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Tacrolimus의 혈중농도 변동성이 간이식 예후에 미치는 영향

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The Effects of Intrapatient Variability in Tacrolimus Concentration on Clinical Outcomes Immediately After Liver Transplantation

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ABSTRACT

Background: Tacrolimus, a calcineurin inhibitor, is an immunosuppressant used in post-transplantation maintenance therapy. The drug has a narrow therapeutic range and requires periodic therapeutic drug monitoring. Although many studies have reported the effects of intrapatient variability of tacrolimus on survival, rejection, and complications in renal transplant recipients, very few studies have reported these effects in liver transplant recipients. The purpose of this study was to evaluate the effect of intrapatient variability of tacrolimus on clinical outcomes after liver transplantation. **Methods:** Intrapatient variability was calculated using individual, averaged tacrolimus concentrations. Patients were divided into two groups according to their median variability value: high-variability and low-variability groups. The rate of deviation from the therapeutic range, incidence of acute rejection, post-transplant diabetes, incidence of infection, and estimated glomerular filtration rate (eGFR) after transplantation were compared between the groups. **Results:** Of the total patients (n=82), the high-variability group (n=41) exhibited significantly greater deviation from the therapeutic range (65.92% vs. 56.84%; $p<0.001$). There was no significant difference in acute rejection or post-transplantation diabetes incidence or eGFR; however, the number of infection in the first 6 months was significantly lower in the low-variability group (0.4 vs. 0.9 times; $p=0.039$). Multiple linear regression analysis showed that the number of infection significantly increased as intrapatient variability increased ($p=0.015$). **Conclusion:** High intrapatient variability in tacrolimus concentrations was strongly associated with an increased frequency of deviation from the suggested therapeutic range and an increased number of infection.

KEYWORDS: Tacrolimus, liver transplantation, intrapatient variability, graft rejection, infections

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Tacrolimus, a calcineurin inhibitor, is the main immunosuppressant used after liver transplantation.[1-3] Tacrolimus suppresses acute rejection, but causes side effects such as infection, chronic renal failure, hypertension, neurotoxicity, and post-transplant diabetes.[3,4] In order to reduce these toxic effects and increase the immunosuppressive efficacy, regimens combining tacrolimus, mycophenolic acid, and a steroid are used. Nevertheless, tacrolimus has a narrow therapeutic concentration range,[5] and therefore requires therapeutic drug monitoring.[6]

Although the target range of tacrolimus varies between institutions, in general, the therapeutic range is 10-15 ng/mL during the first 4-6 weeks after transplantation, and is then gradually reduced to 5-10 ng/mL.[2,7] According to the US tacrolimus (Prograf; Astellas Pharma, Tokyo, Japan) prescribing information, the therapeutic range is generally 5-20 ng/mL during the first year after liver transplantation.

Since tacrolimus demonstrates not only high interpatient variability but also high intrapatient variability (IPV), blood concentration monitoring is necessary.[8] The fluctuation of tacrolimus blood concentrations in an individual patient is evaluated by intrapatient variability,[1,9] which is defined as the range of serum trough level tacrolimus within a patient. In previous studies, high IPV was associated with acute rejection, death, complications, and renal failure in renal transplant recipients.[9-12] In study of liver transplant patients, according to van der Veer *et al*, there was a study that tacrolimus IPV between 6 and 18 months after liver transplantation was not related to graft failure.[13] On the other hand, according to Rayar *et al*, high tacrolimus IPV from POD8 to POD 30 days after liver transplantation increased complications and poor outcome.[14]

It has been reported that exposure to tacrolimus in early liver transplant recipients may lead to chronic nephrotoxicity and death.[7,15] Therefore, this study aimed to investigate the effect of tacrolimus IPV on rejection, complications, and renal function during the first 6 months after liver transplantation.

Methods

Patient selection

All transplantation patient in Seoul National University Bundang Hospital between January 1, 2009 and December 31, 2016 (n=155) were retrospectively analyzed. Patients who were given other immunosuppressant during the study period, had multi-organ transplantation, had surgery at other hospital were excluded from this study. Children and adolescents (<19 years old) were also excluded (n=68). We also excluded patients who died within 6 months after surgery (n=5). Ultimately, our study population consisted of 82 liver transplanted patients treated by oral tracrolimus until 6 months to liver transplantation.

