Pharmacokinetic Study of Mycophenolic Acid in Korean Kidney Transplant Patients

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The purpose of this study was to characterize the pharmacokinetic parameters of mycophenolic acid (MPA) in Korean kidney transplant recipients. Plasma MPA concentrations of 10 Korean kidney transplant recipients administered a lower dose of mycophenolate mofetil (MMF; 750 mg twice a day) were measured at 2 weeks of MMF therapy by high-performance liquid chromatography (HPLC). The plasma MPA concentration-time curve pattern of patients taking lower doses of MPA was consistent with previously reported profiles of patients taking the fully recommended doses. The plasma MPA concentration-time curve was characterized by an early sharp peak within 1 hour and a small second peak in some patients at 4 to 12 hours postdose. The mean C_{max} and AUC were 8.73 ± 4.65 μg/mL and 18.45 ± 4.25 μg•h/mL, respectively. The mean fraction of free MPA was 1.60% ± 0.23%. Patients' age, weight, body surface area, and renal function did not influence the AUC. The free fraction of MPA appeared not to be affected by serum albumin and renal function when creatinine clearance was above 40 mL/min. Regression analysis between each plasma concentration and AUC for the limited sampling strategy of MMF therapeutic drug monitoring demonstrated that the concentrations of predose and 1- and 8-hour postdose were positively correlated with AUC (r = 0.74545, p = 0.0133; r = 0.68485, p = 0.0289; and r = 0.63636, p = 0.0479, respectively). The pattern of the concentration-time profile of MPA in Korean kidney recipients was similar to the results of other studies performed in Caucasians, although there was interindividual variability of AUC, C_{max}, and t_{max}. MPA concentrations of predose and 1- and 8-hour postdose were positively correlated with AUC.

Keywords: *Mycophenolate mofetil; pharmacokinetics; kidney transplant*

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Mycophenolate mofetil (MMF) has shown to be effective in the suppression of acute allograft rejection following renal transplantation when given orally on a twice-daily schedule in combination with cyclosporine and corticosteroids.[1-5] Following oral administration, MMF is rapidly and extensively absorbed and is presystemically hydrolyzed to form 2-morpholinoethyl ester of mycophenolic acid (MPA), the active immunosuppressive agent.[6,7] Following oral administration, the plasma profile of MPA in healthy subjects shows a rapid rise to achieve a peak value of plasma MPA concentration at about 1 hour postdosing. A secondary plasma MPA peak is seen at 6 to 12 hours after oral MMF administration, suggesting enterohepatic circulation.[8] Plasma MPA is highly bound to albumin, with a mean protein binding of 97%, and only the free MPA is available to inhibit IMPDH.[9] The free concentrations of mycophenolic acid, which correlates with pharmacodynamic activity, have shown to be altered in severe renal impairment.[10-13] Limited pharmacokinetic studies of MPA in renal transplant patients show that there is a large variability in the area under the plasma concentration versus time curve (AUC), time to peak plasma concentration (t_{peak}), and maximal plasma concentration (C_{max}).[14,15]

The incidence of intolerance, especially gastrointestinal (GI) intolerance, to MMF in Korean patients is high, so Korean patients are routinely put on a lower

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dose of MMF (500-750 mg bid) instead of a recommended dose of MMF (1000 mg bid). In addition, the pharmacokinetics of MPA in Korean kidney transplant patients have not been characterized previously. The objective of this study was to characterize the pharmacokinetics of MPA after lower doses of MMF in Korean kidney transplant patients who receive cyclosporine as the primary immunosuppressant. A secondary objective was to examine the patients' characteristics that are associated with MPA pharmacokinetics and find the time point that best correlates with an abbreviated MPA AUC.

METHODS

Patients

This study was an open-label evaluation of the pharmacokinetics of MPA in Korean kidney transplant patients. Inclusion criteria were male or female patients in the age group of 18 to 75 who underwent kidney transplantation at the Asan Medical Center in Seoul, Korea, and were treated with MMF in addition to cyclosporine and corticosteroids as immunosuppressants. Exclusion criteria were patients with systemic bacterial, fungal, or viral infection; patients who were currently receiving treatment for acute rejection; patients who were pregnant; and patients with severe gastrointestinal disorders.

