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Intravenous mycophenolate mofetil: safety, tolerability, and pharmacokinetics

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Abstract: An intravenous (i.v.) formulation of mycophenolate mofetil (MMF; CellCept®, Roche Pharmaceuticals, Inc., Palo Alto, CA) that will enable its administration to patients unable to tolerate oral medication is available. Two separate studies, an open-labeled pharmacokinetic (PK) study and a double-blind safety study, were performed. Within 24 h after transplant, 153 (safety study) and 45 (PK study) first or second renal transplant recipients were started on i.v. MMF 1 g Q12h or placebo (used in the safety study only, 2:1 MMF:placebo), given over 2 h via a dedicated peripheral venous catheter. In the safety study, *per os* (p.o.) MMF (1g Q12h) or placebo was administered, starting within 72 h after transplant, whereas in the PK study, p.o. MMF was started on the evening of day 5. Sequential blood samples obtained on study days 5 (i.v. MMF) and 6 (p.o. MMF) before and up to 12 h after the AM dose were analyzed for mycophenolic acid (MPA) and MPA glucuronide (MPAG) concentrations by high-performance liquid chromatography. The area under the concentration curve (AUC) was calculated using the linear trapezoidal rule. The MPA AUC_{0-12} was higher for i.v. MMF than p.o. MMF (40.8 ± 11.4 μg·h/mL vs. 32.9 ± 15, $p < 0.001$). There were no other significant PK differences for plasma MPA or MPAG. In the safety study ($n = 98$ i.v. MMF vs. $n = 55$ placebo), 11 patients (11%, i.v. MMF) and 4 patients (7%, placebo) discontinued their use of the drug because of an adverse event (AE). Overall, AEs were similar between i.v. MMF and placebo. Injection site phlebitis (4%) and thrombosis (4%) were observed only with i.v. MMF. MMF i.v. 1 g twice daily (b.i.d.) should provide efficacy at least equivalent to p.o. MMF without increased toxicity, and it provides an acceptable alternative dose form in the immediate period after transplant.

Key words: intravenous (i.v.) – kidney transplantation – mycophenolate mofetil – pharmacokinetics – safety

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Mycophenolate mofetil (MMF; CellCept, Roche Pharmaceuticals, Inc., Palo Alto, CA), a prodrug immunosuppressive agent, has been approved for the prevention of rejection of heart and kidney transplants (1–4). Following oral administration, MMF undergoes rapid and extensive absorption and complete presystemic hydrolysis to mycophenolic acid (MPA), the active immunosuppressant

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species (5), by both liver and plasma esterases. MPA is a potent and specific inhibitor of *de novo* purine synthesis. As a result of this inhibition, the proliferation of both T and B lymphocytes is blocked (6) and antibody production is inhibited (7, 8). MPA, in turn, is almost completely metabolized to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active (6).

An intravenous (i.v.) formulation of MMF has been recently released. The availability of such a formulation enables MMF to be administered to patients unable to tolerate oral medication. Following intravenous administration, MMF is also rapidly hydrolyzed with a half life of only a few minutes to MPA (5). In pharmacokinetic (PK) studies, i.v. MMF has been administered to normal volunteers (9) and to a limited number of renal and hepatic transplant recipients in the immediate postoperative period. When given to normal individuals, C_{max} was higher (47.2 ± 0.3) after i.v. dosing than oral dosing (34.0 ± 7.1). The MPA area under the concentration curve (AUC) from time 0 to 24 h was significantly higher following i.v. administration compared to *per os* (p.o.) administration, but the total AUC was statistically equivalent. T_{max} was similar (9, 10). Unpublished data from a small open-labeled study of the pharmacokinetics of MMF (1.5 g twice daily [b.i.d.]) p.o., or i.v. infusions of 1 or 3 h in duration, or as a continuous infusion to renal allograft recipients showed that: the MPA AUC values were relatively independent of the infusion time (1); the interdosing-interval MPA AUC values were comparable for the same i.v. and p.o. dose of MMF (2); and that the MPA C_{max} values were inversely related to infusion time (3). From the C_{max} data obtained, it was estimated that an i.v. MMF dose of 1 g b.i.d. administered over 2 h was likely to result in peak plasma MPA concentrations comparable to those following administration of the same dose of p.o. MMF. These data formed the basis for the dosing schedule employed in the present study.

The present study analyzes the results of two related studies (MYCS2172 and MYCS2734) in *de novo* renal transplant patients in the immediate postoperative period. Only a single dose level of i.v. MMF (1 g b.i.d.), the dose of MMF currently recommended for renal transplant recipients, was studied. The PK study (MYCS2734) was designed primarily to compare the bioavailability and pharmacokinetics of MPA after multiple i.v. dosing when switching to p.o. capsules. The design of the safety study allowed an unbiased comparison of the safety of the two methods of administration.

