Long-term Clinical Significance of Tacrolimus Trough Level at the Early Period After Kidney Transplantation

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ABSTRACT

Background. The stable immunosuppressant level at the early period after kidney transplantation (KT) is one of the most important factors for the prognosis of KT. However, the extent of immunosuppression varies according to the policies of each KT center. We investigated the relationship between the clinical outcome and tacrolimus trough level (TTL) at the early post-transplant period.

Materials and Methods. We retrospectively analyzed medical records of patients who underwent KT between July 2007 and June 2016. We investigated TTLs at 3 months after KT. We evaluated the incidence of biopsy-proven acute rejection (BPAR), cytomegalovirus infection, and graft survival according to the TTLs.

Results. A total of 426 patients who received KT during the study period were enrolled. The mean age of KT recipients was 46.3 ± 11.5 years, and 55.5% of patients were men. The incidence of BPAR within 1 year after KT was significantly higher when TTLs at 3 months were less than 4.0 ng/mL ($P = .020$). Death-censored graft survival rates were significantly lower in KT recipients with BPAR and TTL less than 4.0 ng/mL ($P < .001$, $P < .001$, respectively). In multivariate analysis, BPAR and TTL less than 4.0 ng/mL at 3 months after KT were independent risk factors for graft failure.

Conclusion. BPAR and TTL less than 4.0 ng/mL at 3 months after KT are important risk factors for allograft failure. Therefore, TTL should be kept at least 4.0 ng/mL or more at 3 months after KT to reduce the incidence of BPAR within 1 year after KT.

TACROLIMUS is a main maintenance immunosuppressant in kidney transplantation (KT) [1,2], and the level at the early period after KT is very important for the short- and long-term prognosis of the allograft [3,4] because of the increased likelihood of infection by over-immunosuppression or rejection by under-immunosuppression, according to the tacrolimus trough level (TTL) [3,5,6]. However, the common criteria of TTL are uncertain, and the protocols of each KT center varies. We investigated the relationship between the clinical outcome and TTLs in the early post-transplant period.

MATERIALS AND METHODS

Study Design

We retrospectively analyzed 429 patients who received KT between July 2007 and June 2016. We investigated the TTLs for comparison of clinical outcome according to the TTLs at 3 months after KT because that time is known to be the critical period [5–7]. We evaluated the incidence of biopsy-proven acute rejection (BPAR), cytomegalovirus (CMV) infection, BK virus-associated nephropathy (BKVAN), urinary tract infection, and graft and patient survival according to the TTLs.

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Table 1. Comparison of clinical parameters according to tacrolimus trough level at 3 month after kidney transplantation

	TTL 4 (n=26)	TTL≥4 (n=400)	*P*-value
Recipient age at KT, years	47.2 ± 12.5	46.2 ± 11.4	0.674
Donor age at KT, years	42.7 ± 15.0	43.2 ± 13.6	0.869
Recipient male gender, n (%)	12 (46.2)	223 (55.8)	0.417
Donor male gender, n (%)	14 (53.8)	233 (58.3)	0.686
Type of KT, n (%)			0.009
DDKT	20 (76.9)	201 (50.3)	
LDKT	6 (23.1)	199 (49.8)	
ABO-incompatible KT, n (%)	0	29 (7.3)	0.241
KT number, n (%)			0.756
First	24 (92.3)	350 (87.5)	
Second	2 (7.7)	50 (12.5)	
Dialysis type before KT, n (%)			0.146
Hemodialysis	21 (80.8)	294 (73.5)	
Peritoneal dialysis	5 (19.2)	59 (14.8)	
None	0	47 (11.8)	
Cause of end-stage renal disease, n (%)			0.392
Glomerulonephritis	17 (65.4)	298 (74.5)	
Diabetes mellitus	3 (11.5)	22 (5.5)	
Hypertension	6 (23.1)	60 (15.0)	
ADPKD	0	13 (3.3)	
HLA mismatch number	3.6 ± 1.7	3.2 ± 1.7	0.286
Panel reactive antibody ≥ 50%, n (%)	6 (42.9)	39 (23.6)	0.120
Donor specific antibody, n (%)	4 (30.8)	22 (13.5)	0.105
Induction immunosuppressant, n (%)			0.021
Basiliximab	18 (69.2)	347 (86.8)	
Thymoglobulin	8 (30.8)	53 (13.3)	

Values are expressed as means ± SDs, n (%). KT = kidney transplantation, DDKT = deceased donor kidney transplantation, LDKT = living donor kidney transplantation, ADPKD = autosomal dominant polycystic kidney disease, HLA = human leukocyte antigen

The Institutional Review Board of Keimyung University Dongsan Medical Center approved this study (2018–12–034).

