/eIF4E[21].

### **Immunosuppressive mechanism of RAPA**

The first-generation CNIs, such as cyclosporine and tacrolimus (FK506), inhibit T cell proliferation induced by calcium-dependent signal transduction pathways, while RAPA can disrupt T cell proliferation induced by both calcium-dependent and calcium-independent signal transduction pathways[22]. The chemical structure of RAPA is similar to that of FK506, and it mainly binds to the cytoplasmic receptor FK506-binding protein-12 (FKBP-12), but the further mechanism of action of RAPA is completely different from that of FK506[23]. FK506 inhibits the interleukin-2 (IL-2) production by blocking calcineurin which is responsible for the transcriptional activation of the *IL-2* gene, which in turn, results in disrupting the IL-2-mediated calcium-dependent T cell transcription and activation signal pathway and eventually blocks T cell cycle progression from G<sub>0</sub> to G<sub>1</sub> phase[23]. Different from FK506, RAPA first binds with FKBP-12 to form an FKBP12-RAPA complex (Figure 1), which specifically acts on mTOR to phosphorylate the downstream target proteins of the mTOR. Then, it inhibits the post-IL-2 receptor signal transduction and interferes with the protein and DNA synthesis of T lymphocytes induced by IL-2. As a result, it blocks the transition from G<sub>1</sub> to S phases in the T cell proliferation cycle, thereby playing its immunosuppressive role[24]. In addition to inhibiting the proliferation of T lymphocytes, RAPA can also induce receptor immune tolerance and reduce rejection by inhibiting the maturation of dendritic cells and promoting the proliferation of regulatory T cells[25,26].



**Figure 1 Regulatory mechanism of rapamycin on mammalian target of rapamycin signaling.** Rapamycin (RAPA) inhibits mammalian target of rapamycin (mTOR) by binding to its intracellular receptor FK506-binding protein-12. mTOR exists in two functionally distinct complexes, termed mTORC1 and mTORC2. RAPA acutely inhibits mTORC1, while the mTORC2 is affected by chronic exposure. Activated mTORC1 promotes cell growth and proliferation by regulation of lipid synthesis and glutamine metabolism and inhibition of autophagy, and it also could promote mRNA translation by stimulating 4e binding protein 1 (4E-BP1) and inhibiting 4E-BP1. mTORC2 regulates actin cytoskeletal dynamics and cell survival through the above pathways. RAPA: Rapamycin; mTOR: Mammalian target of rapamycin; FKBP12: FK506-binding protein-12; S6K1: S6 kinase 1; 4E-BP1: 4e binding protein 1; PKC: Protein kinase C; PPAR: Peroxisome proliferator-activated receptors.

### Anti-tumor mechanism of RAPA

The anti-tumor effect of RAPA is mainly reflected in the following aspects: (1) Interfering with tumor cell proliferation and growth cycle. The mTOR signal pathway is associated with multiple key pathways of tumor development and progression. The activation of the PI3K/AKT/mTOR signal pathway can inhibit apoptosis activated by multiple factors, thereby promoting tumor cell proliferation[21]. The PI3K/AKT/mTOR signal pathway is also one of the most common activation pathways in HCC, and studies have found that mTORC1 and mTORC2 pathways are up-regulated in 40%-50% of HCC patients[27]. RAPA makes mTOR inactivate and blocks mTOR-related signal transduction to make the cell cycle arrest in the G1 phase, thereby inhibiting the proliferation of tumor cells and exerting anti-tumor effects[23]; (2) inhibiting tumor angiogenesis. RAPA can indirectly exert its anti-tumor effect by inhibiting angiogenesis[28]. New angiogenesis is an indispensable condition for tumor cell growth. Vascular endothelial growth factor (VEGF) is the central regulator of angiogenesis, and RAPA prevents new tumor angiogenesis by interfering with VEGF. This mainly inhibits tumor growth indirectly by reducing tumor blood supply; and (3) RAPA can also induce tumor cell death through apoptosis[29,30].