Patients and methods

Both studies were approved by the institutional review boards at each center. Written informed consent was obtained and the patients were screened for eligibility within 48 h prior to transplantation. Patients were eligible if they were: recipients of a first or second renal transplant (single-organ transplant only); at least 18 yr of age; able to receive p.o. and i.v. medication. Patients were excluded if: they were pregnant or nursing; had severe diarrhea or other gastrointestinal (GI) disorders; had active peptic ulcer disease; if the patient or the donor had serologic evidence of HTLV-1, HIV, or HbsAg; had a malignancy or history of malignancy; had a systemic infection; had a white blood cell count less than $2500/mm^3$, a platelet count less than $100000/mm^3$, or hemoglobin less than 6 g/dL at the time of entry; required concomitant therapy with azathioprine, tacrolimus, rapamycin, or any investigational drug. Antacids were not permitted during the PK study. Patients who fulfilled the inclusion/exclusion criteria were enrolled into the respective studies prior to transplantation.

The safety and tolerability study was a randomized, multicenter, double-blind study (for the first 5 d, with an open-labeled follow-up) parallel group design. Before transplantation, eligible patients were randomized in a 2:1 ratio to groups designated 'MMF i.v.–p.o.' (blinded i.v. MMF 1 g b.i.d. and oral placebo capsules) or 'MMF p.o.–p.o.' (blinded i.v. placebo b.i.d. and p.o. MMF capsules, 1 g b.i.d.) through study day 5, followed by open-labeled p.o. MMF in both groups. Patient randomization was stratified by the center. Treatment with the i.v. study drug began within 24 h after transplantation. Treatment with the p.o. study drug was begun as soon as the patient could take the study capsules, but must have been started within 72 h after transplantation. Patients completed the study on study day 21. Subsequent therapy was determined by the patient's physicians. The PK study was also a multicenter one. It was open-labeled with only one treatment group. Treatment with i.v. MMF began within 24 h after transplantation, followed by a switch to p.o. MMF on the evening of day 5. Patients completed the study on day 6.

The MMF used for i.v. administration was supplied as a lyophilized powder in glass vials containing the equivalent of 500 mg of MMF (542 mg of MMF hydrochloride), polysorbate 80, and anhydrous citric acid. A matching placebo for i.v. MMF contained 250 mg mannitol, 120 mg dextrose, polysorbate 80, riboflavin, and anhydrous

citric acid. The pharmacist at each study site reconstituted and prepared each dose of i.v. study drug. The i.v. solution was prepared and administered within 12 h of reconstitution. The i.v. solution of MMF or placebo was administered, if possible, via a dedicated peripheral venous catheter cleared with D5W prior to infusion of the study drug. A central line could be used if a peripheral line could not be established or if local irritation developed. The i.v. solutions were infused via a pump at a rate of 84 mL/h for 2 consecutive hours. Other drugs were not to be given simultaneously with MMF through the infusion line or mixed in the infusion bag. If possible, in order to permit a more accurate assessment of the local tolerance of MMF, other drugs were not to be administered at any time through the peripheral i.v. line for MMF. Peripheral infusion sites were changed every 72 h.

The MMF and placebo used for oral administration were supplied in blue, opaque, size # 1 capsules. MMF capsules contained 250 mg MMF, pregelatinized starch, croscarmellose sodium, povidone (K-90), and magnesium stearate. Placebo capsules contained pregelatinized starch, croscarmellose sodium, (K-90), and magnesium stearate.

The first day on which the patient received an AM dose of i.v. study drug was designated as study day 1. If the first dose of i.v. study drug was administered PM, this day was designated as study day 0. Subsequent doses of i.v. study drug were given every 12 h through, and including, the morning or the evening of day 5 for the PK and safety studies, respectively. For the safety study, the patients received a total of either 10 or 11 i.v. doses of blinded study drug, depending on whether the first dose was administered on study days 1 or 0, respectively. For the PK study, the patients received a total of either 9 or 10 i.v. doses of open-labeled i.v. MMF, depending on whether the first dose was administered on study days 1 or 0, respectively.

For the safety study, the first dose of oral study drug was administered as soon as the patient could take the capsules. Once oral dosing was initiated, patients received their study capsules at the same time as the start of their i.v. infusions for the remainder of the double-blind phase of the study. Four capsules of oral study drug were administered b.i.d., to be swallowed intact. Open-label MMF capsules were administered (1 g b.i.d.) on study days 6 through 21. During the blinded phase of the safety study (study days 0/1 through 5), no modification of the dose of i.v. or p.o. study drug was allowed. During the open-labeled oral dosing phase (study days 6 through 21), if an adverse event (AE) occurred the dose of MMF could be reduced or interrupted as deemed appropriate by the investigator.

For the PK study, p.o. MMF was administered on the evening of day 5 and the morning of day 6. No modification or interruption of the dose of i.v. or p.o. study drug was allowed. If a patient missed any doses of i.v. or p.o. MMF or was unable to take four MMF capsules by the evening of study day 5, the patient was excluded from the PK evaluation.