Immunosuppression Protocols

We used basiliximab (20.0 mg at days 0 and 4, respectively; Simulect, Novartis, Basel, Switzerland) or antithymocyte globulin (Thymoglobulin, Genzyme, Cambridge, MA, United States; 1.5 mg/kg at day 0 and 1.0 mg/kg between day 1 and day 3) as the immunosuppressant for the induction treatment in the kidney transplant recipients (KTRs) according to the immunologic risks. We used tacrolimus (Prograf, Astellas Pharma Inc, Toyama, Japan), checking its trough levels, prednisolone (30.0 mg, once a day), and mycophenolate mofetil (500.0 mg, twice a day, CellCept, Hoffmann-La Roche Inc, Nutley, United States) as the immunosuppressants for the maintenance treatment.

Demographic and Clinical Data

We evaluated the donor and recipient ages at KT, donor and recipient genders, donor type, the frequency of KT, dialysis type before KT, causes of end-stage renal disease, the number of HLA mismatches, immunosuppressant for induction and maintenance treatments, the proportions of BPAR, panel reactive antibodies >50%, and positive donor specific antibodies. We investigated the incidence of BPAR, CMV infection, BKVAN, urinary tract infection, and clinical outcome of KTRs according to the TTLs.

Statistical Analyses

Student *t* test was performed in continuous variables with normal distributions, and the variables were expressed as the means ± standard deviations. A χ^2 or Fisher's exact test was performed in categorical variables, and the variables were expressed as the

Table 2. Comparison of clinical outcomes according to tacrolimus trough level at 3 month after kidney transplantation

	TTL 4 (n=26)	TTL≥4 (n=400)	*P*-value
BPAR within 1 year after KT, n (%)	6 (23.1)	32 (8.0)	0.020
CMV infection within 1 year after KT, n (%)	11 (78.6)	128 (94.8)	0.054
BKVAN within 1 year after KT, n (%)	0	6 (35.3)	0.281
UTI within 1 year after KT, n (%)	3 (42.9)	19 (63.3)	0.408
Follow-up duration, months	62.1 ± 35.3	55.2 ± 28.1	0.412

Values are expressed as means ± SDs, n (%).
BPAR = biopsy-proven acute rejection, KT = kidney transplantation, CMV = cytomegalovirus, BKVAN = BK virus-associated nephropathy, UTI = urinary tract infection

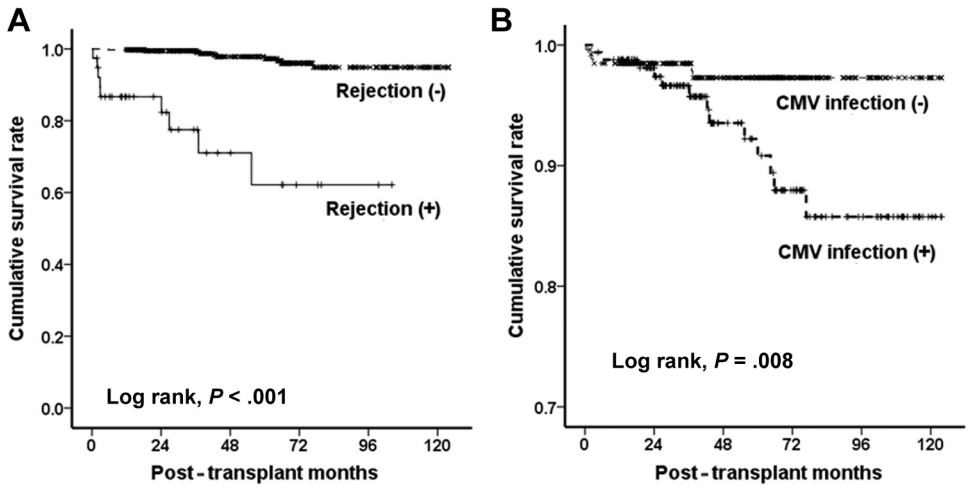

Fig 1. Comparison of death-censored graft survival according to the BPAR **(A)** and CMV infection **(B)**. BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus.

numbers and percentages. Death-censored graft survival rate according to the TTLs was obtained by the Kaplan-Meier analysis with a log-rank test. Risk factors for graft failure were analyzed by Cox regression analysis. *P* values less than .05 were statistically significant. Statistical analysis was performed with the SPSS (version 18.0, SPSS Inc, Chicago, IL, United States) statistical software package.

