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Protocol Biopsy Findings in Living Donor Kidney Transplant Patients Treated With Once-daily or Twice-daily Tacrolimus Formulation

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ABSTRACT

Background. Once-daily extended-release tacrolimus (Tac-QD) has been shown to have equivalent efficacy and safety to the twice-daily formulation (Tac-BID) in kidney transplant patients. However, detailed comparison of allograft pathology found on a protocol biopsy (PB) in Tac-QD– versus Tac-BID–based regimens has not been described.

Methods. We retrospectively investigated 119 de novo living donor kidney transplant patients treated with Tac-QD (n = 90) or Tac-BID (n = 29) and their 3- and 12-month PB results. Other immunosuppressive drugs administered included basiliximab, mycophenolate mofetil, and methylprednisolone. We evaluated daily doses and trough levels of Tac and serum creatinine levels, and compared pathologic findings.

Results. Daily doses were higher in the Tac-QD group, but trough levels and serum creatinine levels were comparable. On 3- and 12-month PB, the frequency of subclinical rejection was similar between the groups, whereas interstitial fibrosis and tubular atrophy (IF/TA) were less common in the Tac-QD group at 12 months (42.2% vs 20.6%, $P = .04$). Univariate and multivariate logistic regression analyses revealed that allograft rejection (borderline changes or higher) was associated with IF/TA (odds ratio 4.09, 95% confidence interval 1.76–10.10, $P = .001$). The Tac-QD–based regimen showed a trend toward the absence of IF/TA but it did not reach statistical significance. Tubular vacuolization and arteriolar hyaline changes were also comparable in the two groups.

Conclusions. We found a trend toward milder IF/TA, but no significant differences in kidney allograft pathology in patients who were administered Tac-QD– versus Tac-BID–based regimens at 12 months. The effects of Tac-QD on chronic allograft injury must be studied by longer observation.

CALCINEURIN inhibitors (CNIs), including cyclosporine and tacrolimus (Tac), have contributed to better graft outcomes in organ transplant patients. Currently, most kidney transplant patients receive antibody induction and triple immunosuppression with CNIs, mycophenolate mofetil (MMF), and corticosteroids. During the maintenance period, treating physicians need to monitor two aspects of CNIs: inhibitory effects on acute rejection and nephrotoxicity. Tac was first developed as a twice-daily formulation (Tac-BID). In 2008, once-daily extended-release Tac (Tac-QD) became available, and its comparative effects on the incidence of rejection, graft survival, and patient survival have already been shown [1,2]. However, detailed allograft pathology, such as differences in subclinical rejection rates and CNI-associated changes on protocol biopsy (PB), has not been well studied. In this study, we reviewed the findings of 3- and 12-month PB in de

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novo kidney transplant patients who had been administered Tac-QD or Tac-BID.

PATIENTS AND METHODS

Study Design and Patient Population

We reviewed 119 consecutive de novo living donor kidney transplant patients who had been administered Tac-based immunosuppression who underwent PBs at Kyushu University Hospital from August 2008 through April 2011. In all patients, immunosuppression was induced with basiliximab and maintained with a triple-drug regimen consisting of Tac (Tac-BID in 29 patients and Tac-QD in 90 patients), MMF, and methylprednisolone (mPSL). Recipients of ABO-incompatible transplants (n = 35, 29.4%) and presensitized patients who tested positive for flow cytometric panel reactive antibodies (flow-PRAs; n = 14, 11.8%) were also pretreated with plasmapheresis and rituximab. We investigated clinical information including daily doses and trough levels of Tac, serum creatinine levels, and PB findings as described below. All PBs analyzed were obtained according to our clinical follow-up protocol, and no extra biopsy specimens or urine/blood samples were obtained for the purpose of the study. Informed written consent was obtained from eligible patients, and this study was approved by the Institutional Review Board at Kyushu University Hospital (protocol #24–54).