The safety study was designed to make direct comparisons between the two treatment groups during the double-blind period. Since AEs occurred between the time of the first i.v. dose (i.e., placebo) and the first dose of p.o. MMF for patients randomized to the p.o. MMF 2 g/d group, patients were declared 'on treatment' at the time they received their first i.v. placebo dose, so that inspection of data for 'delayed' AEs was possible. The summary of AEs – by treatment group – collected while the patients were on double-blind i.v. treatment included all AEs with onset date/time on or after the date/time of the first i.v. infusion up to the date/time of the first open-labeled oral dose. The summary of AEs during the 21 d of study included all AEs that occurred on the day of the first dose of study drug up through the first 21 d on study, and excluded all AEs that occurred after the termination date for those patients prematurely terminating from the trial. The summary of patients with AEs probably or possibly related to the study drug used the relationship as reported by the investigator, and also included AEs for which the relationship was missing. All opportunistic infections (OIs) were included in this summary. Particular attention was paid to the peripheral i.v. infusion sites, that were inspected on study days 0/1, 2, 3, 4, and 5. Beginning immediately prior to and continuing for 2 h after the end of the initial infusion of study drug, patients were monitored utilizing continuous electrocardiogram (ECG), noninvasive arterial oxygen saturation (SaO_2), and supine blood pressure and pulse rates obtained at 30-minute intervals. Pulse rates and supine blood pressure were also recorded prior to, 30 min after the start, and at the completion of the AM i.v. administration of study drug on study days 3 and 5.

For the PK study, the primary objective was to compare MMF bioavailability, determined by the MPA AUC_{0-12}, when switching from the 2-h i.v. infusion on study day 5 to the 250-mg capsule dosage form on study day 6. Patients fasted (water permitted) overnight, beginning at 10 PM on the nights prior to study days 5 and 6. Blood samples

(5 mL each) for the measurement of MPA and MPAG were obtained from either a peripheral or a central line using a port dedicated to drawing blood samples or by venipuncture. If MMF was administered through a peripheral vein, blood samples were not taken from the limb in which the infusion was administered. If MMF was administered through a central line, blood samples were obtained from a peripheral vein. Blood samples were collected in heparinized tubes immediately before dosing (at 0 minutes), at 20, 30, 40, 60, 80, 100, 120, 140, and 160 min, and at 3, 4, 6, 8, and 12 h after the AM dose on study days 5 and 6.

Plasma samples were analyzed for MPA and MPAG concentrations by high-performance liquid chromatography (PHARMout Laboratories, Sunnyvale, CA). The limit of quantitation for MPA in plasma was 0.1 μg/mL. The limit of quantitation for MPAG in plasma was 4.0 μg/mL (2.38 μg/mL in MPA-equivalent units). Actual times were used in the calculation of all computed PK parameters. AUC was calculated using the linear trapezoidal rule. C_{max} was determined by visual inspection of the data, and T_{max} was determined to be the time at which it occurred. All MPAG concentrations were expressed in MPA-equivalent units by multiplying all reported MPAG concentrations by the ratio of MPA molecular weight to MPAG molecular weight (320.35/539.42). Concentrations below the limit of quantitation of the assay were treated as 0 in statistical summaries.

Statistics

For the safety study, the sample size was selected empirically without formal assessment of study power. All patients enrolled in the trial who received at least one dose of study drug were included in the assessment of safety. All safety data were summarized using descriptive statistics. For each patient, multiple or repeated AEs that mapped to a common preferred term were condensed to a single AE.

No hypothesis testing was performed for efficacy because of the short duration of the study and the relatively small sample size. The number of full or partial courses of immunosuppressives for the treatment of rejection during the study was summarized. A full course was at least 1 d of anti-thymocyte globulin (ATG), or ALG, or anti-CD3 rnAb (OKT3), or corticosteroids administered for at least 3 d with a total course dose of 600 mg or more. A partial course was corticosteroids administered for 2 d or less, regardless of dose, or a total dose of less than 600 mg at an average daily dose of at least 100 mg.

For the PK study, the planned enrollment was 40 patients, with the expectation that at least 24 patients would be evaluable. Although this was not a formal crossover bioequivalence study, the goal of 24 evaluable patients was based on bioequivalence criteria, assuming an intra-subject percentage coefficient of variation of 22.5 for log-transformed AUC_{0-12} $\ln(AUC_{0-12})$ (based on a previous unpublished study), with 80% power to show bioequivalence – assuming a difference of no more than 5% between the two routes of administration. The computed parameters were analyzed using ANOVA with terms for patient and route of administration. Statistical analyses were performed using SAS, version 6.09. Ordinary confidence intervals (CIs; 90% and 95%) for the difference in least squares means were constructed and expressed as a percentage (i.v. relative to p.o.) to compare the bioavailability of the two routes of administration.

Results

Safety study

One-hundred and sixty patients (n = 104 i.v.–p.o., and n = 56 p.o.–p.o.) qualified to enter the safety study. Twenty-eight patients were prematurely terminated from the study. Seven patients, 6 in the MMF i.v.–p.o. group and one in the MMF p.o.–p.o. group, were randomized but never received study drug and were not evaluated for safety. Of these, 4 patients did not receive their transplant. Two patients changed their mind about participating in the study. Fifteen patients prematurely terminated from the trial because of AEs: 11 patients (11%) in the i.v.–p.o. group and 4 patients (7%) in the p.o.–p.o. group. These cases are discussed below. One patient received 3 g/d of MMF to treat a rejection episode. Three patients were terminated because they received prohibited medications (OKT3, tacrolimus, and tacrolimus, respectively). One patient was terminated after 16 d because the physician considered him to be over-immunosuppressed. One patient terminated for personal reasons after having received the study drug for 15 d, and one other for non-compliance.