Study Protocol

Cyclosporine (CsA; Neoral®, Novartis) was initially administered in a dose of 10 mg/kg/day in two divided doses. Thereafter, doses of CsA were adjusted to achieve 12-hour trough levels of 300 to 325 ng/mL, as measured by whole-blood radioimmunoassay (RIA). In recipients of a living-donor kidney, CsA was started 24 hours before the surgery; 500 mg of intravenous methylprednisolone sodium succinate was administered on the day of transplant surgery, and then the dose was progressively tapered and maintained at a low dose of oral methylprednisolone. MMF (Cellcept®, Roche Laboratory) was administered orally in a dose of 1000 mg/day in two divided doses starting 2 days before surgery, followed by titration to 1250 mg/day in two divided doses 3 days postoperatively, and finally to 1500 mg/day in two divided doses 6 days after kidney transplantation.

For the prophylaxis of bacterial infection, a double strength of trimethoprim/sulfamethoxazole every other day and 300 mg of isoniazid daily were administered. Patients rinsed their mouths with 500,000 units of nystatin syrup four times a day for the prevention of oral candidiasis. To prevent gastric ulcers, nizatidine and antacids were administered. The interval of time between MMF dosing and the antacids was maintained at least 2 hours to avoid possible drug interactions.

Patients taking 750 mg of MMF twice daily regularly for at least 7 days were studied within 2 weeks of renal transplantation. This means that pharmacokinetic parameters of MPA for all patients were studied on either the 13th or 14th day of posttransplant. Multiple blood samples of patients taking MMF were collected in Vacutainer tubes containing EDTA before dosing and 0.5, 1, 2, 4, 6, and 8 hours after dosing. Plasma samples were obtained immediately after centrifugation and were frozen at –20°C until analysis for MPA by high-performance liquid chromatography (HPLC). Pooled plasma samples were also used to measure the concentrations of free MPA by ultrafiltration. Biochemical parameters such as serum creatinine (Scr), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum albumin, and complete blood count were monitored on the study date. Creatinine clearance (CL_{cr}) was calculated from a 24-hour urine collection using the standard methods.

Measurement of Plasma MPA Concentration

The specified amounts of stock solutions were added to filtered drug-free plasma in the concentration range of 0.1 to 25.0 μg/mL as follows and mixed for 1 hour. These calibrators were assayed, and a calibration curve was obtained from the results. Then, 50 μL of internal standard solution (15 ng/mL diazepam in methanol) and 0.1N HCl were added to 12 × 75-mm polystyrene tubes. Then, 500 μL of each plasma sample was added to respectively labeled tubes and vortexed for 30 seconds, and the samples were processed by solid-phase extraction using C18 cartridges (Sep-Pak, Waters) and a vacuum manifold (Supelco, Bellefont, PA). Plasma concentration of mycophenolic acid was determined by reverse-phase HPLC using a Pico-tag C18 column (3.9 × 300 mm, Waters) maintained at 50°C.[16] The mobile phase was composed of acidified water (pH 4.3-4.7 with 0.1N HCl) and acetonitrile at the ratio of 59:41. It was pumped in isocratic mode for elution of the column, and the flow rate was 1.0 mL/min. Compounds were quantified by UV absorbance at a wavelength of 254 nm. Concentrations were calculated by peak area

values. Calibration factor was calculated by dividing the concentration of the calibrator (2.5 μg/mL) by the peak area ratio, which was the rate of the peak area of mycophenolic acid and internal standard. The result of each patient was calculated by multiplying its peak area ratio by the calibration factor.

To determine the free fraction of plasma MPA, 970 μL of patient plasma obtained 2 hours after administration was spiked with 30 μL of the 1-mg/mL MPA solution to get an approximate of 30 μg/mL. Then, 100 μL of this spiked solution was reserved to estimate total MPA concentration, and the remaining 900 μL was ultrafiltrated to estimate the free MPA concentration. In the ultrafiltration procedure, 900 μL of spiked solution was filled in a filter (Amicon, Millipore) and centrifuged at 3000 rpm for 1 hour.[16,17] This filtrate was taken and underwent the same procedure as the measurement of total MPA. The MPA free fraction was calculated as the percentage between the total concentration and the free concentration of MPA.

