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Factorial Analysis on Individual Variability of Tacrolimus Extended-Release Formulation Pharmacokinetics in the Early Period after Renal Transplantation-Factors for AUTL/AUC Decrease

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Abstract

Background: We have often observed that the blood trough concentration (Ct) of the once-daily, prolonged-release formulation of tacrolimus (Graceptor®; GRC) becomes unstable, and it is difficult to adjust it in the early period after transplantation. Consequently, we compared the relationships between pharmacokinetic parameters and influencing factors in a group of GRC-treated patients compared with those in a group of Prograf® (PRG)-treated patients.

Methods: The study included 8 patients who were newly treated with GRC and 44 patients who were newly treated with PRG. We performed 24-hour therapeutic drug monitoring to compare the relationships between pharmacokinetic parameters, including the area under the curve (AUC), the ratio of the area under the trough level (AUTL)/AUC to indicate the relationships among AUCs, peak concentration (C_p), and C_t. The C_p/C_t values, and dose/body weight (UC/[D/BW]) values reflected bioavailability and the influencing factors; number of days after transplantation and Dose/BW in the GRC-treated and PRG-treated patients.

Results: The C_p/C_t values were higher and the AUTL/AUC and AUC corrected by dose/body weight (AUC/[D/BW]) values were lower with a low number of days after transplantation (particularly within 20 days) and a large dose than a high number of days after transplantation and a small dose in the GRC-treated patients. No such associations were observed in the PRG-treated patients.

Conclusion: Care is required when using GRC as there is a tendency for C_p to increase owing to rapid absorption within 20 days after transplantation. Blood levels may be unstable and side effects may be more prevalent in some patients. Moreover, the utilization rate is low and the dose is high in such patients; therefore, unstable gastrointestinal function caused by a variety of factors may play a role in the early period after transplantation.

Keywords: Tacrolimus extended-release formulation; AUTL/AUC; Pharmacokinetics; Individual variability

Abbreviations: AUC: Area Under the Curve; AUTL: Area Under the Trough Level; BW: Body Weight; Cp: Peak Concentration; Ct: Trough Concentration; D: Dose; GRC: Graceptor®; MMF: Mycofenolate Mofetil; PRG: Prograf®; TAC: Tacrolimus.

Introduction

The most common regimen following kidney transplantation involves treatment with one of four immunosuppressive agents (tacrolimus [TAC], mycofenolate mofetil [MMF], basiliximab, and corticosteroid) and has been shown to achieve excellent outcomes. The pharmacokinetics of Graceptor® (GRC TAC QD) differ slightly from those of tacrolimus BID [Prograf®; PRG] as a result of differences in the inactive ingredients included in the capsules. Some authors have previously reported the use of GRC in patients undergoing kidney transplantation. [1-4]. For example, after renal transplantation, recipients are switched from TAC-BID to an equivalent dose of TAC-ER, and the trough concentration (C_t) of TAC became lower than that before switching. [5-9]. Moreover, we have often observed that the Ct of GRC becomes unstable over time, making it nearly impossible to titrate the dosage up, and it can be difficult to adjust the dosage in the early period after transplantation. Thus, the aim of the present study was to analyze pharmacokinetic parameters to determine the factors leading to unstable Ct in GRC-treated patients in early-phase renal transplantation and compare them to those for PRG-treated patients.

Material and Methods

The study included 8 patients who were newly treated with GRC and 44 patients who were newly treated with PRG. We performed 24-hour therapeutic drug monitoring to compare the relationships between pharmacokinetic parameters and influencing factors in the GRC-treated and PRG-treated patients. In the GRC-treated patients, GRC was administered once a day at 8 AM after breakfast, and blood samples were collected at the following 9 time points: immediately before administration, and 1, 2, 3, 4, 6, 12, 18, and 24 hours after administration. In the PRG-treated patients, equal doses of PRG were

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administered at 8 AM and 8 PM after a meal, and blood samples were collected at the following 7 time points for both administrations: immediately before administration, and 1, 2, 3, 4, 6, and 12 hours after administration. As there were morning-evening differences in the pharmacokinetic parameters among the PRG-treated patients, the parameters were calculated separately for the morning and evening administrations.