Selected demographics of the 153 evaluable patients are summarized (Table 1). The two treatment groups were well balanced for the number of patients with a previous transplant, donor source, panel reactive antibody, and cold ischemic time (not shown). The number of HLA mismatches between donor and recipient was slightly greater in the MMF i.v.–p.o. group than in the MMF p.o.–p.o. group. Induction therapy was administered to 42% of patients (41/98) in the MMF i.v.–p.o. group and to 31% of patients (17/55) in the MMF p.o.–p.o. group.

Table 1. Demographic summary: all evaluable patients enrolled in the safety study

	Treatment group	
	MMF i.v.–p.o. (n = 98)	MMF p.o.–p.o. (n = 55)
Gender: n (%)		
Male	62 (63)	38 (69)
Female	36 (37)	17 (31)
Age (y)		
Mean ± SD	46.6 ± 13.2	44.2 ± 12.8
Range	19–74	20–68
Weight (kg)		
Mean ± SD	75.7 ± 15.5	73.4 ± 16.0
Range	37.0–110.0	50.5–125.0
Race		
Asian	7 (7)	7 (13)
Black	13 (13)	6 (11)
Caucasian	66 (67)	34 (62)
Hispanic	9 (9)	2 (4)
Other	3 (3)	6 (11)

Ninety-nine percent of patients randomized to the MMF i.v.–p.o. group received i.v. MMF for at least 4 d. Ninety-one percent of the patients in the MMF p.o.–p.o. group started oral dosing by 48 h. Three patients in the MMF p.o.–p.o. treatment group were terminated during the double-blind study period for AEs. Excluding doses not taken after the last dose for these prematurely terminated patients, only 14 of 496 (2.8%) double-blind p.o. doses were missed in 5 of 55 (9.1%) patients.

For the 153 patients who received study medication, Fig. 1 displays all specific AEs that occurred in at least 20% of patients from the time of the first dose of i.v. study medication until the time the patient was placed on open-labeled p.o. MMF or was terminated from the study (i.e., prematurely terminated treatment during the i.v. phase of the study). All but one patient (MMF i.v.–p.o. group) experienced at least one AE during the double-blind i.v. phase of the study. With the exception of hypophosphatemia, these AEs, as well as those reported for < 20% of patients, were fairly evenly distributed between the two treatment groups. A small excess of cardiovascular events (chiefly ECG abnormalities) were reported in the MMF i.v.–p.o. group (not shown). These were without hemodynamic consequences (e.g., arrhythmia, atrial fibrillation/flutter, and bigeminy).

In each group, 80% of patients (78/98 MMF i.v.–p.o. patients; 45/55 MMF p.o.–p.o. patients) received at least one dose of i.v. study medication (i.e., MMF and placebo, respectively) via a peripheral infusion. Fifty of 78 patients (64%) in the MMF i.v.–p.o. group and 29 of 45 patients (65%) in the p.o.–p.o. group receiving one or more pe-

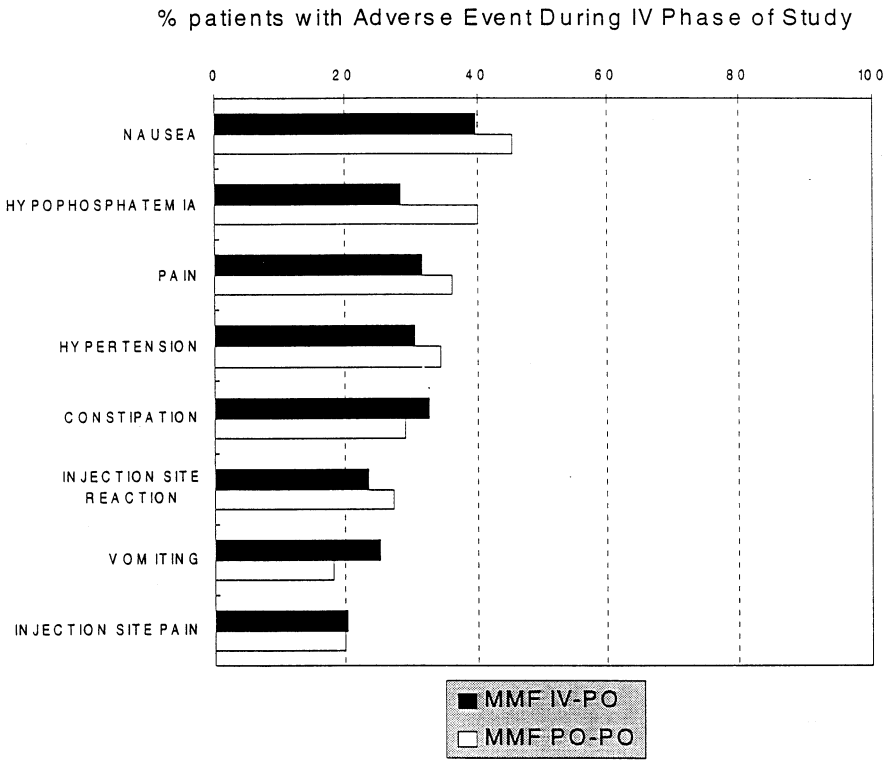

Fig. 1. Frequency of adverse events (AEs) that occurred in at least 20% of patients during the i.v. double-blind phase of the safety study only.