Pharmacokinetic Data Analysis

Pharmacokinetic analysis was performed using WinNonlin® software. Noncompartmental analysis was used to determine several pharmacokinetic parameters such as area under the concentration-time curve (AUC) from 0 to 12 hours, area under the moment curve (AUMC), mean residence time (MRT), time to maximum concentration (t_{max}), maximum concentration (C_{max}), and apparent clearance (CL/F). C_{max} and t_{max} were determined directly from the plasma concentration-time curve and AUC by the trapezoidal rule. AUMC, MRT, and apparent clearance were calculated with standard pharmacokinetic formulas.

Statistics

Correlation analysis between MPA pharmacokinetic parameters and patient characteristics was performed using Spearman's correlation coefficient and the Wilcoxon rank sum test using the SAS program. MPA AUC and free fraction were evaluated from the correlation of demographic factors such as age, sex, donor type, weight, body surface area, and physiologic parameters such as serum creatinine, creatinine clearance, and serum albumin. To identify predictors of MPA AUC and develop a limited sampling strategy for estimating MPA AUC, Spearman's correlation coefficient was used. Results are expressed as the mean ± SD. A *p*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Patient Characteristics

This study was approved by the institutional review board, and patient consent was obtained. A total of 10 kidney transplant recipients (7 men and 3 women) completed the study. Characteristics of these patients are listed in Table I. All patients in this study received living donor grafts, with 4 of them from living-unrelated donors (LURD) and 6 from living-related donors (LRD). There was no case of retransplantation. The mean age was 38.3 ± 13.4 years, and the mean weight was 57.1 ± 7.49 kg. No patient had delayed graft function or severely impaired renal function. The mean serum creatinine of the 10 patients was 1.18 ± 0.34 mg/dL, and the mean creatinine clearance was 66.8 ± 21.85 mL/min. The mean serum albumin was 3.22 ± 0.27 g/dL. The mean cyclosporine dose administered to the patients on the study day was 442.5 ± 92.08 mg/day, and the mean cyclosporine trough concentration was 360.1 ± 63.48 ng/mL. All patients took the same dose (750 mg twice a day) of MMF on the study day. Among the 10 patients, 2 patients experienced acute rejection within 1 month after transplantation and were treated with high-dose steroid therapy. Few patients complained of minor GI adverse events, but no patient experienced any serious side effect to MMF.

Analysis of MPA Plasma Concentration

Reverse-phase chromatography after solid-phase extraction from plasma shows that MPA is well resolved, and the internal standard is clearly separated. The retention times observed were 5.46 ± 0.15 minutes for MPA and 11.09 ± 0.33 minutes for diazepam.

The assay for plasma MPA was linear throughout the range of 0.1 to 25.0 μg/mL. The coefficient of correlation (*r*) between the concentration of the calibrator and the peak area ratio of MPA and internal standard was 0.9963, and the coefficient of determination (r^2) was 0.9912.

MPA Pharmacokinetics of Korean Kidney Transplant Patients

Individual plasma concentrations of MPA in 10 kidney transplantation patients after 2 weeks of MMF treatment are depicted in Figure 1. The pharmacokinetic profiles of MPA are characterized by an early and sharp increase of MPA concentration, with the first peak concentration being reached at 0.5 to 1 hours after dosing.

Table I Patient Demographics

Demographics	
Number of study patients	10
Sex (male, female)	7, 3
Age (years, mean ± SD)	38.3 ± 13.43
Weight (kg, mean ± SD)	57.1 ± 7.49
Body surface area (m^2, mean ± SD)	1.62 ± 0.14
Donor type (LRD, LURD)	6, 4
Retransplant	—
Biochemical parameters (mean ± SD)	
Serum creatinine (mg/dL)	1.18 ± 0.34
Creatinine clearance (mL/min)	66.84 ± 21.85
Aspartate aminotransferase (IU/L)	25.5 ± 6.13
Alanine aminotransferase (IU/L)	43.1 ± 23.32
Total bilirubin (mg/dL)	0.99 ± 0.25
Serum albumin (g/dL)	3.22 ± 0.27
Dose of immunosuppressants (mean ± SD)	
Dose of mycophenolate mofetil (MMF)/weight (mg/kg/day)	26.66 ± 3.36
Dose of MMF/body surface area (mg/m^2/day)	930.57 ± 78.33
Dose of cyclosporine (mg/day)	442.5 ± 92.08
Trough concentration of cyclosporine (ng/mL)	360.1 ± 63.48