We analyzed the relationships among each of the pharmacokinetic parameters, including the ratio of the area under the trough level to the area under the curve (AUTL/AUC), representing the relative involvement of peak concentration (C_p) and C_t in the AUC [10], C_p/C_t, AUC/(dose [D]/body weight [BW]), representing the relative estimate of bioavailability corrected with dose per body weight, and the number of days after transplantation.

Statistical Analyses: Statistical values in the present study are expressed as Mean ± SD for each group. Data were analyzed using a logistic regression analysis (JMP Version 8.0.2, SAS Institute Japan Ltd.). The coefficient of correlation was derived from the Fisher's z transformation. A value of $p<0.05$ was considered statistically significant.

Results

The pharmacokinetic parameters among the GRC-treated and

	GRC (n=8)	PRG (n=44)	
		Morning	Evening
Age (years)	51.6 ± 15.9	45.3 ± 12.6	
Male/female	5/3	30/14	
Dose (mg/day)	6.4 ± 5.2	9.2 ± 4.8	
Weight (kg)	53.4 ± 9.1	53.0 ± 9.6	
Number of days elapsed after transplantation	26.4 ± 15.2	33.8 ± 21.2	
D/BW (mg/kg/day)	0.11 ± 0.09	0.18 ± 0.09	
C_p/(D/BW) (ng/mL)/(mg/kg)	293.4 ± 139.3	292.1 ± 159.9	252.3 ± 141.9
C_t/(D/BW) (ng/mL)/(mg/kg)	122.9 ± 99.9	160.3 ± 110.0	172.8 ± 121.4
AUTL/AUC	0.68 ± 0.21	0.74 ± 0.11	0.82 ± 0.12*
C_p/C_t	3.17 ± 1.45	1.99 ± 0.58*	1.60 ± 0.48*
AUC/(D/BW) (ng/mL·h)/(mg/kg)	3910 ± 2295	2424 ± 1480*	
*p<0.05 (vs. GRC)			

Table 1: Comparison of pharmacokinetic parameters between the GRC-treated patients and the PRG-treated patients.

PRG-treated patients are presented in Table 1. The AUTL/AUC values were significantly lower among the GRC-treated patients than among the PRG-treated patients (evening administration). Additionally, the C_p/C_t values were significantly higher among the GRC-treated patients than among the PRG-treated patients (both morning and evening administration). Moreover, the AUC/(D/BW) values were significantly higher among the GRC-treated patients than among the PRG-treated patients.

With regard to the relationships among each parameter and the number of days after transplantation, the AUTL/AUC and AUC/(D/BW) values were lower and the C_p/C_t values were higher within 20 days post-transplantation than after 20 days post-transplantation in the GRC-treated patients (Figure 1A-1C). With regard to the relationships among each parameter and the D/BW, the AUTL/AUC and AUC/(D/BW) values were lower and the C_p/C_t values were higher with high D/BW values than with low D/BW values in the GRC-treated patients (Figure 2A-2C). No such associations were observed in PRG-treated patients. The observed relationship between the D/BW and AUC/(D/BW) values resulted from the fact that we raised the D/BW values in patients with low AUC/(D/BW) values because the blood levels of the drug did not rise. Negative correlations (correlation coefficient values: r>0.6) were observed for not only GRC administration, but also morning and evening administration of PRG. Furthermore, the AUTL/AUC values were lower and the C_p/C_t values were higher with low AUC/(D/BW) values than with high AUC/(D/BW) values in the GRC-treated patients (Figure 3A and 3B).