### Protective mechanism of RAPA on ischemia-reperfusion injury

Ischemia-reperfusion (IR) injury is an inevitable pathophysiological process in the process of LT, and it may lead to a slow recovery of transplanted liver function and increase the incidence of postoperative complications, even death in some cases[31]. The intracellular signal pathway that leads to IR injury is caused by the increase of reactive oxygen species (ROS). Treatment with RAPA in patients after LT can reduce the production of ROS in the liver and increase the ability of hepatocytes to scavenge ROS by inducing the high expression of heme oxygenase-1 (HO-1) and peroxiredoxin-1 in hepatocytes, thereby reducing IR injury[32,33]. In addition, maintaining an appropriate level of HO-1 in the transplanted liver may reduce the deterioration of liver function after LT[31]. Especially for HCC patients undergoing LT, the increase of



ROS promotes the survival and proliferation of HCC cells but is detrimental to normal hepatocytes[34,35]. Moreover, there is some evidence to indicate that potential IR injury and longer times of ischemia are positively correlated with post-LT tumor recurrence[32].

#### ***Other functional mechanisms of RAPA***

RAPA is metabolized by CYP3A4 isozymes in the intestinal wall and liver, mainly excreted by feces, and a small amount (2.2%) is excreted through urine. Therefore, patients with renal function injury caused by CNIs can be improved through the use of RAPA[12]. RAPA can also inhibit the proliferation of vascular smooth muscle cells and deactivate immune cells in vascular lesions, which has a certain degree of cardioprotective effect[36]. In addition, it was also found that RAPA has the function of neuroprotection and promotion of nerve regeneration, which provides a promising treatment strategy for diseases caused by misfolding and aggregation of proteins, such as Parkinson's disease[37].

### **TRENDS OF RAPA IN SURVIVAL BENEFITS OF TRANSPLANT FOR HCC**

#### ***Immunosuppressant and tumor relapse post-LT***

Immunosuppressive agents are necessary to inhibit graft rejection after organ transplantation. However, immunosuppression plays an important role in the development and progression of tumors. Immunosuppressive therapy after LT makes the patient in a state of immunodeficiency chronically, which weakens the immune surveillance and defense of HCC or other tumors, and increases susceptibility to infection. Ultimately, it may increase the risk of HCC recurrence and metastasis after LT. CNI is a commonly used immunosuppressive agent after transplantation. However, many research data indicated that CNI-based regimens may increase the probability of tumor recurrence and metastasis, and it also has a direct carcinogenic activity that induces the growth and progression of tumors[38,39]. The traditional treatment view holds that there is no other immunosuppressive strategy that can effectively reduce the risk of tumor recurrence except for minimizing the dose of CNI after transplantation[9]. Therefore, it is an urgent problem to be solved whether other strategies can be used to replace or reduce the dose of CNI to minimize the risk of tumor recurrence and improve the prognosis of patients.

#### ***Application of RAPA transformation after transplantation***

RAPA can also have anti-tumor effects by inhibiting tumor cell proliferation and angiogenesis while exerting immunosuppressive effects. RAPA conversion can effectively reduce the risk of post-LT HCC recurrence and prolong the tumor-free survival time of patients during different studies[40,41]. Subsequently, meta-analysis affirmed to varying degrees the survival benefit of RAPA in HCC patients after LT, but these studies have their limitations because of single-center experience[11,42,43]. While RAPA is considered a potential ideal immunosuppressive agent, the therapeutic effect of RAPA in clinical application is still controversial. Although RAPA treatment decreased the recurrence rate and tumor-specific mortality rate (with no statistical difference), it did not bring significant benefits to overall survival[44]. Data from the Scientific Registry of Transplant Recipients, the United States national transplant registry, showed a significant 5-year survival benefit for HCC transplant patients receiving RAPA[40]. To address controversy over whether survival benefits are associated with RAPA action targets and tissue expression levels, some researchers have done such research on HCC patients with LT.

RAPA may have significant benefits in HCC patients with over-activated mTOR pathway[44]. This view has been further confirmed in other studies. Guerrero[45] found that the overexpression of the mTOR pathway in tumor tissues was associated with an increase in post-LT recurrence, and suggested that mTOR inhibitors such as RAPA should be used in patients with histopathologically up-regulated mTOR pathway in tumors, rather than as a unified drug for all HCC transplant patients. Based on this theory, we use animal models to find that RAPA can down-regulate Foxp3<sup>+</sup>Treg mediated tumor immune escape through the mTOR pathway. High expression of mTOR and Treg was associated with a low rat survival time[46].