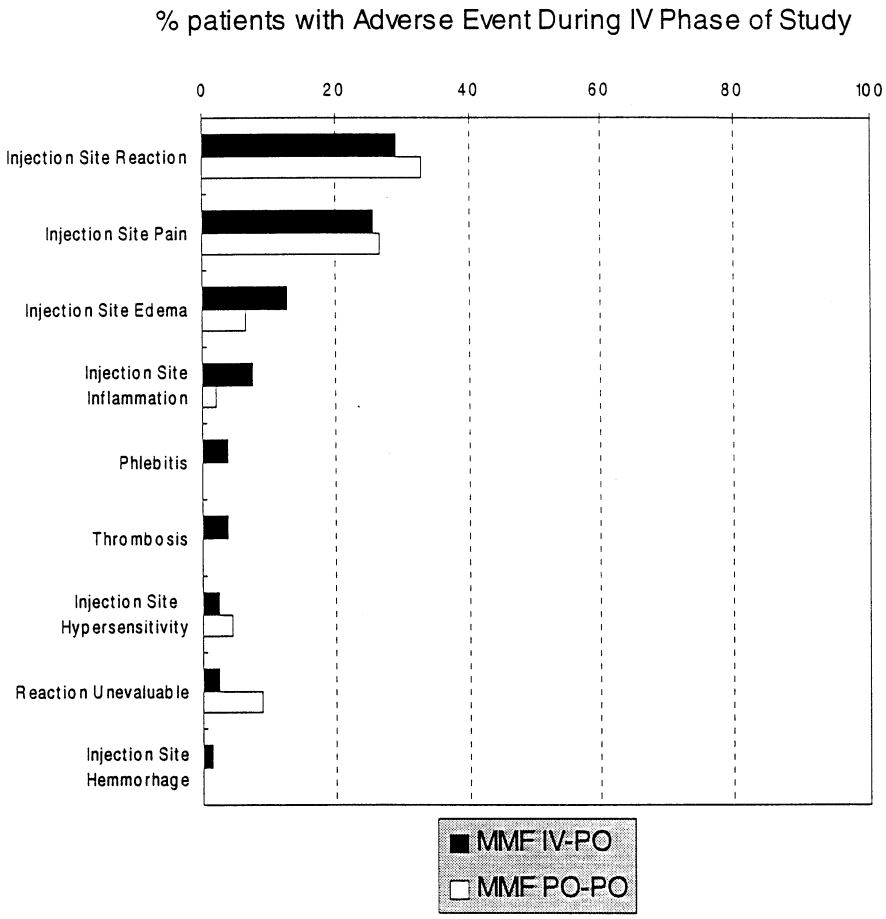

Fig. 2. Frequency of AEs that occurred at the peripheral infusion site for patients who received at least one dose of i.v. study medication via a peripheral infusion.

ripheral infusion reported a peripheral infusion-site reaction (Fig. 2). Venous thrombosis (4 patients, 4.1%), phlebitis, and hemorrhage were only reported in the MMF i.v.–p.o. group. Only 1 patient (MMF p.o.–p.o. group) was terminated from the study for a peripheral infusion-site reaction (infusion-site infiltration and edema).

Table 2 summarizes those events that occurred in 20% or more of patients in at least one of the treatment groups during the first 21 d of the study. Hypophosphatemia occurred in 22/55 patients (40%) during the i.v. placebo period, compared to 28/98 (28.6%) patients during i.v. MMF treatment; however, the hypophosphatemia rate for the period up to 21 d was similar for both groups (41.8% and 39.8%, respectively). Peripheral edema occurred in a similar number of patients during the blinded i.v. treatment phase: 8/55 patients (14.5%) receiving placebo compared to 12/98 (12.2%) patients receiving i.v. MMF; however, during the study, peripheral edema was more frequent in the i.v. MMF group 28/98 (28.6%) versus the p.o. MMF group 8/55 (14.5%).