These profiles were consistent with rapid absorption and rapid conversion of MMF to MPA, followed by rapid distribution and metabolism of the generated MPA. Small secondary increases in plasma MPA levels occurred in 7 patients at 4 to 12 hours after dosing, consistent with previously described enterohepatic circulation of MPAG, which undergoes deglucuronidation and reabsorption as MPA. Because these increases interfered with the accurate calculation of the terminal half-life of MPA, the values for half-life were not determined in this study. The pharmacokinetic parameters of MPA in 10 individual kidney transplant recipients are depicted in Table II. There was a substantial interindividual variation of MPA AUC, C_{max}, and t_{max} values among the patients. The mean MPA AUC at 2 weeks after kidney transplantation in Korean kidney transplantation recipients was 18.45 ± 4.2 μg•h/mL. The mean values of AUMC and MRT were 59.08 ± 17.45 μg•h^2/mL and 3.21 ± 0.68 hours, respectively. The peak concentration of MPA (t_{max}) was reached at 1.1 ± 1.05 hours after dosing, and the mean maximal MPA concentration (C_{max}) was 8.73 ± 4.65 μg/mL. The mean oral MPA clearance (CL/F) was 42.67 ± 9.97 L/h. The mean free fraction of MPA measured at 2 hours after dosing was 1.6% ± 0.2%.

Correlation of Pharmacokinetic Parameter and Patient Characteristics

Correlation analysis between MPA AUC and patients' baseline characteristics was performed to determine the factors affecting the AUC value. The patients' age, weight, and body surface area had no relation with MPA AUC (p = 0.3466, 0.8935, 0.6628, respectively). Renal function also seemed not to have any effect on AUC since serum creatinine and creatinine clearance did not correlate with AUC (p = 0.5843, 0.1497, respectively). However, MPA AUC showed a statistically significant difference according to the patient's gender (p = 0.0227). MPA AUC of females was higher than that of males by 47.15%, even though they were given the same doses of MMF.

The MPA free fraction was assessed to determine the relationship between serum albumin and renal function because it was reported that these factors might affect the protein binding of MPA and free MPA concentration. In this study, serum albumin level, serum creatinine, and creatinine clearance did not show any correlation with the MPA free fraction (p = 0.4846, 0.2271, 0.2600, respectively).

Table II MPA Pharmacokinetic Parameters in Kidney Transplant Patients Given MMF 750 mg bid

Patient	AUC (μg•h/mL)	AUMC (μg•h^2/mL)	t_{max} (h)	C_{max} (μg/mL)	MRT (h)	CL/F (L/h)	Free Fraction
1	18.24	73.61	0.5	3.80	4.04	41.13	1.82
2	17.31	43.07	1	9.96	2.49	43.32	2.03
3	12.42	52.63	4	1.99	4.24	60.38	1.13
4	15.72	52.44	1	3.96	3.34	47.70	1.54
5	13.44	33.94	0.5	11.91	2.53	55.82	1.48
6	24.41	73.84	1	9.83	3.02	30.72	1.60
7	18.42	70.84	1	6.62	3.85	40.71	1.65
8	25.17	89.48	1	9.63	3.55	29.79	1.49
9	17.59	42.49	0.5	12.54	2.42	42.64	1.73
10	21.76	58.50	0.5	17.10	2.69	34.46	1.57
Mean	18.45	59.08	1.1	8.73	3.21	42.67	1.60
SD	± 4.25	± 17.45	± 1.05	± 4.65	± 0.68	± 9.97	± 0.24

AUC, area under the concentration-time curve; AUMC, area under the moment curve; t_{max}, time to maximum concentration; C_{max}, maximum concentration; MRT, mean residence time; CL/F, apparent clearance; MPA, mycophenolic acid; MMF, mycophenolate mofetil.