PB Policy and Pathologic Interpretation

Since August 2008, our hospital has had a fixed PB policy of performing biopsies 3 and 12 months post-transplantation. Our preliminary data revealed the usefulness of this protocol in detecting subclinical acute rejection at 3 months under current immunosuppression [3]. At a 12-month PB, we focus on chronic allograft injuries as well as subclinical rejection. During the study period, all patients were managed with this uniform PB policy. Allograft biopsy was performed under ultrasound guidance using a Bard Magnum device (Bard Biopsy Systems, Tempe, AZ, United States) and 18-gauge needles. For light microscopy, serial tissue sections were stained with hematoxylin and eosin, periodic acid-Schiff, methenamine silver, and Masson's trichrome stains. For immunofluorescence study, we examined the biopsy specimens for immunoglobulin (Ig) G, IgA, IgM, complement (C) 3, C1q, fibrinogen, kappa/lambda light chains, and C4d. All biopsy specimens were scored according to the Banff '09 classification [4]. Patients with rejection were classified into those with borderline changes, acute T-cell–mediated rejection (grade Ia or higher), and/or acute antibody-mediated rejection. PBs were defined as procedures performed without an increase in serum creatinine of greater than 10% from baseline levels (determined by average serum creatinine 3 months before the biopsy) and no previous rejection episodes within 1 month.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) and number (%). JMP version 9.0.2 (SAS Institute, Cary, NC, United States) was used for all statistical analyses. The Student *t*-test and the Mann-Whitney U test were used to assess differences in numerical variables. The chi-square and Fisher exact probability tests were used for categorical data as appropriate. Daily doses, trough levels of Tac, and serum creatinine levels were compared with repeated-measure analysis of variance (ANOVA). To identify the factors associated with interstitial fibrosis and tubular atrophy (IF/TA) at 12 months, we applied univariate and multivariate logistic regression analyses. Recipient age, gender, and factors selected by the backward stepwise method ($P < .1$) were used for the multivariate analysis. After multivariate analysis, we added multiple comparisons with Bonferroni correction. Results were expressed as odds ratios (ORs) with respective 95% confidence intervals (CIs). A P value less than .05 was considered statistically significant.

Table 1. Demographic and Clinical Characteristics of Tac-BID and Tac-QD Groups

	Tac-BID Group (n = 29)	Tac-QD Group (n = 90)	*P* Value
Recipient age (y)	34 ± 15	42 ± 15	.001
Recipient gender (male/female)	22/7	51/39	.07
Donor age (y)	56 ± 10	53 ± 12	.2
Pre-emptive KT (%)	6 (20.7%)	23 (25.6%)	.6
ABO-incompatible KT (%)	6 (20.7%)	29 (32.2%)	.2
Positive flow-PRA test (%)	3 (10.3%)	11 (12.2%)	.8
HLA mismatch count (A, B, DR)	2.6 ± 1.6	2.8 ± 1.4	.4
Primary disease of ESRD			
Chronic glomerulonephritis	19 (65.5%)	57 (63.3%)	
Diabetes mellitus	5 (17.2%)	15 (16.7%)	.7
Others	5 (17.2%)	18 (20.0%)	
MMF dose at 3 mo	1250 ± 481	1126 ± 267	.09
12 mo	911 ± 238	913 ± 193	.9
mPSL dose at 3 mo	4.2 ± 1.9	3.8 ± 0.7	.08
12 mo	3.1 ± 1.5	3.2 ± 1.2	.9

Abbreviations: Tac, tacrolimus; BID, twice daily; QD, once daily; KT, kidney transplantation; flow-PRA, flow-cytometric panel reactive antibody; HLA, human leukocyte antigen; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; mPSL, methylprednisolone.

RESULTS

Demographic and Clinical Characteristics of the Patients

Demographic characteristics of participating patients are presented in Table 1. Recipient gender, donor age, frequencies of ABO-incompatible transplantation and presensitized recipient, pre-emptive transplantation, HLA-mismatch count, primary diseases, and doses of MMF and mPSL at 12 months were not different between the two groups. The Tac-QD group had a higher mean recipient age ($P = .01$) than the Tac-BID group. There were trends toward lower doses of MMF and mPSL in the Tac-QD group than in the Tac-BID group at 3 months, and the percentage of female recipients in the Tac-QD group was higher, but these differences did not reach statistical significance. All patients were followed in our outpatient clinic for at least 2 years; follow-up periods in the Tac-BID and Tac-QD groups were 1473 ± 170 days and 1018 ± 194 days, respectively.

Daily Doses and Trough Levels of Tac, and Serum Creatinine Levels in Tac-BID and Tac-QD Groups

Daily doses and trough levels of Tac, and serum creatinine levels for the first 24 months after transplantation are shown in Fig 1. Daily doses of Tac were significantly higher in the Tac-QD group than in the Tac-BID group ($P < .01$, repeated-measure ANOVA), as reported in our preliminary