RESULTS

Baseline Characteristics of the Study Population

Mean follow-up duration was 54.0 ± 31.0 months. A total of 426 patients who received KT during the study period were enrolled. The mean age of KTRs was 46.3 ± 11.5 years, and men were 55.5% of the recipients. Mean ± standard deviation values for TTLs at 3 months in the study population were 7.1 ± 2.4 ng/mL. The average TTLs at 3 months after KT were assessed by means of receiver operating characteristic (ROC) curve analysis. The highest value of the area under the ROC curve was the TTL at 3 months (area under the curve = 0.41 ± 0.08; 95% CI, 0.26–0.57). TTLs at 3 months < 4.0 ng/mL had a prognostic sensitivity of 73.7% and a specificity of 6.4%. ROC curve analysis showed a low specificity at a TTL < 4.0 ng/mL but showed significantly clinical outcomes at the standard TTL of 4.0 ng/mL at 3 months after KT.

Comparison of Clinical Parameters and Outcomes According to TTL at 3 Months After KT

The proportion of deceased donor kidney transplantation was significantly higher in the group with TTL less than 4.0 ng/mL in comparison with that with TTL more than 4.0 ng/mL. There were no significant differences in the donor and recipient ages at KT, donor and recipient genders, the frequency of KT, dialysis type before KT, causes of end-stage renal disease, the number of HLA mismatches, and immunosuppressants for induction and maintenance treatments (Table 1).

The incidence of BPAR within 1 year after KT was significantly higher when TTLs at 3 months were less than 4.0 ng/mL ($P = .020$). However, there were no significant differences in the incidences of CMV infection, BKVAN, and urinary tract infection within 1 year after KT between the 2 groups (Table 2).

Comparison of Death-Censored Graft and Patient Survivals According to TTL at 3 Months After KT

Death-censored graft survival rate was significantly lower in KTRs with BPAR ($P < .001$) (Fig 1A) and CMV infection ($P = .008$) (Fig 1B). In multivariate analysis, BPAR was an independent risk factor for graft failure, but not CMV

Table 3. Risk factors associated with graft failure in kidney transplantation

	Univariate			Multivariate*		
Variables	HR	95% C.I.	*P*-value	HR	95% C.I.	*P*-value
Deceased donor kidney transplantation	4.021	1.333-12.125	0.013			
Thymoglobulin induction	3.729	1.133-12.271	0.030			
CMV infection	3.450	1.310-9.083	0.012			
Delayed recovery of graft function	3.317	1.192-9.228	0.022	6.418	1.941-21.222	0.002
BK virus-associated nephropathy	8.317	1.908-36.260	0.005	8.328	1.579-43.935	0.012
Biopsy-proven acute rejection	15.219	5.783-40.053	0.000	17.699	5.418-57.820	0.000
TTL less than 4 ng/mL at 3 months after KT	6.668	2.397-18.554	0.000	12.044	2.843-51.018	0.001

Abbreviation: HR = hazard ratio, C.I. = confidence interval, CMV = cytomegalovirus, TTL = tacrolimus trough level, KT = kidney transplantation

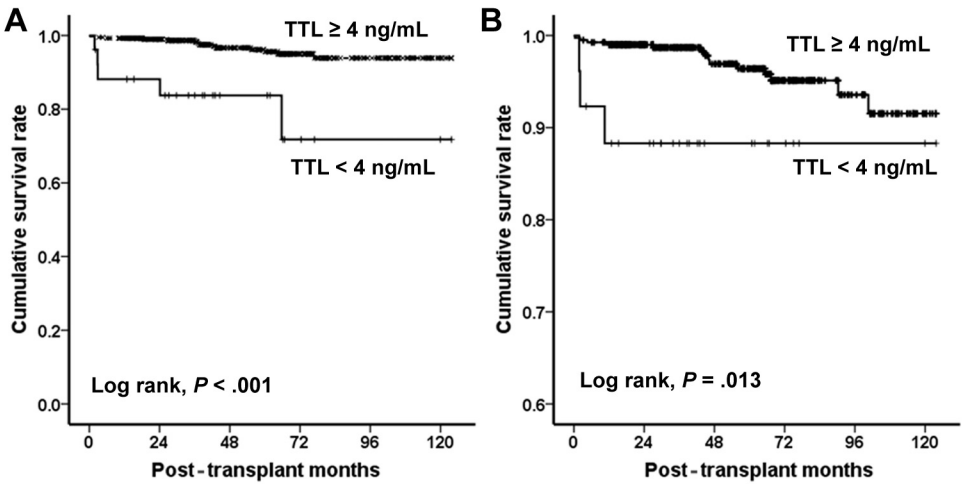

Fig 2. Comparison of death-censored graft survival **(A)** and patient survival **(B)** according to tacrolimus trough level at 3 months after kidney transplantation. TTL, tacrolimus trough level.

infection (Table 3). Death-censored graft survival rate was significantly lower in the group with a TTL less than 4.0 ng/mL in comparison with that with TTL more than 4.0 ng/mL at 3 months after KT ($P < .001$) (Fig 2A). In multivariate analysis, TTL less than 4.0 ng/mL at 3 months after KT was an independent risk factor for graft failure (Table 3).

