Differential impact of tacrolimus intra-patient variability on liver transplant outcomes in patients with and without hepatocellular carcinoma

Hyun Jeong Kim, Jae Geun Lee, Dong Jin Joo, Myoung Soo Kim, Soon Il Kim, Juhan Lee

Department of Surgery-Transplantation, Yonsei University College of Medicine, Seoul, Korea

Background: The recurrence rate for hepatocellular carcinoma (HCC) after liver transplant is high as 15%–20% despite a careful selection of candidates. Although immunosuppression plays an important role in post-transplant HCC recurrence, optimal immunosuppressive strategies have not been clearly defined. Patients with high tacrolimus intra-patient variability (IPV) may be at risk of overexposure and adverse effects, such as malignancy and infection. We investigated the association between tacrolimus IPV and transplant outcomes in patients with and without HCC.

Methods: We analyzed tacrolimus IPV using the coefficient of variability from months 3–12 after transplantation in 526 liver transplant recipients between 2009 and 2018 at the Severance Hospital. Patients were grouped according to the presence or absence of HCC and tacrolimus IPV. High tacrolimus IPV was defined as a coefficient of variation greater than 30%.

Results: Among 526 patients, 260 were HCC and 266 were non-HCC. The association between high tacrolimus IPV and patient survival was evident in the HCC group. Overall patient survival in the HCC group was significantly impaired with high tacrolimus IPV ($P<0.001$). A multivariable Cox regression analysis confirmed that high tacrolimus IPV was independently associated with overall mortality in the HCC group (hazard ratio [HR], 3.262; 95% confidence interval [CI], 1.954–5.447; $P<0.001$). HCC recurred in 48 patients (18.5%) after liver transplantation. After adjusting tumor characteristics, high tacrolimus IPV was independently associated with an increased risk of HCC recurrence (HR, 2.310; 95% CI, 1.362–3.918; $P=0.002$). In contrast, overall patient survival of non-HCC group was not significantly different according to the tacrolimus IPV.

Conclusions: High tacrolimus IPV significantly increases the risk of all-cause mortality and HCC recurrence in liver transplant patients with HCC.

Corresponding author: Hyun Jeong Kim

E-mail: HJKIM0110@yuhs.ac

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