Discussion

The findings of the present study indicate that in the GRC-treated patients, the gastrointestinal function reduced within 20 days post-transplantation owing to various postoperative influences and the bioavailability (AUC/[D/BW]) easily decreased; thus, high doses (D/BW) were administered in some patients, which resulted in unstable blood levels. In addition, the dose of GRC was twice as much as that of PRG, which resulted in a larger amount of GRC than PRG being present in the gastrointestinal tract. Consequently, when the extended drug release was changed by some factors and the absorption rate increased, the abrupt absorption of a large amount of GRC present in the gastrointestinal tract occurred, which caused more frequent increases in the C_p/C_t values and decreases in the AUTL/AUC values compared to those with PRG [5] (Figure 4).

In such patients, controlling blood levels is difficult, and side effects can easily occur owing to increased C_p. Furthermore, an overdose may occur if the target C_t value is not adjusted according to the increase in the C_p value in order to maintain the AUC value.

Therefore, it should be noted that during the administration of GRC, changes such as those described here may occur in the early period after transplantation. Additionally, in such patients, it may be necessary to use PRG in the early period after transplantation and switch to GRC after the condition stabilizes. However, as the number

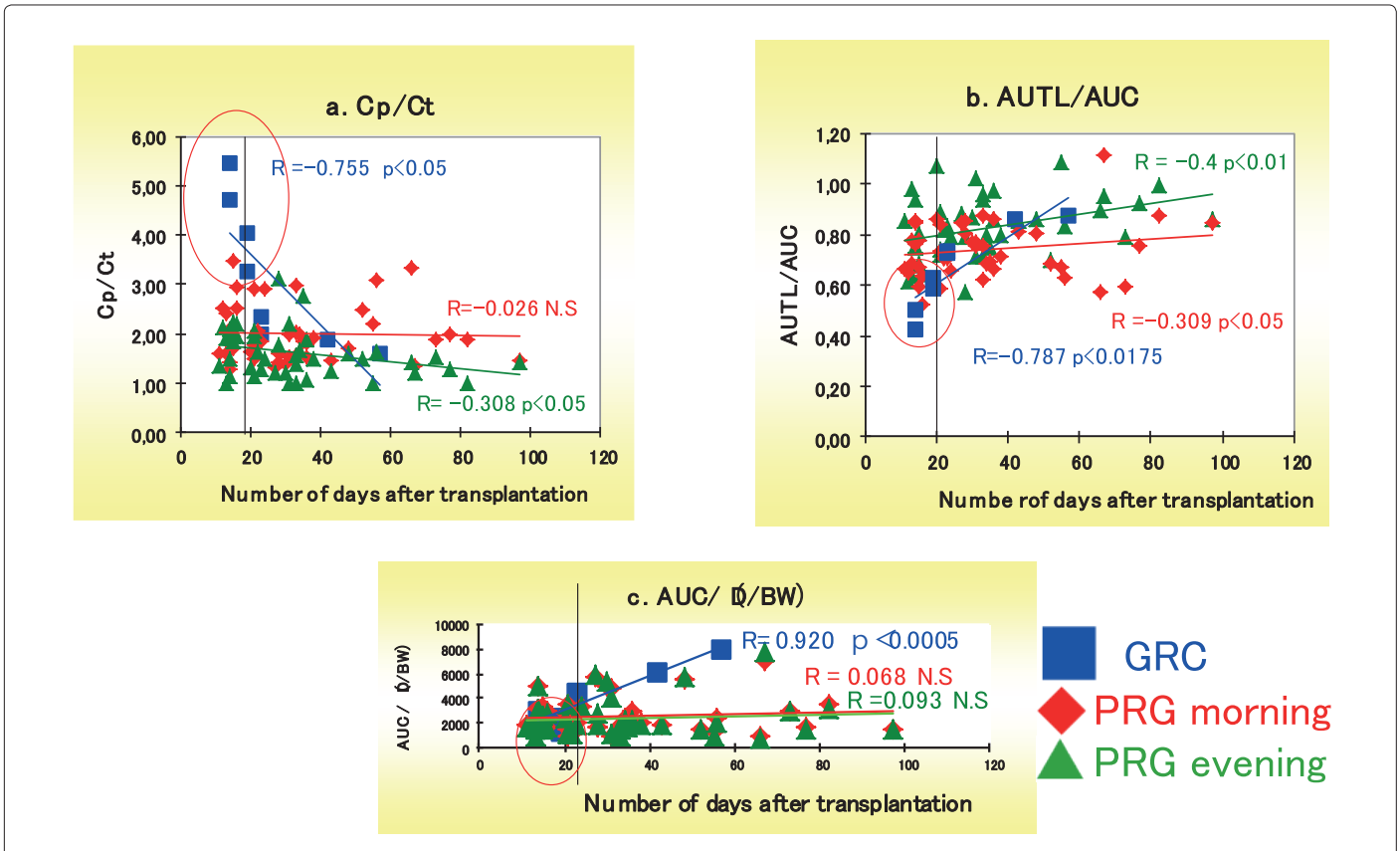

Figure 1: Correlation among pharmacokinetics parameters and number of days after transplantation.

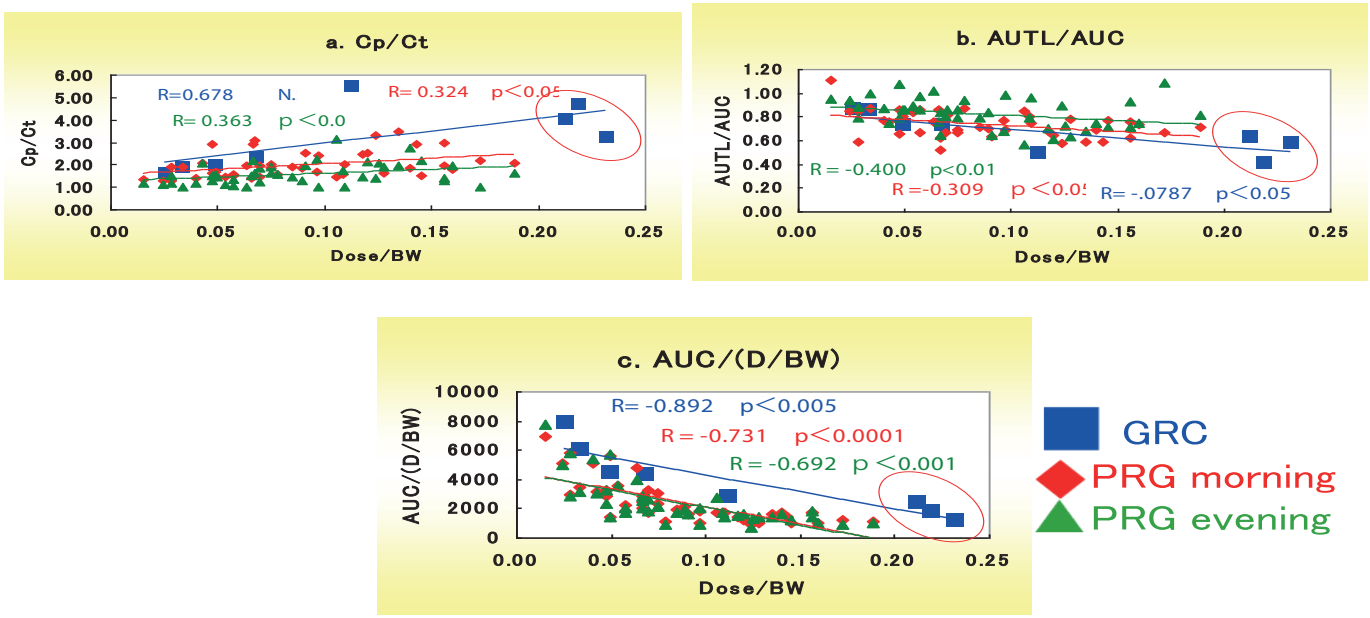

Figure 2: Correlation among pharmacokinetics parameters and dose.