#### ***Clinical study of RAPA conversion therapy***

A multicenter prospective randomized controlled phase 3 clinical trial (Table 1), the

**Table 1 Clinical trials with reported results for rapamycin in post-liver transplantation hepatocellular carcinoma**

Ref.	Patients (N)	Treatment	1-yr OS (%)	3-yr OS (%)	5-yr OS (%)	HCC recurrence HR (95%CI)
Grigg <i>et al</i> [11], 2019	968	RAPA <i>vs</i> CNI	NA	NA	67.6 <i>vs</i> 59.7	NA
Zhou <i>et al</i> [13], 2018	36	RAPA <i>vs</i> RAPA free	100 <i>vs</i> 77.8	94.5 <i>vs</i> 0	77.8 <i>vs</i> 0	NA
Toso <i>et al</i> [40], 2010	2491	RAPA <i>vs</i> RAPA free	NA	85.6 <i>vs</i> 79.2	83.1 <i>vs</i> 68.7	NA
Ling <i>et al</i> [41], 2020	204	RAPA <i>vs</i> RAPA free	97.4 <i>vs</i> 82.0	85.5 <i>vs</i> 71.9	NA	NA
Menon <i>et al</i> [42], 2013	474	RAPA <i>vs</i> CNI	94-95 <i>vs</i> 79-83	85 <i>vs</i> 66	80 <i>vs</i> 59-62	NA
Liang <i>et al</i> [43], 2012	2815	RAPA <i>vs</i> RAPA free	NA	NA	81.5 <i>vs</i> 68.1	NA
Yanik <i>et al</i> [44], 2016	3936	RAPA <i>vs</i> RAPA free	NA	NA	75.0 <i>vs</i> 75.0	0.86 <i>vs</i> 0.83
Geissler <i>et al</i> [47], 2016	525	RAPA <i>vs</i> RAPA free	96.0 <i>vs</i> 91.4	86.1 <i>vs</i> 78.5	79.4 <i>vs</i> 70.3	NA
Schnitzbauer <i>et al</i> [48], 2020	508	RAPA > 3 mo <i>vs</i> RAPA ≤ 3 mo	100 <i>vs</i> 89.9	87.7 <i>vs</i> 76.3	80.1 <i>vs</i> 67.0	NA
Xu <i>et al</i> [49], 2016	142	RAPA <i>vs</i> RAPA free	81.1 <i>vs</i> 85.3	60.3 <i>vs</i> 71.2	40.7 <i>vs</i> 43.5	NA
Na <i>et al</i> [61], 2016	39	RAPA + SOR <i>vs</i> RAPA + SOR free	NA	NA	NA	NA
Yang <i>et al</i> [65], 2020	64	RAPA <i>vs</i> TAC	54.5 <i>vs</i> 29.0	NA	NA	NA

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; RAPA: Rapamycin; CNI: Calcineurin inhibitor; NA: Not applicable; SOR: Sorafenib; TAC: Tacrolimus; LT: Liver transplantation.

