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Contents

Monthly Volume 14 Number 8 August 27, 2022

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Retrospective Study

Observational Study

World Journal of Gastrointestinal Surgery

Monthly Volume 14 Number 8 August 27, 2022

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 14 Number 8 August 27, 2022

Contents

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LETTER TO THE EDITOR

Sirolimus *vs* tacrolimus: Which one is the best therapeutic option for patients undergoing liver transplantation for hepatocellular carcinoma?

Faiza Ahmed, Faiza Zakaria, Godsgift Enebong Nya, Mohamad Mouchli

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Abstract

Liver transplantation (LT) withstands as the most preferred therapeutic option for patients afflicted with hepatocellular carcinoma (HCC) and cirrhosis. To improve prognosis post-transplant, as well as to prevent the occurrence of rejection, a life-long immunosuppression strategy is implemented. The following letter to the editor highlights and provides novel evidence from recently published literature on topics discussed within the review article titled "Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma" in *World J Gastrointest Surg* 2021; 13: 953-966. In the recent manuscript, the authors compared immunosuppressive drugs such as the newer option first-generation mammalian target of rapamycin inhibitor, also known as sirolimus, with the most widely used first-generation calcineurin inhibitors, such as tacrolimus (TAC). TAC is commonly known as the most effective immunosuppressive drug after LT, but it has been reported to cause intolerable side effects such as nephrotoxicity, neurotoxicity, diabetes, hypertension, gastrointestinal disturbances, increased risk of infections, and malignancies. It is necessary for physicians to be aware of recent advances in tacrolimus and sirolimus therapies to compare and understand distinctly the effectiveness and tolerability of these drugs. This will assist clinicians in making the best treatment decisions and improve the clinical prognosis of LT recipients with HCC.

Key Words: Rapamycin; Tacrolimus; Sirolimus; Immunosuppressants; Hepatocellular carcinoma; Liver transplantation

Core Tip: Post-transplant rejection holds significance in the long-term survival of patients with hepatocellular carcinoma (HCC) receiving a liver transplant (LT). The role of the mammalian target of rapamycin inhibitor (mTOR inhibitors) in preventing HCC recurrence after LT is still under debate. The major goal of this letter is to summarize the most relevant existing data on sirolimus, an mTOR inhibitor, and tacrolimus, a calcineurin inhibitor, therapy involvement in the progression of such patients.

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TO THE EDITOR

We read with profound interest the review by Zhao *et al*[1], "Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma", published in the September 2021 issue of the *World Journal of Gastrointestinal Surgery*.

Hepatocellular carcinoma (HCC) is the second greatest cause of cancer fatalities worldwide and three times more frequent among males[2,3]. According to the World Health Organization, 905677 new cases were identified globally in 2020, with 830180 deaths[4]. By 2030, the worldwide burden of HCC mortality is anticipated to surpass one million[5]. Apart from poor prognosis, HCC has a five-year survival rate of less than 10%, and the outcome is worsened by the lack of therapy options. If detected early, HCC can be treated with surgery or liver transplantation (LT). However, more than 85% of cases are discovered at an advanced stage, when surgical treatment is not possible[6].

The most important indication for LT is concurrent HCC and cirrhosis. For end-stage liver diseases, LT is the most effective strategy[7]. However, tumor recurrence remains a significant challenge. The risk of HCC recurrence postoperatively within five years after LT is as high as 30% and remains the primary reason for mortality in such patients[8]. Life-long immunosuppression is required to prevent rejection. In recent years, post LT immunosuppression remains the subject of intense research.