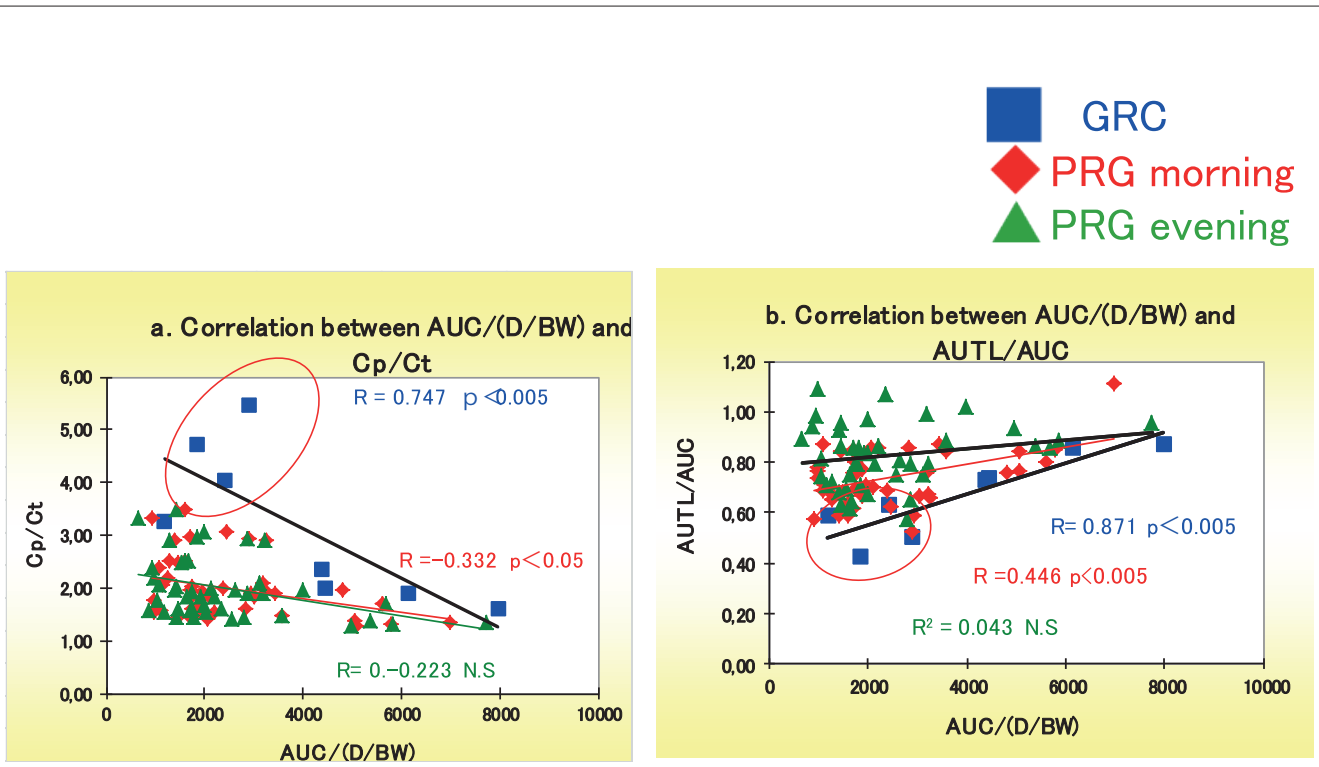

Figure 3: Correlation among pharmacokinetics parameters and bioavailability.