Siliver trial[47], showed that RAPA improved the recurrence-free survival and overall survival rates in the first 3 to 5 years in LT recipients with HCC, especially for low-risk patients defined according to the Milan criteria, but for patients with advanced HCC or a long-term survival of more than 5 years, RAPA does not significantly improve recurrence-free survival and mortality compared with traditional CNIs. This trial provides a high reference value for the clinical application of RAPA-based immunosuppressive regimens in LT patients with HCC. At the same time, it also puts forward an important problem that needs to be solved, namely, how to improve long-term HCC recurrence-free and overall survival outcomes after 5 years in HCC patients undergoing LT. Whether to combine other treatments, such as targeted therapy, to improve patient survival benefits is an issue that needs to be considered. Subsequently, Schnitzbauer *et al*[48] conducted an exploratory multivariate analysis of the data in the Siliver trial and proposed that RAPA treatment for more than 3 mo was an independent factor for overall survival, and compared with less than 3 mo of RAPA treatment, the risk of death was decreased by 30%. When another variable (AFP index) was jointly evaluated, the risk of death decreased by 41% in patients with AFP ≥ 10 ng/mL and RAPA treatment for more than 3 mo. Besides, RAPA treatment can delay tumor recurrence, and patients have a longer survival time after recurrence[48]. Coincidentally, Xu *et al*[49] found that the recurrence-free survival rate of HCC transplant patients meeting the Milan criteria was not significantly different between the RAPA group and the control group, but under the intervention of RAPA, the overall survival time of the patients after recurrence was significantly longer than that of the control group. As one of the earliest transplant centers to use RAPA conversion therapy in China[13,50], we suggested that early conversion of RAPA after transplantation can improve the survival benefits of patients. The results of our previous study showed that RAPA-based therapy improved post-LT survival rates and decreased recurrence rates compared with the control group after LT. Moreover, our previous study also indicated that the therapeutic concentration of RAPA does not depend on drug dosage, but primarily on liver and renal function, rejection status, and anti-tumor effect. Furthermore, to avoid severe adverse reactions, we also suggested that serum RAPA levels should be maintained at ≤ 10 ng/mL[13].

Taken together, it is of clinical importance to clarify the conditions under which liver transplant patients with HCC are most likely to benefit from RAPA treatment. In particular, patients with the overexpression of the mTOR pathway in HCC can significantly benefit from the treatment of RAPA. However, overexpression of the mTOR pathway is not uniformly present in all HCC tumors, and there is no clear evidence for a benefit of RAPA use for non-mTOR pathway-dependent HCC. More-

over, a few studies have found that RAPA-based immunosuppressive regimens are associated with increased mortality[51]. Poor solubility is a disadvantage of RAPA in clinical application. Additionally, RAPA is unstable in physiological conditions, and it is not suitable for oral administration because of a large decrease in hydrolytic activity under the condition of physiological PH. Besides, like other effective immunosuppressive drugs, the use of RAPA can also cause many side effects, including dyslipidemia, dysglycemia, peripheral edema, anemia, leukopenia, delayed wound healing, *etc.*[52], and these side effects are relatively mild and easy to manage. The above adverse reactions could be alleviated or disappeared after a reduction in the instillation rate or drug withdrawal. Patients with dyslipidemia or dysglycemia can choose corresponding lipid-lowering or glucose-lowering drugs, combined with diet and appropriate exercise therapy[53,54]. For patients undergoing transplant for HCC, how to establish an appropriate balance between risks and benefits still needs further research. RAPA-related derivatives have a considerable prospect in improving the poor solubility and stability of RAPA. The RAPA-derivative everolimus is also used as one of the main treatment options for HCC after LT[11]. The immune activity and anti-tumor effect of everolimus *in vivo* are similar to those of RAPA. The aqueous solubility of everolimus is superior to that of RAPA, and its blood concentration is more stable. Compared with RAPA, everolimus has higher oral bioavailability and metabolic stability[55], and it also has a more significant protective effect on renal function[56]. However, everolimus is also associated with a high incidence of adverse effects. In particular, stomatitis is a common clinical symptom in everolimus users, with an incidence up to 42.6%[57]. Besides, dyslipidemia is also more common[58]. The development of the derivatives of RAPA may produce better results in clinical application, and more in-depth research on its mechanisms is still needed in the future.

## TRENDS OF COMBINED THERAPY OF RAPA AND ANTI-TUMOR DRUGS IN SURVIVAL BENEFITS OF TRANSPLANT FOR HCC

RAPA may be a promising immunosuppressive option in patients undergoing transplant for HCC, although there is no sufficient evidence for sustained benefit of this therapy. How to improve the efficacy of RAPA in the long-term prognosis should be the main research direction in the future. So far, multiple studies have shown that the use of RAPA alone may have a limited anti-tumor effect, and it is still not completely clear whether the combination of anti-tumor drugs and RAPA can achieve better synergistic anti-tumor effects, such as molecular targeted drugs, immune checkpoint inhibitors, and anticancer traditional Chinese medicine (TCM). Such combination therapy has been reported and analyzed, and the prerequisite for combined therapy is that the anti-tumor mechanisms of the two drugs are different or have a synergistic effect, which can increase the anti-tumor effect in different degrees.