Medical care after liver transplantation

After liver transplantation, all patients begin treatment with immunosuppressants of tacrolimus, mycophenolate, and corticosteroids. Tacrolimus starts in the evening the next day after liver transplant surgery, the initial dose was 0.075 mg/kg twice a day. The target of tacrolimus trough concentration is 8-12 ng/ml until 1 month, 6-8 ng/mL until 6 months to 1 month, 5 ng/mL after 6 months. The dose of tacrolimus was adjusted so that the blood concentration of tacrolimus reached the target concentration.

Tacrolimus IPV calculation

Serum tacrolimus trough levels were calculated from the outpatient or inpatient serum trough concentration. Blood concentrations were measured using the chemiluminescent microparticle immunoassay. The formula used to calculate each patient's IPV using blood concentrations over the 6 months period was:[10]

$$\text{IPV}\ (\%) = \frac{\Sigma \text{abs}(\text{tac}_{\text{mean}} - \text{tac}_{\text{x}})/\text{n}}{\text{tac}_{\text{mean}}} \times 100$$

where tac_{mean} is the individual average of the trough concentration of tacrolimus, tac_{x} is the tacrolimus trough concentration in each blood sample, and n is the number of blood samples. Since a certain period is needed to achieve the tacrolimus target range, serum levels up to 7 days after transplantation were excluded.

According to the previous study, we calculated the patient's tacrolimus IPV and divided it into high and low groups based on median. [9,12]

Outcome

To analyze the patients' IPV-related outcomes, we collected data on the rates of acute rejection, infection, diabetes, and renal function for 6 months after liver transplantation. Liver biopsies were routinely performed according to our institution's protocol: after liver transplantation and when there were indications of hepatic function abnormality. The occurrence of infection was based on a diagnosis via bacterial identification

during the 6-months period. If either the primary site of infection or the identified bacteria were different, we considered it to be a different infection. If the same bacteria were repeatedly identified, we considered it to be the same infection. In addition, data on the rejection activity index score, the number of incidences of infection, infection site, pathogenic bacteria, new onset diabetes mellitus, and estimated glomerular filtration rate (eGFR) using the CKD-EPI formula were collected. And MELD is calculated 'MELD score=9.6× ln (creatinine mg/dL)+3.8×ln (bilirubin mg/dL)+11.2×ln (INR) +6.4'. This study was approved by an Institutional Review Board (No. B-1708/414-104).

Statistics

For statistical analysis, the incidence of acute rejection, infection and post-transplantation diabetes were compared using the chi-square test, and the number of infection was compared using the t-test. Multiple linear regression analysis was used to investigate the factors influencing the number of infections. Renal function was calculated using both a t-test and a linear mixed model in order to compare the changes in eGFR during the 6-months period after transplantation in both patient groups. Analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY). All data were judged to be significant when the *p*-value was less than 0.05.

Results

During the study period, 82 patients received tacrolimus after liver transplantation. The distribution of their tacrolimus IPV is shown in Fig 1. Based on the IPV data distribution, the patients were divided into two groups: a high variability group (HV; IPV >25.5%), and a low variability group (LV; IPV <25.5%). The average IPV in the HV and LV groups was 32.6% and 20.6%, respectively.

The baseline characteristics of the patients in both groups are described in Table 1. There were no significant differences in age, height, sex, and weight, donor age, MELD score, baseline eGFR between the two groups. In the LV and HV groups, living donor liver transplantation was performed in 27 (66%) and 26 (63%) patients, and deceased donor liver transplantation in 14 (34%) and 15 (37%) patients, respectively. The indications for liver transplantation were HBV and HCC in 9 (22%) and 14 (34%), HBV in 6 (15%) and 9 (22%), HCC in 4 (10%) and 4 (10%), and alcoholic liver cirrhosis in 10 (24%) and 5 (12%) patients, in the LV and HV groups, respectively. There were no significant differences in the type or indication for liver transplantation between the two groups.

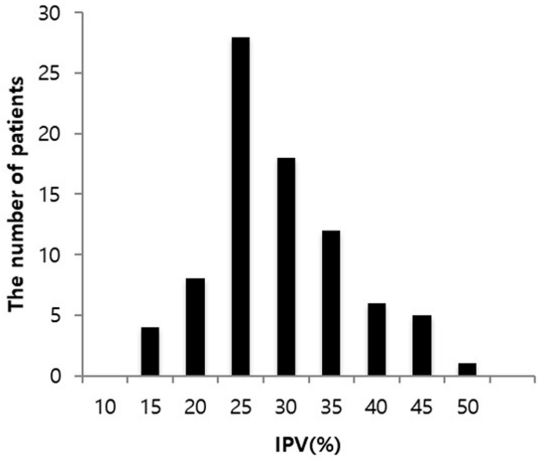

Fig. 1. Frequency distribution of variability in tacrolimus concentration
IPV, intrapatient variability

Serum tacrolimus trough level

The average tacrolimus trough blood concentration and rate of deviation from the therapeutic range in both the LV and HV groups are shown in Table 2. The mean tacrolimus trough blood concentrations were 8.99 and 8.87 ng/mL in the LV and HV groups, respectively, which were not significantly different.

