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Pharmacokinetics of mycophenolic acid in Chinese kidney transplant patients*

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Abstract: To assess the influence of cyclosporin A (CsA) and tacrolimus (FK506) on mycophenolic acid (MPA) and correlation analysis of the pharmacokinetic parameters and patient characteristics, clinical outcome in Chinese kidney transplant recipients, the pharmacokinetics of 1000 mg mycophenolate mofetil (MMF) twice daily was measured by high-performance liquid chromatography (HPLC). PKS (Pharmaceutical Kinetics Software) 1.0.2 software package was used for the calculation of pharmacokinetic parameters. The mean C_{max}, t_{max}, and $AUC_{(0-12)}$ were (21.88±10.52) μg/ml, (1.20±0.95) h, and (52.546±13.215) μg·h/ml, respectively. The level of $AUC_{(0-12)}$ in the FK506 group was significantly higher than that in the CsA group. MPA appeared not to be affected by renal function. MPA $AUC_{(0-12)}$ showed statistically significant difference according to the patient's gender.

Key words: Mycophenolate mofetil, Mycophenolic acid, Pharmacokinetics, Kidney transplant
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INTRODUCTION

Mycophenolic acid (MPA) is the active metabolite of the registered prodrug mycophenolate mofetil (MMF) often used in combination with cyclosporin A (CsA) or tacrolimus (FK506) as an immunosuppressive agent after organ transplantation for the prophylaxis of acute rejection (Takahashi *et al*., 1995; Shaw *et al*., 1998). Following oral administration, MMF is completely absorbed and rapidly hydrolyzed to MPA by esterase present in the gut wall, liver, and possibly lung and peripheral tissues (Bullingham *et al*., 1996a).

MPA serves as a potent, selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme in de novo purine biosynthesis of guanine nucleotides required as a building block for DNA and RNA synthesis (Young and Sollinger, 1994; Lee *et al*., 1985). MPA has stronger cytostatic effect on lymphocytes than on other cells, since the de novo synthesis of purines is essential for the proliferation of T and B lymphocytes, unlike other types of cells that can use the salvage pathway for the generation of these compounds. A depletion of the guanine nucleotide pool in lymphocytes leads to a reduction in DNA synthesis, proliferation of lymphocytes, and subsequent immunosuppression. In addition to antilymphocyte activity, MPA prevents arterial smooth muscle cell proliferation, in contrast to conventional immunosuppressants, such as CsA. This property has potential benefits in opposing obliterative arteriopathy associated with chronic organ rejection (Rasom, 1995).

After oral administration, MPA is highly bound to serum albumin (97%) (Bullingham *et al*., 1998) and only the free fraction of the drug is pharmacologically active. It has been shown that the free concentration of MPA is variable in renal transplant patients with different renal function. The bioavailabil-

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ity of MPA is around 94% and the maximum plasma concentration of MPA following an oral dose is reached in around 0.8 h. The average plasma half-life for healthy adults is approximately 16 h (Shaw *et al*., 1995; Matsuzawa and Nakase, 1984).

MPA is extensively metabolized by uridine diphosphate glucuronosyltransferase (UDP-GT), mainly into the pharmacologically inactive metabolite MPA-glucuronide (MPAG). Due to enterohepatic recirculation MPAG plays an important role in the maintenance of steady-state plasma MPA level (Bullingham *et al*., 1996b; Shaw *et al*., 2002) and the appearance of a second plasma peak of MPA at 6 to 12 h following MMF administration. In addition, MPA is further metabolized to acyl glucuronide (AcMPAG) and 7-O-glucoside (Bullingham *et al*., 1998).

The pharmacokinetics of MPA varies widely between and within patients and with time post-transplant (Johnson *et al*., 1999). Further, it was shown that the pharmacokinetics of MPA is influenced by co-administration of calcineurin inhibitors such as CsA and FK506 (Bullingham *et al*., 1996a; Gregoor *et al*., 1999). Some changes in free MPA concentrations, due to patient characteristics such as severe renal impairment and gender, will lead to an altered efficacy or toxicity profile.

The first dose of MMF should be administered within 72 h from transplantation. The recommended fix-dose strategy of 2 g/day reduces the acute rejection rate and hence improves long-term allograft survival (European Mycophenolate Mofetil Cooperative Study Group, 1995; Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group, 1996). Consequently, in our experiments this dosage is accepted. In addition, the pharmacokinetics of MPA in Chinese kidney transplant patients has not been characterized previously. The aims of this study were to assess the influence of CsA and FK506 on the pharmacokinetics of MPA, to conduct correlation analysis of pharmacokinetic parameters and characteristics of renal transplant patients receiving FK506 in combination with MMF, as opposed to a matched group of patients receiving the same dose of MMF in combination with CsA. A secondary objective was to conduct correlation analysis of pharmacokinetic parameters and renal impairment, gender, clinical outcome.