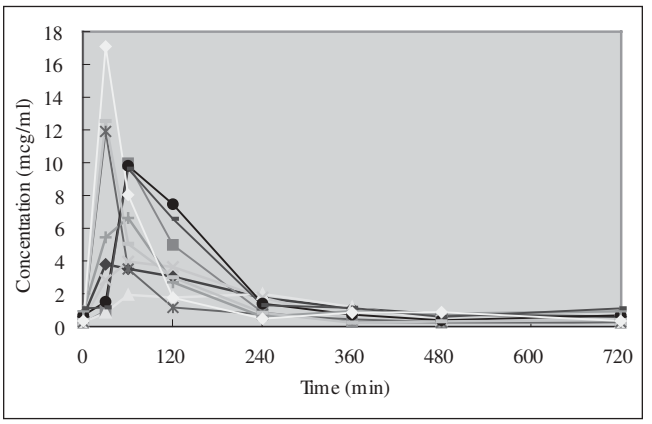

Figure 1. Mycophenolic acid (MPA) plasma concentration-time profile of 10 Korean kidney transplant patients.

Predictors of MPA AUC for an Abbreviated Sampling Strategy for MMF TDM

For the purpose of using MPA plasma concentrations practicably in individualizing MMF doses, analysis to identify the predictable time point of AUC was performed. When the plasma concentration of each time point was analyzed based on the correlation with the AUC value, concentrations of predose (C_{time0h}), 1 hour postdose (C_{time1h}), and 8 hours postdose (C_{time8h}) showed a significantly positive relationship (Table III). Spearman's correlation coefficients for C_{time0h}, C_{time1h}, and C_{time8h} were 0.74545 (p = 0.0133), 0.68485 (p = 0.0289), 0.63636 (p = 0.0479), respectively.

DISCUSSION

As a variety of studies on MPA pharmacokinetics in kidney transplant patients have been performed, MPA pharmacokinetics have come to be better known. However, MPA pharmacokinetics in Korean patients have never been characterized until this study, and moreover, Korean kidney transplant patients are not put on a therapeutic dose of MMF (1000 mg twice a day) due to a high incidence of GI intolerance. Therefore, there have been doubts about the appropriateness of an MMF regimen in Korean kidney transplant patients. In this respect, this pharmacokinetic study on MPA is thought to be essential.

When the plasma concentration of MPA in 10 Korean kidney transplant patients was analyzed in this study, it was found that the pattern of the concentration-time profile was similar to the results of other studies performed with Caucasians, although there was interindividual variability of MPA AUC, C_{max}, and t_{max}. In this investigation, a rapid increase in plasma concentration was observed within 1 hour of dosing, and a second peak was observed at 4 to 12 hours, which is consistent with the results reported by Weber et al.[13] In addition, the free fraction of MPA in Korean patients does not seem to be different from reported data by Weber et al.[13]

The mean MPA AUC of Korean patients in this study was calculated as 18.45 ± 4.25 μg•h/mL. When this AUC value is compared to the data of Shaw et al,[17] the MPA AUC of the Korean patients administered with MMF 750 mg twice a day and the AUC value adjusted to the dose of 1000 mg bid proportionately are not

Table III Correlation Coefficient between MPA AUC and Each MPA Concentration

	C_{time0_h}	$C_{time0.5_h}$	C_{time1_h}	C_{time2_h}	C_{time4_h}	C_{time6_h}	C_{time8_h}
MPA AUC	0.74545	0.16364	0.68485	0.49091	–0.3212	0.21212	0.63636
p-value	0.0133	0.6515	0.0289	0.1497	0.3655	0.5563	0.0479

MPA, mycophenolic acid; AUC, area under the concentration-time curve.

higher than that of Caucasian (33.3 ± 13.7 μg•h/mL) or African American patients (26.8 ± 14.3 μg•h/mL) who took 1000 mg twice a day. Moreover, it is lower in comparison with the target range of 30 to 60 μg•h/mL reported by Shaw et al.[17] When we consider the fact that the MPA AUC in our Korean patients did not reach Shaw et al's therapeutic range, which is generally considered to decrease the risk of acute rejection, and that 2 of 10 patients experienced acute rejection within 1 month after kidney transplantation, despite the therapeutic trough concentration of cyclosporine, we may suggest that the dose of MMF should be titrated to 1000 mg twice daily in Korean kidney transplant recipients. However, since the relationship between the AUC of MPA and the efficacy or adverse effects of MPA in Korean kidney transplant patients has not been firmly established, we should be cautious in raising the dose of MMF in this patient population.