Based on the protocol at Seoul National University Bundang Hospital, the target trough level was set to 8-12 ng/mL for the first month postoperatively and 6-8 ng/mL between months 1 and 6.[15] We calculate the rate of deviation from the therapeutic range is this formula: 'Rate of deviation from the therapeutic range=(The number of samples with concentrations outside the therapeutic range/Total number of tacrolimus blood concentration samples)*100'. The rate of deviation from the therapeutic range was significantly different between the two groups, 56.84% in the LV group and 65.92% in the HV group (p<0.001). Moreover, when considering that 5-12 ng/mL is the commonly utilized therapeutic range of tacrolimus, the rate of deviation from the therapeutic range was 19.22% in the LV group and 33.73% in the HV group (p<0.001; Table 2).

Acute rejection, infection, and post-transplant diabetes

The incidence of acute rejection and post-transplant diabetes during the 6-months period after liver transplantation in both groups is shown in Table 3. There were 16 patients with acute

Table 1. Baseline characteristics of the study population (N=82)

	IPV		*p*-value
	Low variability (N=41)	High variability (N=41)	
Age (mean)[a]	51.5	53.3	0.373
Sex (men (N), %)[b]	23 (56%)	27 (65%)	0.371
Height (cm, mean)[a]	163.2	162.4	0.796
Weight (kg, mean)[a]	64.8	69.8	0.154
Donor age (mean)[a]	32.5	31.9	0.409
MELD score (mean)[a]	22.0	21.1	0.895
Baseline eGFR (mL/min/1.73 m^2, mean)[a]	105.4	87.7	0.664
Type of transplant (N, %)[b]			0.817
LDLT	27 (66%)	26 (63%)	
DDLT	14 (34%)	15 (37%)	
Indication of liver transplantation (N, %)[b]			0.436
HBV and HCC	9 (22%)	14 (34%)	
HBV	6 (15%)	9 (22%)	
HCC	4 (10%)	4 (10%)	
Alcoholic-LC	10 (24%)	5 (12%)	
Others[c]	12 (29%)	9 (22%)	

IPV, intrapatient variability; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation
HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis
[a]*p*-values were obtained by t-test.
[b]*p*-values were obtained by χ^2-test.
[c]Others: HCV and HCC, HCV alone, fulminant hepatitis, Wilson's disease, or toxic hepatitis.

Table 2. Effects of IPV on tacrolimus trough levels between the low- and high-variability groups

	IPV		*p*-value
	Low variability (N=41)	High variability (N=41)	
Mean tacrolimus trough level (ng/mL, mean±SD)	8.99±1.4	8.87±1.4	0.751
Rate of deviation from the therapeutic range[a] (%, mean±SD)	56.84±10.5	65.92±13.0	<0.001[b]
Rate of deviation from the therapeutic range[c] (%, mean±SD)	19.22±12.7	33.73±5.9	<0.001[b]

IPV, intrapatient variability
[a]Therapeutic range: 8-12 ng/mL (first postoperative month), 6-8 ng/mL (months 1-6) according to the protocol at the Seoul National University Bundang Hospital.
[b]Statistically significant at $p<0.05$ with t-teat.
[c]Therapeutic range: 5-12 ng/mL according to the protocol at the Seoul National University Bundang Hospital.

Table 3. Difference in clinical outcomes between the low- and high-variability groups

	IPV		*p*-value
	Low variability (N=41)	High variability (N=41)	
Number of patients with (N, %)[a]			
Acute rejection	16 (39%)	14 (34%)	0.647
Infection	14 (34%)	17 (41%)	0.494
Post-transplant diabetes	11 (27%)	10 (24%)	0.800
Average number of infections (SD)[b]	0.4 (0.5)	0.9 (1.5)	0.039[c]

IPV, intrapatient variability
[a]*p*-values were obtained by χ^2-test.
[b]*p*-values were obtained by t-test.
[c]Statistically significant at $p<0.05$.