During the study, 33% of all evaluable patients (51/153) experienced one or more severe AE as graded by the investigator: 33% of patients (32/98) in the MMF i.v.–p.o. group and 35% of patients (19/55) in the MMF p.o.–p.o. group. Eighty-two percent of all evaluable patients (126/153) experienced one or more AEs that were judged by the investigator to be probably or possibly related to study medication: 83% of patients (81/98) in the MMF i.v.–p.o. group and 82% of patients (45/55) in the MMF p.o.–p.o. group. Forty percent of all evaluable patients (61/153) experienced one or more AE that led to dose reduction or interruption: 42% of patients (41/98) in the MMF i.v.–p.o. group and 36% of patients (20/55) in the MMF p.o.–p.o. group. Three patients experienced GI hemorrhage that required hospitalization (1 in the MMF p.o.–p.o. group and 2 in the MMF i.v.–p.o. group). One additional patient (MMF i.v.–p.o. group) was noted as having moderate gastric erosions approximately 3 months after the study drug was discontinued. One patient (MMF i.v.–p.o. group) experienced a GI perforation. In general,

Table 2. Comparison of number (%) of patients with AEs with onset during the first 21 d on study[a] to AEs with onset while on i.v. treatment

Body system	Preferred term for adverse event	Number and percentage (%) of patients with adverse events			
		During first 21 d on study (i.v., n = 98)	During first 21 d on study (p.o., n = 55)	While on i.v. treatment (i.v., n = 98)	While on i.v. treatment (p.o., n = 55)
Body as a whole	Pain	41 (41.8)	26 (47.3)	31 (31.6)	20 (36.4)
	Injection site reaction	23 (23.5)	15 (27.3)	23 (23.5)	15 (27.3)
	Fever	23 (23.5)	10 (18.2)	20 (20.4)	7 (12.7)
	Injection site pain	20 (20.4)	12 (21.8)	20 (20.4)	11 (20.0)
	Reaction unevaluable	14 (14.3)	13 (23.6)	10 (10.2)	7 (12.7)
	Abdominal pain	14 (14.3)	11 (20.0)	8 (8.2)	6 (10.9)
Metabolic and nutritional disease	Hypophosphatemia	39 (39.8)	23 (41.8)	28 (28.6)	22 (40.0)
	Peripheral edema	28 (28.6)	8 (14.5)	12 (12.2)	8 (14.5)
Digestive System	Nausea	47 (48.0)	27 (49.1)	40 (40.8)	25 (45.5)
	Constipation	40 (40.8)	20 (36.4)	32 (32.7)	16 (29.1)
	Diarrhea	32 (32.7)	12 (21.8)	19 (19.4)	6 (10.9)
	Vomiting	33 (33.7)	11 (20.0)	26 (26.5)	10 (18.2)
	Dyspepsia	19 (19.4)	11 (20.0)	16 (16.3)	9 (16.4)
Cardiovascular system	Hypertension	44 (44.9)	22 (40.0)	30 (30.6)	19 (34.5)
Nervous system	Insomnia	16 (16.3)	13 (23.6)	11 (11.2)	8 (14.5)
Hemic and lymph system	Anemia	22 (22.4)	9 (16.4)	19 (19.4)	8 (14.5)

[a] Occurring in 20% or more of patients in either treatment group during the first 21 d.

AEs were fairly evenly distributed between the two treatment groups.

Ten percent of all evaluable patients (15/153) prematurely terminated study treatment because of AEs. These included 11% (11/98) of patients in the MMF i.v.–p.o. group and 7% (4/55) patients in the MMF p.o.–p.o. group. Only two patients in the i.v.–p.o. group terminated during the double-blind phase; one for atrial fibrillation and thrombosis, and the second for increased liver enzymes (serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase to 341 IU/L and 425 IU/L, respectively). Likewise, only 3 patients in the p.o.–p.o. group terminated during the double-blind phase; 2 for nausea and vomiting and 1 for injection site reaction.

Pulse rate and systolic and diastolic blood pressure results showed no difference either within or between groups when comparing baseline (pre-infusion) measurements with those taken every 30 min for 4 h after the first dose of i.v. study drugs, or between baseline measurements and those taken after 30 minutes and at the end of the AM infusions on study days 3 and 5 (not shown). Similarly no differences were observed in results from continuous ECG and arterial oxygen saturation monitoring for 4 h after the first dose of i.v. study drugs (not shown).

Seven percent of all evaluable patients (10/153) developed an opportunistic OI (Table 3). Of the 6 patients in the MMF i.v.–p.o. group who developed an OI, 3 had received induction therapy (2 with OKT3 and one with ATG); one additional patient in the MMF i.v.–p.o. group had received augmented immunosuppression for the treatment of a rejection episode prior to the onset of the OI. Of the 4 patients in the MMF p.o.–p.o. group who developed an OI, 1 had received induction therapy (OKT3); none had received augmented immunosuppression for the treatment of a rejection episode. The 1 patient who developed CMV viremia/syndrome (MMF i.v.–p.o. group) was cytomegalovirus (CMV) seropositive before trans-

Table 3. Summary of patients with opportunistic infections while on study

Diagnostic category	Treatment group			
	MMF i.v.–p.o. (n = 98)		MMF p.o.–p.o. (n = 55)	
	n	%	n	%
Any opportunistic infection	6	6	4	7
Candida, mucocutaneous	4	4	3	6
Herpes simplex	1	1	1	2
CMV viremia/syndrome	1	1	0	0
Herpes zoster, cutaneous	0	0	1	2

Table 4. Number of full course(s) of immunosuppressive therapy administered for rejection during the study

	Treatment group			
	MMF i.v.–p.o. (n = 98)		MMF p.o.–p.o. (n = 55)	
	n	%	n	%
Patients administered one or more full courses of immunosuppressive therapy	24	24.5	9	16.4
One course	21	21.4	9	16.4
Two or more courses	3	3.1	0	0
Patients administered one or more full courses of immunosuppressives by type of immunosuppressive				
OKT3/ATG/ALG only	6	6.1	5	9.1
Corticosteroids only	17	17.3	4	7.3
OKT3/ATG/ALG plus corticosteroids	1	1.0	0	0

plant and received a kidney from a CMV seropositive donor.

