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The use of mycophenolate mofetil suspension in pediatric renal allograft recipients

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Abstract Mycophenolate mofetil (MMF) is widely used to prevent acute rejection in adults after renal, cardiac, and liver transplantation. This study investigated the safety, tolerability, and pharmacokinetics of MMF suspension in pediatric renal allograft recipients. One hundred renal allograft recipients were enrolled into three age groups (33 patients, 3 months to <6 years; 34 patients, 6 to <12 years; 33 patients, 12 to 18 years). Patients received MMF 600 mg/m^2 b.i.d. concomitantly with cyclosporine and corticosteroids with or without antilymphocyte antibody induction. One year after transplantation, patient and graft survival (including death) were 98% and 93%, respectively. Twenty-five patients (25%) experienced a biopsy-proven (Banff grade borderline or higher) or presumptive acute rejection within the first 6 months post-transplantation. Analysis of pharmacokinetic parameters for mycophenolic acid (MPA) and mycophenolic acid glucuronide showed no clinically significant differences among the age groups. The dosing regimen of MMF 600 mg/m^2 b.i.d. achieved the targeted early post-transplantation MPA 12-h area under concentration-time curve ($AUC_{0–12}$) of 27.2 μg h per ml. Adverse events had similar frequencies among the age groups (with the exception of diarrhea, leukopenia, sepsis, and anemia, which were more frequent in the <6 years age group) and led to withdrawal of MMF in about 10% of patients. Administration of MMF 600 mg/m^2 b.i.d. is effective in prevention of acute rejection, provides predictable pharmacokinetics, and is associated with an acceptable safety profile in pediatric renal transplant recipients.

Keywords Mycophenolate mofetil · Pharmacokinetics · Renal transplantation · Pediatric · Mycophenolic acid

Introduction

Mycophenolate mofetil (MMF) is a morpholinoethyl ester of mycophenolic acid (MPA) that inhibits inosine monophosphate dehydrogenase, an enzyme required for purine biosynthesis [1, 2, 3, 4, 5, 6, 7]. The immunosuppressive efficacy of MMF in preventing acute rejection has been demonstrated in clinical trials of adult patients after renal [8, 9, 10], cardiac [11], or liver [12] transplantation, when used in conjunction with cyclosporine and corticosteroids.

An earlier dose-ranging pilot study evaluated the safety and tolerability of MMF for the prevention of acute rejection in pediatric renal allograft recipients and provided initial pharmacokinetic data for the active metabolite MPA, and for the inactive metabolite mycophenolic acid glucuronide (MPAG), in pediatric patients [13]. The current study presents the 12-month results from a second clinical trial aimed at evaluating the safety, tolerability, and pharmacokinetics of MMF suspension at the recommended pediatric dose. The anticipated follow-up period for the entire study is 36 months.

Patients and methods

Patients

This is an ongoing, multicenter, open-label, single-arm study of MMF oral suspension in pediatric renal transplant patients. Patients included in the study were male or female, aged 3 months to 18 years, weighing at least 5.4 kg (approximately 12 lb). They were recipients of a first or second ABO-compatible single-organ (kidney) allograft from a living or cadaver donor, were able to tolerate oral medication, and were without any contraindication for the co-administration of cyclosporine and corticosteroids.

Exclusion criteria included the following: active systemic infection; an absolute neutrophil count <1300 granulocytes/mm^3 at study entry; active peptic ulcer disease; severe diarrhea or other gastrointestinal disorder that might interfere with absorption of oral medication; serologic evidence of human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infection; pregnancy/breast-feeding; history of malignancy (excluding adequately treated basal or squamous cell skin carcinoma); recurrent focal segmental glomerular sclerosis; prior exposure to MMF; or use of tacrolimus.

Monitoring for renal function, rejection episodes, adverse events (AEs), opportunistic infections, and malignancy was begun at the time of transplantation and at regularly scheduled clinical assessments thereafter. Renal transplant biopsies were performed, unless medically contraindicated, to confirm the diagnosis of acute rejection.

Patients were permitted to withdraw from the study at any time for any reason. If patients withdrew, they were to be followed for a period of 36 months after transplantation for rejection, graft loss, death, malignancies, and opportunistic infections.