### **Combination of RAPA and molecular targeted drugs**

Till now, molecular targeted drugs are one of the first-line choices for patients with advanced HCC, but there are still many problems in the application of these drugs, such as individual differences in drug sensitivity, drug resistance, and serious side effects caused by high doses of drugs. Therefore, how to improve the sensitivity of liver cancer cells to targeted drugs while reducing drug dose is an urgent problem to be solved in clinical practice. Sorafenib (SOR) has been the main targeting drug for patients with advanced HCC since it was approved in 2007, and it can not only directly inhibit tumor cell growth by inhibiting the RAF/MEK/ERK signal transduction pathway, but also indirectly exert its anti-tumor effect by inhibiting tumor angiogenesis. Previous studies have proposed that the anti-angiogenic effect of SOR in combination with RAPA is enhanced[59]. In the clinical retrospective study, Gomez-Martin *et al*[60] reported that the combination of SOR and RAPA could achieve a better anti-tumor effect in patients with post-LT recurrence but without the chance of secondary operation, and suggested that high-risk HCC transplant patients should choose RAPA-based immunosuppressive regimen combined with SOR to prevent HCC recurrence. For patients in the palliative treatment group (mainly including arterial chemoembolization, chemotherapy, or radiotherapy after post-LT recurrence), the survival rate of patients under the combined treatment of SOR and RAPA was significantly improved, but for patients in the radical treatment group (mainly including surgical resection or ablation after post-LT recurrence), the combined treatment did not show survival benefits[61]. It is also noteworthy that some patients in the above studies had varying degrees of toxic and side effects, such as diarrhea and

proteinuria. The superposition of toxicity and side effects may be the main obstacle to limiting the combined use of SOR and RAPA, and further studies are warranted to evaluate their advantages and disadvantages in the future.

In 2017, the American Clinical Oncology Annual Meeting (ASCO) released the REFLECT data of a phase 3 clinical trial of lenvatinib[62]. Then, lenvatinib was recommended as the first-line targeted therapy for unresectable HCC by the United States Food and Drug Administration, Japan, and the Chinese Society of Clinical Oncology, breaking the dominant position of SOR in first-line therapy. Lenvatinib is a multi-target tyrosine kinase inhibitor that can inhibit VEGF receptor and fibroblast growth factor receptor, which was known as the landmark development of targeting drugs in liver cancer[63,64]. The overall survival of patients with advanced HCC treated with lenvatinib was similar to that of patients treated with SOR, and the objective remission rate (40.6% *vs* 12.4%) and progression-free survival time (7.3 mo *vs* 3.6 mo) of patients in the lenvatinib group were significantly higher than those in the SOR group[60]. Especially for Asian HCC patients, the over survival of patients in the lenvatinib group was significantly longer than that in the SOR group, which suggests that Asian HCC patients be the dominant group of patients suitable for lenvatinib treatment[62]. Yang *et al*[65] found that the post-LT recurrence patients in the SOR ineffective or tolerant group had significantly improved overall survival after switching to lenvatinib. Six of these patients received combined therapy of lenvatinib and RAPA after reoperation, and the overall survival was 80% at 2 years, which was significantly longer than that in the control group. Although the sample size of this group is small with a limited reference value, we suggest that the combined therapy of lenvatinib and RAPA may not only be a potentially beneficial choice, but also can serve as a bridge approach before LT for some advanced patients, which needs further research in the future. Our recent data showed that the application of lenvatinib in patients beyond UCSF or Hangzhou criterion can enhance the rate of LT by inhibiting tumor progression or eliminating satellite lesions (unpublished data) (Table 1).