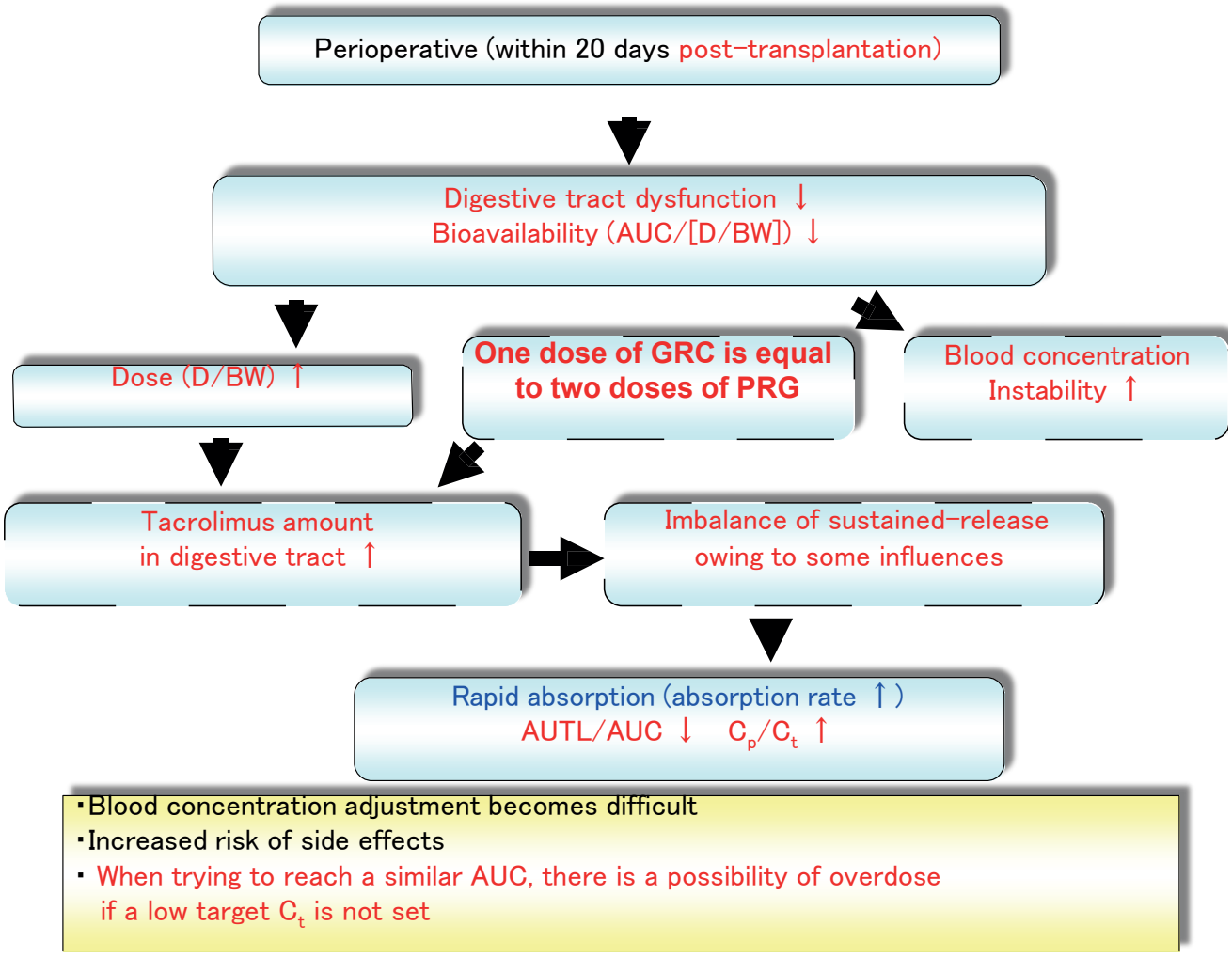

Figure 4: Estimation of the mechanism of reduced AUTL/AUC and increased C_p/C_t.

of GRC-treated patients included here was low, future studies need to examine numbers of GRC-treated patients.

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