Drug treatment

The dosage of MMF oral suspension was 600 mg/m^2 b.i.d. (up to 1 g b.i.d.), used concomitantly with cyclosporine and corticosteroids according to each center's standard of care. Antilymphocyte antibody induction therapy was also allowed according to center practice.

The targeted MPA area under the concentration-time curve (AUC) was derived from studies in adults that demonstrated the safety and efficacy of the 1 g b.i.d. MMF dose in that population [14]. Body surface area (BSA) in the current pediatric trial was calculated using the Mosteller equation [15], and individual dosing was adjusted, based on changes in BSA, as needed.

Administration of high-dose corticosteroids and the use of antilymphocyte antibody preparations were permitted, according to center-specified regimens and at the discretion of the investigator, for the treatment of biopsy-confirmed/presumptive acute rejection episodes. Nine months after transplantation, a switch from the suspension to the capsule formulation of MMF was permitted if protocol-defined criteria were satisfied (BSA ≥1.25 m^2, patient able to swallow capsules, and more convenient for patient).

Pharmacokinetics

At selected study sites, plasma samples were collected for 12-h pharmacokinetic profiles on day 7 and at months 3, 9, 24, and 36. Samples were drawn at 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 8, and 12 h after the dose was given. Blood samples were also requested during serious adverse events or acute rejection episodes (pharmacokinetic AE samples).

Ethics and quality control

The study was conducted in full compliance with the Declaration of Helsinki (as amended in Tokyo, Venice, and Hong Kong) or in compliance with the laws and regulations of the country in which the research was conducted, whichever provided greater protection to the patient. Written informed consent was obtained from all patients or the patient's parent or legal guardian, following explanation of the aims, methods, and anticipated benefits as well as potential hazards of the study. Data quality was monitored throughout the course of the study.

Safety and efficacy analysis

All enrolled patients who received at least one dose of study drug were included in the safety analyses. The primary efficacy parameter was the proportion of patients experiencing a biopsy-proven rejection (BPR) episode within the first 6 months post-transplantation. Additional efficacy endpoints were the proportion of patients who lost their graft by 6 and 12 months, the proportion of patients who died at 6 and 12 months, and the proportion of patients who received anti-rejection therapy at 6 months post-transplantation. A BPR episode was defined as a core renal biopsy demonstrating a severity that was borderline or higher, according to the Banff schema for classification of renal allograft pathology [16]. Presumptive rejection included those patients receiving a protocol-defined full course of immunosuppressive therapy for rejection when biopsy confirmation was not possible. Graft loss was defined as chronic dialysis (>42 consecutive days), transplant nephrectomy, or re-transplantation.

Pharmacokinetic statistics

Pharmacokinetic parameters were assessed using Analysis of Variance where appropriate. Descriptive summary statistics (mean, standard deviation, and number of patients) are presented in Table 1 for pharmacokinetic parameters, as well as plasma concentrations by each sampling time and by the three age groups. Pharmacokinetic AE samples for selected serious adverse events [including leukopenia, vomiting, cytomegalovirus (CMV), and diarrhea] and for all rejection episodes were compared with mean data at similar time points from patients having 12-h pharmacokinetic profiles. Plasma concentrations of MPA and MPAG were determined by PHARMout Laboratories, Inc. (Sunnyvale, California) using a sensitive and specific high-performance liquid chromatography method [17]. The limit of quantification was 0.100 µg/ml for MPA and 4.00 µg/ml for MPAG (MPA equivalent 2.38 µg/ml, determined by multiplying all reported MPAG concentrations by the ratio of molecular weights, MPA:MPAG).

Table 1 Mean computed pharmacokinetic parameters of mycophenolic acid by age and time after transplantation. Pharmacokinetic parameters (T_{max} time to maximum concentration, *Adjusted* C_{max} maximum concentration adjusted to a dose of 600 mg/m², *Adjusted* AUC_{0-12} 12-h area under concentration-time curve adjusted to a dose of 600 mg/m²) are expressed as mean ±SD with 95% confidence intervals in parentheses. *P* value indicates the significance of differences among the three major age groups (*NS* not significant, *P*>0.05). The <2 years group is a subset of the <6 years group and no separate statistical comparisons were made