EXPERIMENTAL DETAILS

Subjects

This study was a open-label and randomized evaluation of the pharmacokinetics of MPA in Chinese kidney transplant patients. Inclusion criteria were aged 24 to 74 male or female patients who underwent kidney transplantation for the first time at the renal disease center of the first affiliated hospital, Zhejiang University, and were treated with MMF in addition to cyclosporine or tacrolimus plus prednisone as immunosuppressants. Exclusion criteria were patients with systemic bacterial, fungal, or viral infection; patients who were pregnant or lactant; patients who had a history of malignant tumor; patients who had received combined organ transplantation; patients who are positive with hepatitis B surface antigen; patients who were peptic ulcer or severe gastrointestinal abnormalities; patients who had symptoms of anemia and decreased blood cells or platelet; patients who were allergic or intolerant to hormones, MMF, MPA, cyclosporine, and tacrolimus. Written informed consent to undergo pharmacokinetic studies was obtained from each patient.

Study design

The study was approved by the Ethical Committee of the First Affiliated Hospital, Zhejiang University and was carried out in accordance with the Declaration of Helsinki. To evaluate the pharmacokinetics of MMF, two clinical studies were conducted. After operation, 22 patients involved in the first study took 1000 mg MMF twice daily, prednisone 10~20 mg/d, and CsA 100~480 mg/d; the other 7 patients taking 1000 mg MMF twice daily, prednisone 10~20 mg/d, and FK506 6~8 mg/d were in the second study. The MPA pharmacokinetic parameters of all patients were studied for more than 7 d post-transplant when steady serum concentration was reached. Blood samples were collected before dosing and 0.33, 0.66, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, and 12 h after dosing. Serum sample was obtained by centrifuging blood at 3500 r/min for 15 min in our laboratory. The obtained serum was pooled and stored frozen at −20 °C until analysis for MPA by HPLC. Biochemical parameters such as serum creatinine (sCr), creatinine clearance (CCr), glutamate-pyruvate transaminase (GPT), glutamine oxaloacetic transa-

minase (GOT), total bilirubin (TB), and direct bilirubin (DB) were monitored on the study date.

Measurement of MPA in serum

A stock solution of MPA in acetonitrile was prepared at 500 μg/ml and further diluted with free serum to obtain 0.1 to 10.0 μg/ml standard solutions as calibrators. Then 1 ml of these standard calibration samples was vortex-mixed vigorously with 10% phosphoric acid solution for 30 s and centrifuged at 13500 r/min for 5 min. The mixtures' supernatants were introduced into solid-phase extraction cartridges (Oasis, Waters) pre-conditioned with methanol (1 ml) followed by water (1 ml). The loaded cartridges were washed with 5% methanol (1 ml). The analytes were eluted with methanol and solvents of all samples were removed by using a stream of nitrogen (40 °C). The residue was redissolved in acetonitrile (100 μl). An aliquot (10 μl) of the mixture was injected into the column.

Serum concentration of MPA was carried out using a Waters 2690 high-performance liquid chromatography (HPLC) system with a Waters 996 diode array UV detector. Waters Symmetry C_{18} cartridges (4.6 mm×250 mm, 5 μm) fitted with a Security guard cartridge were used and maintained at a temperature of 25 °C. The mobile phase consisted of acetonitrile and potassium dihydrogen phosphate buffer (2.5 mmol/L, pH 4.5) at ratio of 50:50 with a flow rate of 1.0 ml/min. Compounds were quantified by UV absorbance at a wavelength of 210 nm. The chromatography data were collected and processed on Millennium^{32} software.

Pharmacokinetic data analysis

PKS (Pharmaceutical Kinetics Software) 1.0.2 software package (Shanghai Hongneng Software Co. Ltd., China) was used for calculation of pharmacokinetic parameters. Noncompartmental analysis was used to determine several pharmacokinetic parameters. The maximum concentration (C_{max}) and maximum time (t_{max}) were the observed values. The area under the curve ($AUC_{(0-12)}$) was estimated by trapezoidal rule with extrapolation, and apparent clearance (CL/F) was determined as dose/AUC. Mean residence time (MRT) was calculated by the formula $AUMC_{(0-12)}$ (area under the first moment curve)/$AUC_{(0-12)}$.