In the article, Zhao *et al*[1] highlight investigations involving the use of different types of potential options to treat post-LT recurrence in HCC patients. The study also compares immunosuppressive drugs such as the newer option first-generation mammalian target of rapamycin (mTOR) inhibitor, also known as sirolimus (SRL), with the most widely used first-generation calcineurin inhibitors (CNIs), such as tacrolimus (TAC). However, CNIs have been proven to increase malignant development, with studies indicating a dose-dependent connection with tumor recurrence in HCC patients[9]. TAC is commonly known as the most effective immunosuppressive drug after LT, but it has been reported to cause side effects such as nephrotoxicity, neurotoxicity, diabetes, hypertension, gastrointestinal disturbances, increased risk of infections, and malignancies[10]. In contrast, mTOR inhibitors are considered to have anti-tumor properties *via* inhibiting angiogenesis, cellular proliferation, and have demonstrated tolerable safety with promising outcomes[11]. However, since there is inadequate data available to support the use of mTOR inhibitors in the treatment of HCC recurrence after transplantation, their role is yet to be determined. Nevertheless, we would like to draw the authors' attention to several recently published literature on this topic.

Five studies individually evaluated SRL therapy. A retrospective cohort study[12] compared the mTOR inhibitors group with a control group that did not receive any mTOR inhibitor therapy. The authors' demonstrated that the use of mTOR inhibitors, either SRL or everolimus (EVL), a rapamycin derivative, in the immunosuppressive regime of LT recipients increased survival after recurrence (median 21.0 ± 4.1 *vs* 11.2 ± 2.5 mo, $P = 0.04$). The mTOR inhibitors group had decreased recurrent tumors (2 *vs* 5, $P = 0.02$) compared to the control group. Supportive care was provided to a small number of patients (4% *vs* 36%, $P < 0.001$), and more aggressive therapies such as radiation (39% *vs* 22%, $P = 0.03$) and targeted therapy (59% *vs* 23%, $P < 0.001$) were actively utilized in mTOR inhibitors group. The results also confirmed that mTOR inhibitors enhanced survival, and subgroup analysis of patients who received SRL or EVL had no significant change in survival outcomes (19.1 ± 5.7 *vs* 21.0 ± 4.4 mo, $P = 0.88$). Furthermore, the study reported no changes in survival between patients who received mTOR inhibitors alone and those who received mTOR inhibitors in combination with TAC.

A systematic review and meta-analysis reported that SRL or EVL improved one, two, three and five-year overall survival (OS) [randomised controlled trials: 1-year, relative risk (RR) =1.04, 95%CI: 1.00-1.08; 2-year, RR = 1.09, 95%CI: 1.02-1.16; 3-year, RR = 1.13, 95%CI: 1.04-1.24; 5-year, RR = 1.13, 95%CI: 1.02-1.26) *vs* (cohort studies: 1-year, RR = 1.13, 95%CI: 1.06-1.20; 2-year, RR = 1.24, 95%CI: 1.16-1.32; 3-year, RR = 1.24, 95%CI: 1.15-1.34; 5-year, RR = 1.17, 95%CI: 1.10-1.24)), respectively[7]. A 13% improvement in OS was demonstrated over five years, with 14% survival benefit in three years, and minimal risk of nephrotoxicity was noticed (RR = 0.75, 95%CI: 0.60-0.93) in the mTOR inhibitors group.

Ye *et al*[13] was the first study that retrospectively integrated a molecular index, tuberous sclerosis 1-tuberous sclerosis 2 complex (TSC 1/2) expression levels, in predicting the SRL's impact on the prognosis of HCC-LT patients exceeding the Milan criteria. According to the researchers, SRL enhanced outcomes in HCC-LT patients with low TSC 1/2 expression [disease-free survival (DFS): P = 0.046, OS: P = 0.006 for TSC1; DFS: P = 0.05, OS: P = 0.003 for TSC2). However, the influence of lower dosages of CNIs, which have been reported to improve the anticancer activity of SRL, cannot be ruled out. Wei *et al*[14] also analyzed TSC mutations in LT for HCC and resulted in no notable disparity in survival rates among the SRL and non-SRL patients (P = 0.761). There was no distinction noted between the two treatment groups for the five-year disease-free survival rate. Overall, patients with TSC 1/2 mutations achieved a good prognosis from the use of SRL.

Zhao *et al*[1] also cited the SiLVER trial, which demonstrated in the first three to five years an improved recurrence-free survival (RFS) and OS, especially in low-risk patients with tumor characteristics within Milan criteria[15]. Research conducted by Ekpanyapong *et al*[16] also supports this benefit.