### **Combination of RAPA and programmed death protein-1 inhibitors**

Programmed death protein-1 (PD-1) is an important negative regulatory molecule of T cells, B cells, and other immune cells, and the binding of PD-1 to programmed death ligand-1 (PD-L1) on T cell surface can inhibit T cell activation and reduce tumor-killing effect[66,67]. PD-1 is also expressed on the surface of B cells and natural killer cells, and their function will be limited after binding to PD-L1[68,69]. Therefore, blocking the PD-1/PD-L1 pathway can enhance the anti-tumor effect of immune cells and promote tumor destruction. The immune checkpoint inhibitors of the PD-1/PD-L1 pathway are a research hotspot in HCC therapy in recent years, and the high expression of PD-1/PD-L1 on HCC cells promotes the growth of tumors and is closely related to tumor invasiveness and prognosis of patients[70]. It has been proved that immune checkpoint inhibitors can provide a longer disease-free survival than other targeted therapies (such as SOR)[71,72]. However, considering the risk of rejection induced by using immune checkpoint inhibitors, its effectiveness and safety in HCC transplant patients need to be further verified. We have attempted to apply RAPA and anti PD-1 antibodies in patients with negative expression of PD-L1, and such patients obtained survival benefit with little rejection (unpublished data). This finding needs confirmation using long-term studies with a large sample size.

Although formal testing has not been conducted in HCC transplant patients, a small number of cases have reported that the use of immune checkpoint inhibitors does not cause rejection[73]. mTOR immunosuppressive agents combined with immune checkpoint inhibitors may be a potentially useful therapeutic strategy for patients with HCC after LT. The combination of the two drugs can improve the anti-tumor effects, block mTOR-related tumor growth pathways, and reduce the expression of PD-1 in different immune cells[70]. The synergistic anti-tumor mechanism of mTOR inhibitors and PD-1 blockers may lie in the complete inhibition of RPS6 and eIF4E, the downstream targets of mTORC1[70]. RPS6 and eIF4E play different roles in the development and progression of HCC with AKT/RAS activation, and the simultaneous inhibition of both can inhibit the growth of such HCC. RAPA only selectively inhibits RPS6, while PD-1 can physically bind with RPS6 and eIF4E and promote their phosphorylation. Therefore, RAPA combined with PD-1 inhibitor has a synergistic anti-tumor effect[21]. So far, there have been few reports about the clinical application of RAPA combined with a PD-1 inhibitor in HCC transplant patients, and the effectiveness and safety of the combination therapy need more data support. How to balance the changes of the anti-tumor and anti-rejection immune microenvironment needs more in-depth exploration.



### Combination of RAPA and anti-tumor TCM

TCM has been used to treat inflammation and cancer in China for more than 1600 years[74]. TCM has a long-lasting anti-tumor effect and low recurrence rate. Recently, it has been demonstrated that anti-tumor TCM is a promising way in the treatment of HCC. Huaier granule (PS-T) is a representative anti-tumor TCM, which has been recommended as an adjuvant drug of radiotherapy and chemotherapy by the Chinese Clinical Oncology Association. Clinically, it has a good anti-tumor effect on liver cancer, lung cancer, gastric cancer, and breast cancer[75,76]. PS-T is a multi-target drug that contains the active ingredient of proteoglycan, which can improve immune function and kill tumor cells[77]. PS-T can inhibit angiogenesis in HCC tissue by down-regulating VEGF levels[78]. It can also inhibit the tumorigenicity of cells through the mTOR signaling pathway and enhance the sensitivity of cells to RAPA [76]. Based on the above theoretical basis, the study of RAPA combined with PS-T in the treatment of LT for HCC has been carried out in many centers in China[50,79]. We believe that RAPA combined with PS-T adjuvant therapy after LT for HCC is expected to improve the quality of life and prolong the survival time of patients, and its specific mechanism needs to be further studied.

In our previous clinical study, we found that the combination of RAPA and PS-T significantly prolonged the postoperative survival time of HCC transplant patients beyond the UCSF standard, and proved the effectiveness and safety of this combination therapy[13,50]. Based on clinical research, we further found that RAPA-based therapy has an anti-tumor effect by reducing FoxP3<sup>+</sup>Tregs and its inhibitory cytokines, and the application of PS-T enhances the anti-tumor effect of RAPA. This synergistic effect is mediated by the mTOR signal pathway[46]. To further verify the long-term efficacy and specific mechanism of the combination of RAPA and PS-T, it is necessary to perform multicenter, large sample randomized controlled trials.