Statistics

The effect of CsA and FK506 on the pharmacokinetics of MPA and analysis of correlation between MPA pharmacokinetic parameters and patient characteristics was performed using a two tailed *t*-test. MPA $AUC_{(0-12)}$ was chosen for the correlation analysis. Results are expressed as the mean±*SD*. A *P*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

A total of 29 kidney transplant recipients (17 men and 12 women) completed the study. Characteristics of these patients are listed in Table 1. There was no case of retransplantation. The mean age was (40.0±12.0) years and the mean body weight was (58.0±10.0) kg. The mean sCr of the 29 subjects was (141.79±68.54) μg/L, and the mean CCr was (58.09±19.60) ml/min. The mean GPT and GOT were (35.50±29.20) μg/L and (23.60±11.10) μg/L, respectively. The mean TB and DB were (8.0±3.95) U/L, and (2.60±1.80) U/L, respectively. The mean CsA, FK506, and prednisone dose administered were (318.0±82.30) mg/d, (7.14±1.21) mg/d, and (19.10±2.43) mg/d, respectively. All the patients took

Table 1 Patients characteristics

Item	Values
Demographics	
Number of study patients	29
Sex (male, female)	17, 12
Age (years, mean±*SD*)	40.0±12.0
Weight (kg, mean±*SD*)	58.0±10.0
Number of rejection patients	3
Retransplant	–
Biochemical parameters (mean±*SD*)	
Serum creatinine (μg/L)	141.79±68.54
Creatinine clearance (ml/min)	58.09±19.60
Glutamate-pyruvate transaminase (μg/L)	35.50±29.20
Glutamine oxaloacetic transaminase (μg/L)	23.60±11.10
Total bilirubin (U/L)	8.0±3.95
Direct bilirubin (U/L)	2.60±1.80
Dose of immunosuppressants (mean±*SD*)	
Dose of mycophenolate mofetil (mg/d)	2000
Dose of cyclosporine A (mg/d)	318.0±82.30
Dose of tacrolimus (mg/d)	7.14±1.21
Dose of prednisone (mg/d)	19.10±2.43

the same dose (1000 mg twice daily) of MMF on the study day. Among the 29 patients, 3 patients experienced rejection within 1 month after transplantation.

Determination of MPA in serum

The calibration curve of MPA in serum was linear in the range of 0.1 to 10.0 μg/ml. The concentrations (C) were calculated by peak area (A) values. The regression equation of the calibration curve was $C=2.12\times10^{-6}A+2.84\times10^{-2}$, $r=0.9999$. The minimum detectable concentration of MPA (signal-to-noise ratio of 3) in serum was determined to be approximately 0.05 μg/ml. The overall precision, expressed as %*RSD* (Relative Standard Deviation) (n=5), was not less than 3.64% and 2.62% for intra-day and inter-day assay, respectively. The absolute and relative recovery (n=5) was 78.92% to 88.96% and 95.85% to 104.12%, respectively.

MPA pharmacokinetics of Chinese kidney transplant patients

A large interindividual variation of pharmacokinetics data was observed. The mean serum concentration-time profile of MPA in 29 kidney transplantation patients after 10 d of MMF treatment is depicted in Fig.1. The pharmacokinetic parameters of MPA in 29 individual kidney transplant recipients are depicted in Table 2. There was substantial interindividual variation of MPA $AUC_{(0-12)}$, C_{max}, t_{max}, and CL/F values among the patients. The mean MPA $AUC_{(0-12)}$ after kidney transplantation in Chinese kidney transplantation recipients was (52.546±13.215) μg·h/ml. The mean values of CL/F, and $AUMC_{(0-12)}$, and $MRT_{(0-12)}$ were (20.30±5.70) L/h, (172.73± 52.87) μg·h/ml, and (3.3100±0.6295) h, respectively. t_{max} was reached at (1.20±0.95) h after dosing, and C_{max} was (21.88±10.52) μg/ml.