Table 4 summarizes the use of full courses of immunosuppressive therapy for the treatment of rejection during the study. Additionally, 3 patients in the MMF i.v.–p.o. group and 1 patient in the MMF p.o.–p.o. group each received a single partial course of corticosteroids for the treatment of rejection during the study. Five patients (MMF i.v.–p.o., n = 4; MMF p.o.–p.o., n = 1) experienced graft loss during the study and underwent transplant nephrectomy. For the i.v.–p.o. group, the reason for the graft losses (and the days after transplantation) were rejection (day 10), technical complication (day 12), perinephric hematoma (day 12), and renal vein thrombosis (day 5). In the MMF p.o.–p.o. group, one graft was lost at 8 d from technical complications. No patient died during the first 21 d of treatment.

PK study

A total of 45 patients from eight centers qualified to enter the PK study. All patients enrolled into this study received their transplants and at least one dose of study drug. The demographics for the patients in the PK study were similar to the double-blind safety study (data not shown). Three patients who completed the study normally were not evaluable for pharmacokinetics because of problems with blood sampling. Eleven patients did not complete the PK study because of AE (n = 5), unsatisfactory therapeutic response (rejection, n = 1), prohibited medication (use of tacrolimus, n = 1), and other reasons (n = 4, 3 for dialysis). The safety profile was similar to that seen with the double-blind study (data not shown).

Thirty-one patients were evaluable for the PK analyses. Statistically significant differences in mean plasma MPA concentration between the i.v. and p.o. routes of administration were observed for the 0.33-, 0.67-, 1.0-, 1.33-, 1.67-, 2.0-, and 2.33-h time points (Fig. 3). Statistically significant differences between the routes were observed for AUC_{0-12} ($p < 0.001$) but not C_{max} ($p = 0.252$) (Table 5). The apparent discrepancy between the C_{max} seen in Fig. 3 and the C_{max} in Table 5 results from the method of calculating the respective results. In Fig. 3, the data are the average of the individual results at each defined time point. In Table 5, the C_{max} is the average of the individual C_{max}, regardless of the time at which it occurs. The ordinary CIs (90%) for the difference in least squares means were constructed and expressed as a percentage (i.v. relative to p.o.) for the computed parameters AUC_{0-12} C_{max} and T_{max} (Table 5). The percentages for AUC_{0-12} and C_{max} fall outside the 80–120% (non-transformed) or 80–125% (log-transformed, not shown) bounds required to conclude that the formulations were bioequivalent. The ratio for $\ln(AUC_{0-12})$ was 129% (90% CI of 119–139%) while that for $\ln(C_{max})$ was 120% (90% CI of 101–143%).

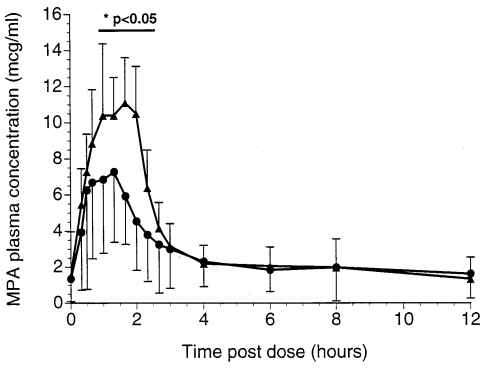

Fig. 3. Mean pharmacokinetic (PK) profiles of mycophenolic acid (MPA) over time (n = 31). The i.v. MMF dose (▲) compared to the p.o. MMF dose (●) produced significantly greater MPA concentrations over the time ($p < 0.05$, indicated by the bar).

Table 5. Plasma MPA and MPAG computed parameters, AUC_{0-12} and C_{max}: i.v. versus p.o. dosing (n = 31)

	MMF i.v.[a]	MMF p.o.[a]	p-value[b]	Ratio i.v./p.o. (%)	90% CI
MPA					
AUC_{0-12} (μg·h/mL)	40.8 ± 11.4	32.9 ± 15.0	< 0.001	123.9	112.6, 135.2
C_{max} (μg/mL)	12.0 ± 3.8	10.7 ± 4.8	0.252	112.5	90.7, 134.3
T_{max} (h)	1.58 ± 0.46	1.33 ± 1.05	0.231	118.8	87.4, 150.2
MPAG					
AUC_{0-12} (μg·h/mL)	720 ± 316	746 ± 302	0.324	96.5	90.5, 102.4
C_{max} (μg/mL)	74.6 ± 27.3	80.2 ± 27.5	0.086	93.0	86.4, 99.7
T_{max} (h)	3.42 ± 2.03	3.61 ± 2.73	0.713	94.8	70.9, 118.7

[a] Results are mean ± SD obtained from the 31 evaluable patients.
[b] p-value compares results of MMF i.v. versus MMF p.o. for each PK parameter.