Patient survival rate was significantly lower in the group with TTL less than 4.0 ng/mL in comparison with that with TTL more than 4.0 ng/mL at 3 months after KT ($P = .013$) (Fig 2B).

DISCUSSION

We analyzed clinical outcomes of the TTLs at 3 months after KT. At 3 months, the meaningful value of the TTL was 4.0 ng/mL. When we divided the patients into the 2 groups at a TTL of 4.0 ng/mL, the proportion of BPAR within 1 year after KT was significantly higher in the TTL less than 4.0 ng/mL group in comparison with the TTL of more than 4.0 ng/mL group. This was consistent with other studies [6]. In our transplant center, we maintained the trough level of tacrolimus at 5.0 to 10.0 ng/mL at the early period after KT because a lower level showed a high incidence of BPAR at that time, especially a TTL less than 4.0 ng/mL. The proportion of CMV infection within 1 year after KT tended to be higher in the less than 4.0 ng/mL group in comparison with the more than 4.0 ng/mL group, but there was no significant difference between the 2 groups. Although the TTLs were not associated with the incidence of CMV, BKVAN, and urinary tract infection in our study, allograft function within 1 year after KT was better in patients with higher TTLs.

We evaluated the death-censored graft survival according to the BPAR and CMV infection. In the Kaplan-Meier curve, death-censored graft survival rates were significantly lower in the BPAR and CMV infection groups, but in multivariate analysis, only BPAR was significantly associated with graft failure. We also evaluated the death-censored graft survival according to a TTL of 4.0 ng/mL at 3 months after KT. In the Kaplan-Meier curve, death-censored graft survival rate was significantly lower in the group with a TTL less than 4 ng/mL in comparison with that with a TTL more than 4.0 ng/mL at 3 months after KT. These results suggest that a TTL less than 4.0 ng/mL at 3 months after KT was an independent risk factor for graft failure because of the higher incidence of BPAR.

The patient survival rate was significantly lower in the less than 4.0 ng/mL group in comparison with in the more than 4.0 ng/mL group at 3 months after KT. This suggests that the incidence of BPAR increased in patients with less than 4.0 ng/mL TTL, and uncontrolled infection status, such as *Pneumocystis jirovecii* pneumonia, CMV pneumonitis, and bacterial pneumonia, after a strong immunosuppressive treatment against BPAR resulted in low patient survival rate.

In conclusion, BPAR and TTL less than 4.0 ng/mL at 3 months after KT are important risk factors for allograft failure. Therefore, TTL should be kept at least 4.0 ng/mL or more at 3 months after KT to reduce the incidence of BPAR within 1 year after KT.

REFERENCES

[1] Lim MA, Kohli J, Bloom RD. Immunosuppression for kidney transplantation: where are we now and where are we going? Transplant Rev (Orlando) 2017;31:10–7.

[2] Chang JY, Yu J, Chung BH, Yang J, Kim SJ, Kim CD, et al. Immunosuppressant prescription pattern and trend in kidney transplantation: a multicenter study in Korea. PLoS One 2017;12:e0183826.

[3] Akturk S, Erdogmus S, Kumru G, Elhan AH, Sengul S, Tuzuner A, et al. Average tacrolimus trough level in the first month after transplantation may predict acute rejection. Transplant Proc 2017;49:430–5.

[4] Townamchai N, Safa K, Chandraker A. Immunologic monitoring in kidney transplant recipients. Kidney Res Clin Pract 2013;32:52–61.

[5] Gaynor JJ, Ciancio G, Guerra G, Sageshima J, Roth D, Goldstein MJ, et al. Lower tacrolimus trough levels are associated with subsequently higher acute rejection risk during the first 12 months after kidney transplantation. Transpl Int 2016;29:216–26.

[6] Israni AK, Riad SM, Leduc R, Oetting WS, Guan W, Schladt D, et al. Tacrolimus trough levels after month 3 as a predictor of acute rejection following kidney transplantation: a lesson learned from DeKAF Genomics. Transpl Int 2013;26:982–9.

[7] Okidi OO, Van Dellen D, Sobajo C, Summers A, Greer JR, Augustine T. Kidney transplant recipients requiring critical care admission within one year of transplant. Exp Clin Transplant 2017;15:40–6.