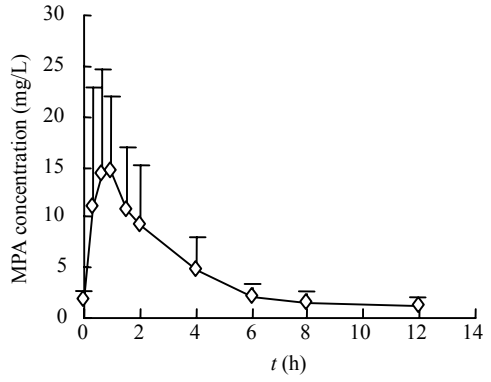

Fig.1 Mycophenolic acid (MPA) serum concentration-time profile of 29 Chinese kidney transplant patients

Effect of CsA and FK506 on the pharmacokinetics of MPA

There were differences in the baseline characteristics of the two groups. Mean C_0 MPA in patients receiving FK506 was significantly higher than that in the CsA group: 2.45 μg/ml versus 1.45 μg/ml (P=0.004). MPA $AUC_{(0-12)}$ in the FK506 group was statistically higher: (60.9467±11.6779) μg·h/ml than that in the CsA group: (48.184±10.6598) μg·h/ml (P=0.0045).

Correlation analysis of pharmacokinetic parameters and patient characteristics

Correlation analysis between MPA AUC and patients' renal function and gender was performed to determine the factors affecting the AUC value among the patients who were administered CsA. The patients' renal function seemed not to have any effect on AUC since creatinine clearance did not correlate with AUC (P=0.9473). However, MPA AUC showed a statistically significant difference according to the patient's gender (P=0.0006). MPA AUC of females was higher than that of males by 34.32%, even though they were given the same doses of MMF.

Correlation analysis of pharmacokinetic parameters and clinical outcome

Among the 29 patients, 3 patients (10.3%) experienced acute rejection (AR) within 1 month after transplantation. MPA $AUC_{(0-12)}$ in the AR group was statistically lower ((40.93±14.28) μg·h/ml) than that in the non AR group ((53.88±12.70) μg·h/ml) (P=0.038). There was no statistical difference of the accident rate of infection between the patients of MPA $AUC_{(0-12)}>60$ μg·h/ml and MPA $AUC_{(0-12)}<60$ μg·h/ml.

DISCUSSION

The pharmacokinetics of MPA in kidney transplant patients has been reviewed many times, although few studies on the MPA pharmacokinetics in Chinese patients have been reported. Moreover, co-administration of calcineurin inhibitors such as

Table 2 MPA pharmacokinetic parameters in Chinese kidney transplant patients given MMF 1000 mg bid

Patient	t_{max} (h)	C_{max} (μg/ml)	CL/F (L/h)	$AUC_{(0-12)}$ (μg·h/ml)	$AUMC_{(0-12)}$ (μg·h/ml)	MRT (h)
1	2.00	14.672	24.37122	41.032	132.25	3.2231
2	0.67	7.295	28.11279	35.571	140.76	3.9572
3	0.33	13.708	19.95490	50.113	192.04	3.8321
4	1.00	17.441	21.20621	47.156	158.99	3.3715
5	1.00	14.530	21.96692	45.523	155.27	3.4107
6	1.50	18.443	20.25727	49.365	150.87	3.0562
7	0.67	22.752	20.41191	48.991	137.03	2.7970
8	0.67	28.483	26.27430	38.060	95.63	2.5125
9	0.67	22.768	19.03457	52.536	150.14	2.8578
10	1.00	25.623	27.02191	37.007	122.87	3.3201
11	1.00	15.238	21.90245	45.657	137.28	3.0067
12	0.33	53.766	15.16990	65.920	100.94	1.5313
13	0.33	42.521	18.23719	54.833	155.35	2.8331
14	0.33	15.793	20.92619	47.787	190.21	3.9804
15	1.00	27.037	13.23872	75.536	233.50	3.0912
16	4.00	11.626	22.52252	44.400	200.16	4.5081
17	4.00	16.136	19.97363	50.066	237.69	4.7474
18	1.50	11.644	17.22594	58.052	228.62	3.9382
19	0.67	22.752	20.74818	48.197	135.44	2.8102
20	0.67	18.134	19.38698	51.581	179.04	3.4710
21	2.00	5.627	40.84967	24.480	93.28	3.8109
22	0.33	37.470	16.21587	61.668	208.80	3.3858
23	1.00	21.780	13.23276	75.570	268.23	3.5495
24	1.50	16.118	24.05581	41.570	125.07	3.0086
25	0.67	30.750	16.87194	59.270	163.05	2.7508
26	2.00	30.771	17.01259	58.780	170.99	2.9090
27	2.00	17.074	16.57275	60.340	198.27	3.2859
28	0.33	22.967	14.25517	70.150	231.03	3.2935
29	1.50	31.492	11.81614	84.630	316.44	3.7392
Mean	1.20	21.880	20.30436	52.546	172.73	3.3100
SD	0.95	10.520	5.703189	13.215	52.87	0.6295

CsA and FK506 and patients characteristics will have effect on the pharmacokinetic parameters of MPA. In this respect, the pharmacokinetic study of MPA in Chinese kidney transplant patients will be very essential.