Table 4. Factors associated with the number of infections during the first 6 months after transplantation

	Univariate analysis		Multivariate analysis[a]	
	Unstandardized β (95% CI)	*p*-value	Unstandardized β (95% CI)	*p*-value
Recipients' characteristic				
Recipient age	0.016 (-0.013,0.044)	0.277		
Female (vs male)	0.241 (-0.292,0.774)	0.370		
Clinical factors				
MELD score	0.004 (-0.021,0.029)	0.760		
Baseline eGFR	-0.003 (-0.008,0.002)	0.235		
IPV in HV group (vs LV group)	0.537 (0.028,1.045)	0.039[b]	0.611 (0.122,1.100)	0.015[b]
LDLT (vs DDLT)	0.448 (-0.090,0.985)	0.101	0.394 (-0.121,0.910)	0.132
Indication of liver transplantation				
HBV and HCC	-0.205 (-0.879,0.469)	0.547		
HBV	-0.217 (-0.796,0.363)	0.459		
HCC	-0.149 (-1.028,0.731)	0.738		
Alcoholic-LC	-0.531 (-1.197,0.134)	0.116	-0.007 (-0.680,0.667)	0.984
Others[c]	0.876 (0.310,1.442)	0.003[b]	0.897 (0.323,1.471)	0.003[b]

MELD, model for end-stage liver disease; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); IPV, intrapatient variability; HV, high variability; CI, confidence interval; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis
[a]Covariates with $p<0.2$ in univariate analysis were retained and entered in multiple linear regression model.
[b]Statistically significant at $p<0.05$
[c]Others: HCV and HCC, HCV alone, fulminant hepatitis, Wilson's disease, or toxic hepatitis.

rejection in the LV group and 14 in the HV group (p=0.647). In addition, there were 14 patients with infection in LV group and 17 in the HV group (p=0.494). The average number of infections during the 6-months period in the HV group was significantly higher than that in the LV group (0.9 vs. 0.4; p=0.039). The type of infections includes pneumonia, sepsis, intra-abdominal infection, peritonitis, etc. The number of patients diagnosed with post-transplant diabetes was 11 in the LV group and 10 in the HV group, which was not significantly different (p=0.800).

Multiple linear regression analysis conducted to investigate the factors influencing the number of infection during the 6-months after transplantation found that the number of infections increased as IPV increased (p=0.015; Table 4).

Renal function

The average monthly eGFR during the 6-months period after transplantation in the two groups is shown in Table 5. There was no significant difference in the mean eGFR value between the two groups. Additionally, there was no significant difference in the degree of deterioration of renal function during the 6-months period according to the linear mixed model (p=0.918).

Table 5. Changes in the averaged eGFR according to IPV during the first 6 months after transplantation, by IPV

Mean eGFR (mL/min/1.73 m^2)	IPV		*p*-value[a]
	Low variability (N=41)	High variability (N=41)	
Baseline	91.8	89.4	0.732
1st month	86.9	78.6	0.237
2nd month	84.8	82.3	0.683
3rd month	81.5	74.8	0.245
4th month	83.1	75.6	0.371
5th month	77.1	71.2	0.390
6th month	77.2	73.8	0.597

eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); IPV, intrapatient variability
[a]*p*-values were obtained by t-test.

Discussion

In this study, we investigated the effect of IPV on acute rejection, infection, post-transplant diabetes, and renal function within 6 months of liver transplantation. As a result, it was showing the greater number of infections in higher intrapatient variability group. However, there were no significant differences in acute rejection, post-transplant diabetes, and renal function.

Tacrolimus is a drug with high variability that is used for immunosuppression following organ transplantation. Thus, therapeutic drug monitoring is usually performed to assess interpatient variability. And IPV can be calculated to assess intrapatient variability.[9] Several previous studies have investigated the effect of IPV of tacrolimus on renal transplantation outcomes.[9-12] According to Whalen *et al*., the high IPV group had a lower survival rate, higher incidence of acute rejection, and lower mean eGFR during the 6 to 12 months after transplantation.[11] According to Shuker *et al*., the high IPV group had a lower survival rate, and IPV was associated with acute rejection.[11] In addition, when analyzed using multiple linear regression analysis, graft failure, acute rejection, glomerulopathy, and blood creatinine levels all increased as IPV increased. In a study of liver transplant patients, according to van der Veer *et al*, there was a study that the tacrolimus IPV between 6 and 18 months after transplantation did not affect graft failure.[13] However, according to Rayar *et al*, there were more complications and poorer outcomes (ICU stay, hospitalization duration, 1-year graft survival) in the high IPV group.[14] Although the number of patients in this study was 82 fewer than that of Rayar's studies, this study has shown that the number of infections is increased in those with high IPV of tacrolimus.