### Advice on RAPA application

The unified recommended scheme for the prevention and treatment of HCC recurrence after LT has not been previously reported in the global transplantation field. Given the demonstration of the global multicenter results of RAPA and the first-line recommended use of lenvatinib as well as the comprehensive treatment strategy of early RAPA transformation combined with lenvatinib, minimizing hormone exposure and CIN dose should be adopted for HCC patients undergoing LT. RAPA can be efficient at establishing clinical immune tolerance and supporting long-time survival of the graft. Therefore, we believe that it is necessary to construct systematic and individualized prevention and treatment strategy based on RAPA, which is helpful to protect the function of grafts while preventing the recurrence of HCC. Meanwhile, the development of a comprehensive program to combat the recurrence of HCC after LT should integrate the progress of molecular targeting drugs and immunotherapy. First, for HCC patients who satisfy the Milan Criteria, we recommend the "dual regimen" of RAPA combined with lenvatinib, RAPA conversion therapy within 1 mo, no hormone during operation, and rapid decrease of the low-dose hormone after the operation. Second, for patients beyond Milan criteria and with the overexpression of the mTOR pathway and active HCC (AFP positive), we recommend the "triple regimen", that is, combination with thymalfasin based on "dual regimen". In the meantime, the regimen with no hormone during operation and rapid decrease of low dose hormone after the operation can be used. Third, for advanced HCC exceeding the UCSF standard, preoperative neoadjuvant therapy with lenvatinib can be considered to eliminate satellite lesions in the liver and residual cancer cells in the blood. The "dual regimen" combined with bevacizumab can be considered a systematic and comprehensive prevention and treatment strategy. Additionally, whether the PD-1/PD-L1 inhibitors can be used in preoperative neoadjuvant and postoperative combined treatment should be based on the expression of PD-1 in cancer tissues or PD-L1 in immune cells.

## CONCLUSION

With the increasing incidence of HCC, the selection criteria for LT recipients for HCC in many transplantation centers are gradually expanding, but the prevention and treatment strategies for post-LT recurrence are not perfect. The problem of tumor recurrence after transplantation is still an important clinical challenge. It has been more than 50 years since the advent of RAPA. From the initial antifungal agent, it has gradually become a multi-effect drug with both immunosuppressive and anti-tumor effects. A large number of studies have begun to focus on whether RAPA can bring

more survival benefits to HCC transplant patients. So far, most studies have shown that RAPA has a positive impact on the prognosis of HCC patients undergoing LT. Especially, HCC patients with overexpression of the PI3K/Akt/mTOR pathway can significantly benefit from RAPA-based immunosuppression regimen. However, there is still no consensus on the specific indications and therapeutic dose recommendations for the clinical application of RAPA. Although the research of RAPA has made gratifying achievements, whether this drug can achieve more ideal efficacy in clinical application still needs to be further explored. Given the variability of the occurrence and development of HCC and the activity of human cell signaling pathways, the application of RAPA to HCC transplant patients may be quite different. How to formulate scientific individualized drug use still requires the support of high-level evidence-based medical evidence, such as large-sample, multicenter randomized controlled trials.

The key role of the mTOR signal pathway in the development of HCC has well-proven and RAPA treatment after LT for HCC leads to higher survival rates in some groups of post-LT HCC patients. With the progress of technology and the continuous accumulation of understanding of RAPA, the research on RAPA will continue to deepen. The future research on RAPA will focus on the following aspects. First, RAPA-sensitive HCC transplant patients should be scientifically screened to maximize the clinical efficacy of RAPA. Second, chemical modification of the chemical structure of RAPA and screening of RAPA analogs are conducted to develop more functional and targeted mTOR inhibitors.

It is promising in HCC comprehensive treatment to improve and establish a treatment system to prevent tumor recurrence after LT by applying RAPA with lenvatinib treatment. In addition, the combination of RAPA and other anti-tumor drugs has a synergistic and sensitizing effect, especially for patients with advanced HCC. Future research should be directed to find and screen the patients who are suitable for the combination of immune checkpoint therapy and to improve their safety and effectiveness. Combination therapy may be an important research direction to break through the bottleneck of RAPA in LT patients with HCC. Only by carrying out targeted relevant research can we effectively promote the application of RAPA in LT for HCC.

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