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 h after dosing. These profiles were consistent with the rapid absorption and rapid conversion of MMF to MPA, followed by rapid distribution and metabolism of the generated MPA. Analysis of MPA concentration in the 29 Chinese patients in this study revealed that the pattern of the concentration-time profile was similar to the results of other studies (Pescovitz *et al*., 2003; Cho *et al*., 2004), although there was some variability of $AUC_{(0-12)}$, C_{max} and t_{max}. The mean MPA AUC ((52.546±13.215) μg·h/ml) of Chinese kidney transplant patients treated with 1000 mg MMF twice daily was higher than that of Caucasian patients ((33.3±13.7) μg·h/ml), African American patients ((26.8±14.3) μg·h/ml) who took the same dose as that in our study (Shaw *et al*., 2000), and Korean patients ((18.45±4.25) μg·h/ml) taking MMF 750 mg twice a day. Only 3 of our 29 patients experienced acute rejection within 1 month after operation, maybe it was partly due to the high MPA AUC in the target range of 30 to 60 μg·h/ml reported to decrease the risk of acute rejection (Shaw *et al*., 2000). But we must be careful

when the patient simultaneously has CsA and MPA AUC concentrations such as above 3 acute rejection patients.

In our study, calcineurin antagonists such as comedications seem to affect the MPA pharmacokinetics. For equivalent doses of MMF, combination therapy with FK506 had been reported to result in higher MPA AUC than does a CsA-based regimen (Zucker *et al*., 1997). Furthermore, our study confirmed previous observations (Kuriata-kordek *et al*., 2003) of significantly higher MPA C_0 in the FK506-treated group than that in patients receiving CsA. It was reported (Filler *et al*., 2000) that equal MPA exposure to that achieved without calcineurin inhibitors was obtained with a 40% reduced dose in combination with FK506, or a 20% increased dose with CsA. (Zucker *et al*., 1999) during an in vitro study to investigate the effect of FK506 and CsA on uridine diphosphate glucuronosyltransferase (UDPGT), an enzyme that converts MPA to MPAG. The author suggests that FK506 inhibits UDPGT significantly more efficiently than CsA through not yet determined mechanisms.

MPA $AUC_{(0-12)}$ was significantly different between men and women and serum creatinine did not correlate with MPA $AUC_{(0-12)}$, which is consistent with the report by Cho *et al*.(2004).

As so many factors affect the pharmacokinetics of MPA, MPA monitoring may be beneficial for renal transplant recipients receiving MMF. Although this study has some limitations such as incomplete correlation analysis, small number of patients, and short follow-up, this is a relatively complete study to evaluate the pharmacokinetics of MPA in Chinese kidney transplant recipients. Comparison of rejection rate and side effects according to the AUC of MPA in Chinese kidney transplant patients has not been conducted, so future study in our laboratory will address this issue.

References

Bullingham, R.E., Nicholls, A., Hale, M., 1996a. Pharmacokinetics of mycophenolate mofetil (RS61443): A short review. *Transplant. Proc.*, **28**(2):925-929.

Bullingham, R.E., Monroe, S., Nicholls, A., Hale, M., 1996b. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. *J. Clin. Pharmacol.*, **36**(4):315-324.

Bullingham, R.E., Nicholls, A.J., Kamm, B.R., 1998. Pharmacokinetics of mycophenolate mofetil. *Clin. Pharmacokinet.*, **34**(6):429-455.

Cho, E.K., Han, D.J., Kim, S.C., Burckart, G.J., Venkataramanan, R., Oh, J.M., 2004. Pharmacokinetic study of mycophenolic acid in Korean kidney transplant patients. *J. Clin. Pharmacol.*, **44**(7):743-750.

European Mycophenolate Mofetil Cooperative Study Group, 1995. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet.*, **345**(8961):1321-1325.

Filler, G., Zimmering, M., Mai, I., 2000. Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. *Pediatr. Nephrol.*, **14**(2):100-104.

Gregoor, P.J., de Sevaux, R.G., Hene, R.J., Hesse, C.J., Hilbrands, L.B., Vos, P., van Gelder, T., Hoitsma, A.J., Weimar, W., 1999. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation*, **68**(10):1603-1606.