The patients' age, weight, and body surface area were not related to the MPA AUC value. The MPA AUC was significantly different between men and women, but the effect of sex on AUC cannot be concluded definitely due to the small sample size. Serum creatinine and creatinine clearance also did not correlate with MPA AUC. Whether there is a discrepancy in AUC according to the existence of a rejection episode was not assessed because the sample size was too small to analyze, and the follow-up period was not long enough. Moreover, the time that a patient experienced biopsy-proven rejection in this study was during the dose titration of MMF. MPA is highly bound to plasma protein, and its free form is pharmacologically active. It was reported that the free fraction of MPA is influenced by the degree of serum albumin and renal impairment.[18,19] Specifically, renal insufficiency decreases the protein binding of MPA, which increases the concentration of free MPA. However, in this study, correlations between the renal function and free fraction of MPA were not found. Upon evaluation, this result is thought to occur from the fact that the sample size was too small to detect any relationship between them and also that all patients maintained close to normal renal functions (serum creatinine range: 0.7-1.4 mg/dL; creatinine clearance range: 39.9-115.4 mL/min). In the previous study by Meier-Kriesche et al,[12] a twofold increase in both the free fraction and the free MPA concentration was observed in patients with a creatinine clearance less than 20 mL/min when compared to patients with preserved renal function. Considering that all patients included in this study had functioning grafts (creatinine clearance > 30 mL/min), it can be thought that the MPA free fraction is not affected by renal function when the level of creatinine clearance is above 40 mL/min.

We opted not to measure the MPAG concentration in our patients because no pharmacokinetic studies have shown that its concentration relates to either toxicity or acute rejection.

Clinical trials to date have been performed using the fixed doses (e.g., 1 g twice daily) of MMF.[1-3] Lately, however, a growing number of investigators have suggested the individualization of the MMF dose guided by the plasma concentration of MPA.[16,20] There are several rationales for the possible role of therapeutic drug monitoring as a therapeutic strategy with MMF.[18] The pharmacokinetic and pharmacodynamic relationship between MPA exposure (MPA AUC) and acute rejection was confirmed by randomized, double-blind studies.[19,21] Also, it was evident that the pharmacokinetics of MPA show inter- and intraindividual variability in transplant recipients,[13-15] especially in patients with renal dysfunction.[10-13] Moreover, there is the possibility of clinically significant drug-drug interactions between MMF and concomitant immunosuppressants,[22-26] as well as antacids[27] and certain antibiotics,[28] influencing the pharmacokinetics of MMF. These facts support that the optimization of the MMF dose based on individual MPA AUC may have merit.

However, to apply the MPA plasma concentration in clinical settings practically, the predictable time point of the MPA AUC must be determined. Analysis in each of the 10 Korean kidney transplant patients showed that the predictors of MPA AUC were the concentration of predose and 1- and 8-hour postdose. Trough concentration seemed to be the best predictor of MPA AUC since the predose concentration was proven to have the highest correlation coefficient in this study. This result was also supported with the report from Van Gelder

et al,[22] in which the trough concentration was the predictive value of acute rejection. The trough concentration reflects the elimination phase, while the concentration at 1 hour indicates the absorption phase. Therefore, concentrations of predose and 1 hour postdose may make it possible to estimate MPA AUC accurately. However, if this method of an individualized dosing strategy is to be used practically, a carefully designed prospective study should be performed to determine the best sampling time and its target range in transplant patient populations. Although this present study has some limitations with the small number of patients and short follow-up, this is the first study to characterize the pharmacokinetic parameter of MPA in Korean kidney transplant recipients. This study demonstrated that a trial of the administration of 1000 mg bid of MMF is warranted in Korean kidney transplant patients, particularly in men, to achieve the serum concentration that other studies have proposed to be therapeutic. However, prospective studies comparing the rejection rate and side effects according to the AUC of MPA in Korean kidney transplant patients must be conducted first. A confirmatory study assessing whether the same therapeutic range of MMF must be maintained in Korean transplant patients to provide a similar rate of protection from acute rejection reported in Caucasian kidney transplant patients should be performed.

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