Based on the results of these studies, we investigated the effects of IPV on outcomes in liver transplant recipients. To measure blood concentration variability, we used the IPV formula from O' Regan *et al.*[10] The IPV values in this study were higher than those of the previous study; however, the previous study examined patients that had their tacrolimus dose stabilized 6 months post-transplantation, while in our study, the dose was changed frequently during the first 6 months after transplantation. Based on a review of previous research, this study was designed to compare the outcomes of liver transplantation in two groups, an HV group and LV group, based on the median individual IPV.[9-11]

There was no significant difference in either baseline characteristics or mean blood concentrations of tacrolimus. This implies that the differences in the mean blood concentrations of tacrolimus and baseline characteristics between both groups can be excluded from the effects on post-transplantation outcomes.

In addition, the rate of deviation from the therapeutic range in the HV group was significantly higher than in the LV group. The higher the IPV, the greater the risk of rejection, toxicity, infection, and malignancy due to the hazards of either excessively low or high immunosuppression.[16] Therefore, monitoring the IPV of tacrolimus may improve outcomes after liver transplantation. Tacrolimus is used clinically as a maintenance immunosuppressant along with mycophenolate mofetil, and prednisolone.

The mean number of infection within 6 months after transplantation was significantly higher in the HV group than in the LV group. In addition, multiple linear regression showed that IPV was associated with the number of infection during this period. In other words, the higher the IPV of tacrolimus, the greater the risk of infection. This suggests that intensive monitoring of IPV is necessary to reduce the risk of infection.

According to previous studies on kidney transplant recipients, the lower IPV groups had a higher survival rate at 6-12 months after transplantation, a lower incidence of acute rejection, and a tendency to maintain a high eGFR.[9-11] In this study of liver transplant recipients, the low IPV group maintained on a therapeutic dose for up to 6 months after transplantation and their number of infections was low, but there was no significant difference in renal function. Since nephrotoxicity occurs in a tacrolimus dose-dependent manner, monitoring of renal function is important.[17] Therefore, although there was no significant difference in renal function between both groups in this study, observation of both the efficacy and safety of tacrolimus is essential. However, in the study by Agarwala *et al.*, the eGFR was significantly decreased at 1 month after transplantation compared to 1 year after transplantation in patients on tacrolimus.[18] Therefore, the eGFR would have been expected to decline after 6 months post-transplantation. This suggests that the differences in eGFR between the HV and LV groups during the first 6 months would be expected to be small. To further elucidate the influence of tacrolimus IPV on survival, acute rejection, and renal function in liver transplant patients, studies with larger populations and longer durations than 6 months are necessary.

Concurrent medications, diet, and genetic factors could affect tacrolimus IPV. According to Goodall *et al.*, the high IPV group presented for outpatient follow-up less frequently than the low IPV group.[16] This is important since has adjusting the immunosuppressant dose cannot be performed adequately through outpatient visits. Since outpatient visits can be considered as a surrogate measure of treatment adherence, assessing IPV may an indirect tool for examining adherence as well. Nonadherence to the immunosuppression regimen

may lead to antibody-mediated rejection, and eventually graft failure.[19] Therefore, IPV monitoring can predict compliance to the immunosuppressant medication. By improving compliance through patient education, IPV levels can be lowered, which would improve the prognosis after transplantation. Another option for ensuring compliance and keeping IPV levels low, would be to change to a single daily dosage form of tacrolimus.[20]

There are some limitations to our study. Additionally, only 82 patients were included in this study, and additional studies with an increased number of patients may be needed. Also, the blood samples used for this study where taken at admission and at outpatient visits starting approximately 1month after discharge. Therefore, the intermittent measuring of blood concentrations is a limitation. We believe that further studies on the long-term effects of IPV in liver transplantation recipients are necessary to further validate our results.

Despite these limitations, our study is one of the first on the effect of tacrolimus IPV on clinical outcomes in liver transplant recipients. In addition, to improve clinical outcomes after liver transplantation, monitoring both the blood concentration and IPV is essential.

Tacrolimus blood concentration monitoring is currently being conducted in the clinical setting, but this study suggests that IPV monitoring is also needed to improve transplant clinical outcomes. Additional studies with larger patient populations and longer follow-up periods will be necessary. We believe that our study will be the upon which future studies will be built.

Declaration of Conflicting interest

All authors declare that there is no conflict of interest.

Abbreviations

eGFR, estimated glomerular filtration rate

HV, high variability

IPV, intrapatient variability

LV, low variability

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