Johnson, A.G., Rigby, R.J., Taylor, P.J., Jones, C.E., Allen, J., Franzen, K., Falk, M.C., Nicol, D., 1999. The kinetics of mycophenolic acid and its glucuronide metabolite in adult kidney transplant recipients. *Clin. Pharmacol. Ther.*, **66**(5):492-500.

Kuriata-kordek, M., Boratynska, M., Falkiewicz, K., Porazko, T., Urbaniak, J., Wozniak, M., Patrzalek, D., Szyber, P., Klinger, M., 2003. The influence of calcineurin inhibitors on mycophenolic acid pharmacokinetics. *Transplant. Proc.*, **35**(6):2369-2371.

Lee, H.J., Pawlak, K., Nguyen, B.T., Robinsm, R.K., Sadee, W., 1985. Biochemical differences among four inosinate dehydrogenase inhibitors, mycophenolic acid, ribavirin, tiazofurin, and selenazofurin, studies in mouse lymphoma cell culture. *Cancer Res.*, **45**:5512-5520.

Matsuzawa, Y., Nakase, T., 1984. Metabolic fate of ethyl O-[N-(*p*-carboxyphenyl)-carbamoyl] mycophenolate (CAM), a new antitumor agent, in experimental animals. *J. Pharmacobiodyn.*, **7**(10):776-783.

Pescovitz, M.D., Guasch, A., Gaston, R., Rajagopalan, P., Tomlanovich, S., Weinstein, S., Bumgardner, G.L., Melton, L., Ducray, P.S., Banken, L., *et al*., 2003. Equivalent pharmacokinetics of mycophenolate mofetil in African-American and Caucasian male and female stable renal allograft recipients. *Am. J. Transplant.*, **3**(12):1581-1586.

Rasom, J.T., 1995. Mechanism of action of mycophenolate mofetil. *Ther. Drug. Monit.*, **17**(6):681-684.

Shaw, L.M., Sollinger, H.W., Halloran, P., Morris, R.E., Yatscoff, R.W., Ransom, J., Tsina, I, Keown, P., Holt, D.W., Lieberman, R., 1995. Mycophenolate mofetil: A report of the consensus panel. *Ther. Drug. Monit.*, **17**(6):690-699.

Shaw, L.M., Nicholl, A., Hale, M., Armstrong, V.W., Oellerich, M., Yatscoff, R., Morris, R.E., Holt, D.W., Venkataramanan, R., Haley, J., *et al*., 1998. Therapeutic monitoring of mycophenolic acid: A consensus panel

report. *Clin. Biochem.*, **31**(5):317-322.

Shaw, L.M., Kaplan, B., DeNofrio, D., Korecka, M., Brayman, K.L., 2000. Pharmacokinetics and concentration-control investigations of mycophenolic acid in adults after transplantation. *Ther. Drug. Monit.*, **22**(1):14-19.

Shaw, L.M., Pawinski, T., Korecka, M., Nawrocki, A., 2002. Monitoring of mycophenolic acid in clinical transplantation. *Ther. Drug. Monit.*, **24**(1):68-73.

Takahashi, K., Ochiai, T., Uchida, K., Yasumara, T., Ishibashi, M., Suzuki, S., Otsubo, O., Isono, K., Takagi, H., Oka, T., 1995. Pilot study of mycophenolate mofetil (RS-61443) in the prevention of acute rejection following renal transplantation in Japanese patients. RS-61443 Investigation Committee−Japan. *Transplant. Proc.*, **27**(1): 1421-1424.

Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group, 1996. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation*, **61**(7):1029-1037.

Young, C.J., Sollinger, H.W., 1994. RS-61443: A new immunosuppressive agent. *Transplant. Proc.*, **26**(6):3144-3146.

Zucker, K., Rosen, A., Tsaroucha, A., de Faria, L., Roth, D., Ciancio, G., Esquenazi, V., Burke, G., Tzakis, A., Miller, J., 1997. Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mucophenolate mofetil in combination therapy, an analogous in vitro findings. *Transpl. Immunol.*, **5**(3):225-232.

Zucker, K., Tsaroucha, A., Olsen, L., Esquenazi, V., Tzakis, A., Miller, J., 1999. Evidence that tacrolimus augments the bioavailability of mycophenolate mofetil through the inhibition of mycophenolic acid glucuronidation. *Ther. Drug. Monit.*, **21**(1):35-43.