No statistically significant difference between the i.v. and p.o. routes of administration was observed for mean plasma MPAG concentrations at any time point (Fig. 4), or for MPAG AUC_{0-12} and C_{max} (Table 5). As opposed to the findings with MPA, the ordinary CIs (90 and 95%) for the difference in least squares means for both AUC_{0-12} and C_{max} fell within the 80–120% (non-transformed) or 80–125% (log-transformed) bounds for bioequivalence (not shown).

Discussion

Overall, the AE experience of patients receiving i.v. MMF in the safety study (and confirmed in the smaller open-labeled PK study) appeared to be comparable to those receiving i.v. placebo during both the 5-day, double-blind i.v. phase of the study and the open-labeled oral follow-on phase. The overall incidence of local site reactions of peripherally administered infusions appeared to be unrelated to treatment with either i.v. MMF or placebo. However, the peripheral i.v. infusion of MMF appeared to be associated with a higher incidence of local edema and inflammation. Injection site hemorrhage, phlebitis, and thrombosis were observed only in the MMF i.v.–p.o. treatment group, and may be caused by the i.v. MMF formulation. Although none of these events resulted in the interruption or discontinuation of i.v. administration of MMF, a central venous line for infusion may be a preferred alternative, if available. However, with the overall low incidence of infusion-site complications, it is probably not worth placing a central line solely for the administration of i.v. MMF.

The difference in edema rates for the period up to 21 d may be associated with overall differences in the characteristics of the two groups that were reflected in other measures of renal function. It is improbable that this apparent post-i.v. treatment increase was a consequence of a 'delayed effect' of i.v. administration in the MMF i.v.–p.o. group. The increased fever in the MMF i.v.–p.o. group may reflect the more frequent use of ATGAM in this group. Vomiting and diarrhea, known side effects of p.o. MMF (1), were not avoided, and, in fact, perhaps accentuated by the higher levels following the i.v. infusion of MMF. This suggests that vomiting and diarrhea result from a systemic effect of MPA and not simply a local GI effect.

Mean MPA $\ln(AUC_{0-12})$ during multiple-dose i.v. treatment with MMF (1 g b.i.d. over 2 h) was 29% greater than that measured following the transition to p.o. MMF (1 g b.i.d. as 4 × 250 mg capsules). The mean MPA $\ln(C_{max})$ associated with the i.v. infusion was approximately 20% greater than that following p.o. MMF. Similar results in a normal volunteer study indicate that this effect is not due to concurrent medications, postoperative GI motility, or renal dysfunction (9). This indicates that the 2-h infusion of i.v. MMF is not bioequivalent to the 2 g p.o. dose of MMF. The MPA concentration–time profile after i.v. administration (Fig. 3), however, is nearly identical to that follow-

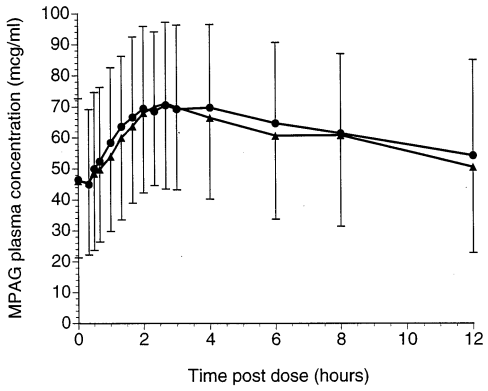

Fig. 4. Mean PK profiles of the phenolic glucuronide of MPA (MPAG) over time (n = 31). As opposed to the results with MPA, MPAG levels following the i.v. MMF dose (▲) were comparable to those following the p.o. MMF dose (●) at all time points.

ing p.o. dosing, indicating that a 2-h infusion nearly mimics p.o. dosing. Based on the known PK/PD relationship for MPA AUC, it is anticipated that a 1 g i.v. dose of MMF administered twice daily according to the above regimen will provide efficacy at least as good as p.o. treatment (11). Shaw et al. (12), using p.o. MMF, reported that renal transplant recipients with an average MPA AUC of 40.9 μg·h/mL (similar to that seen in this study with i.v. administration) had a rejection rate of 8.5%, which was considerably less than the 25.5% rate seen with an AUC of 22.1 μg·h/mL. With an AUC of 64.2 μg·h/mL the rejection rate was decreased even further to 5.8%.

Despite the greater drug exposure, the safety profile was comparable, at least over the short term. It is uncertain if there will be an advantage to using higher doses of i.v. MMF (e.g., 1.5 g b.i.d.) in high risk groups or if this will lead to increased toxicity. From a safety perspective, the i.v. form of MMF (1 g administered over 2 h, given twice daily) provides an acceptable alternative dose form to p.o. MMF in those patients unable to take p.o. medication.

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