One recent article by Gastaca *et al*[17] retrospectively evaluated TAC therapy. The authors aimed to assess the impact of early post LT TAC trough levels on prognosis after LT. They concluded that no significant effect was appreciated on the function of the kidneys, immunosuppression-related morbidity, and five-year patient or graft survival. Therefore, small variations in mean TAC levels during the first month were reported to be insignificant predictors of long-term immunosuppression-related morbidity and patient survival; hence, long-term results appeared to be influenced by increased exposure.

Finally, we found three comparative research published on SRL and TAC regimens. A prospective, randomized, multicenter phase II trial compared both drugs' oncological outcomes in living donor LT patients exceeding the Milan criteria. The three-year RFS and OS rates were higher in the TAC group compared to the SRL group (77.3% *vs* 60%; and 81.8% *vs* 77%), respectively. On multivariate analysis, serum alpha-fetoprotein level > 150 ng/mL and positron emission tomography standardized uptake value ratio (tumor/background liver) > 1.15 were crucial risk factors for both RFS and OS. SRL therapy enhanced OS (TAC hazard ratio: 15.0, 95%CI: 1.302-172.8, P = 0.03) but had no impact on RFS. In regards to adverse events, the authors reported a higher incidence of wound complication and dyslipidemia in the SRL group; however, the variation was not statistically relevant. Overall, SRL did not reduce HCC recurrence, but it did extend the patients' OS time[18].

In a retrospective study, Sung *et al*[19] found that individuals with impaired renal function improved significantly after 12 mo of using mTOR inhibitors. The median eGFR values at 1, 3, 6, and 12 mo after switching to mTOR inhibitors were 90, 75.5, 74.5, and 76.8 mL/min. Moreover, the mean eGFR in TAC-withdrawn individuals after switching to mTOR inhibitors at 1, 3, 6, and 12 mo was 110, 98, 87.5, and 82 mL/min, respectively. In comparison, TAC-minimized patients at 1 and 6 mo after switching to mTOR inhibitors had significantly lower eGFR compared to the TAC withdrawn group. Hence, the TAC-withdrawn group demonstrated enhanced kidney function compared to the TAC-minimized group. Common adverse events such as thrombocytopenia (7.1%), proteinuria (11.9%), mouth ulceration (6%), and gastrointestinal adverse effects (9.5%) occurred within 2 mo after mTOR inhibitor use. Comprehensively, the authors confirmed that substituting with mTOR inhibitors is advantageous when renal function diminishes.

The authors, Zhao *et al*[1], also mentioned one of the side effects of SRL, which is delayed wound healing, as a generally moderate and easy to treat condition. They stated that adverse reactions were subsided by lowering the installation rate or stopping the medicine, whereas a case report by Lao *et al*[20] presents a different scenario. Initially, the 54-year-old woman patient with *CYP3A* mutation was provided TAC for treatment, but later on, was substituted with SRL at the first sign of acute renal injury. The transition was undertaken since SRL is not known to induce kidney and liver toxicity; however, the arterial anastomosis ruptured unexpectedly a few days after the medication was initiated. Before the arterial anastomosis ruptured, a postoperative Doppler ultrasonography was performed every 2-3 d and displayed no signs of either an abscess or a pseudoaneurysm. She received 6 mg of SRL as a loading dose for 2 d followed by a 2 mg maintenance dose. The loading dose and increased levels of SRL exposure damaged the durability of the arterial anastomosis, contributing to its rupture. Thus, the authors concluded that it is better to avoid using SRL at the early stage after LT considering its effect on wound healing.

In conclusion, Zhao *et al*[1] presented interesting points concerning LT for HCC patients by the usage of SRL and TAC therapy. We agree with the authors' insight that TAC significantly influences renal function, leading to acute and chronic kidney diseases after LT. However, further investigations are warranted regarding the safety profile of SRL to better understand its impact as a substitution for TAC. In addition, studies discussing cost-effectiveness analysis of these drugs are also necessary since they

will aid physicians in decision-making and individualizing treatment to improve OS and RFS with minimal adverse effects.

FOOTNOTES

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