Time after transplantation	Age group	*n*	T_{max} (h)	Adjusted C_{max} (μg/ml)	Adjusted AUC_{0-12} (μg h per ml)
Day 7	<6 years	17	1.63±2.85	13.2±7.16	27.4±9.54 (22.8–31.9)
	6 to <12 years	16	0.940±0.546	13.1±6.30	33.2±12.1 (27.3–39.2)
	12 to 18 years	21	1.16±0.830	11.7±10.7	26.3±9.14 (22.3–30.3)[a]
	P value		NS	NS	NS
	<2 years	6	3.03±4.70	10.3±5.80	22.5±6.68 (17.2–27.8)
Month 3	<6 years	15	0.989±0.511	22.7±10.1	49.7±18.2
	6 to <12 years	14[b]	1.21±0.532	27.8±14.3	61.9±19.6
	12 to 18 years	17	0.978±0.484	17.9±9.57	53.6±20.2[c]
	P value		NS	NS	NS
	<2 years	4	0.725±0.276	23.8±13.4	47.4±14.7
Month 9	<6 years	12	0.869±0.479	30.4±9.16	60.9±10.7
	6 to <12 years	11	1.12±0.462	29.2±12.6	66.8±21.2
	12 to 18 years	14	1.07±0.518	18.1±7.29	56.7±14.0
	P value		NS	0.004	NS
	<2 years	4	0.604±0.208	25.6±4.25	55.8±11.6

[a] *n*=20
[b] Data for one patient were unavailable because of a sampling error
[c] *n*=16

Table 2 Summary of first biopsy-proven rejection (*BPR*) or presumptive rejection during the first 6 months after transplantation (pediatric criteria). Numbers, with percentages in parentheses, are the results of intent-to-treat analysis using local site biopsy readings

BPR/presumptive rejection	Number of rejections (%) by age group			
	<6 years (*n*=33)	6 to <12 years (*n*=34)	12 to 18 years (*n*=33)	Total (*n*=100)
Borderline	2 (6.1)[a]	1 (2.9)	3 (9.1)[b]	6 (6)[a]
Grade I	2 (6.1)	7 (20.6)	2 (6.1)	11 (11)
Grade IIA	1 (3.0)	1 (2.9)	2 (6.1)	4 (4)
Grade IIB	0	0	2 (6.1)	2 (2)
Grade III	0	0	0	0
Total BPR	5 (15.2)	9 (26.5)	9 (27.3)	23 (23)
BPR or presumptive rejection	7 (21.2)	9 (26.5)	9 (27.3)	25 (25)

[a] One patient was treated for presumptive rejection and later experienced borderline rejection; this patient is counted as presumptive rejection in this table
[b] Two patients had a second rejection episode with a Banff score of grade III; these are not recorded in the grade III events in this table

Results

Patients and demographics

A total of 100 patients, 68 males and 32 females, were enrolled in the study into 3 age groups: 3 months to <6 years, 6 years to <12 years, and 12 years to 18 years. The distribution of patients by sex and race was similar across age groups. Sixty-four patients were from North America, 4 from Australia, and 32 from Europe. At least one patient was represented in each age year through to age 18. The most common reason for renal failure for patients enrolled in the study was congenital abnormality (48%), followed by glomerulonephritis (26%). For most patients (87%), this was their first renal transplant, and 54% of grafts were from a living related donor. The number of A+B+DR mismatches was distributed evenly across age groups. The majority of patients received antibody induction therapy (73%), which consisted primarily of antithymocyte globulin (54%), but also included muromonab-CD3 (OKT3, 9%), daclizumab (7%), and antilymphocyte globulin (3%).

Of 100 patients enrolled, 72 were ongoing after the first 12 months and 28 withdrew before completing 12 months. Ten of the 28 patients withdrew prematurely because they needed medication that was prohibited by the study protocol, comprising patients switched to tacrolimus to avoid side effects of cyclosporine (*n*=5), patients experiencing chronic rejection (*n*=3), and patients switched to cyclophosphamide (*n*=2) for recurrent focal segmental glomerulosclerosis. Adverse events accounted for an additional ten withdrawals (see Safety and tolerability Section below for details).

Efficacy

Twenty-five patients (25%) experienced either a first BPR (23 patients) or a presumptive rejection (two patients) within the first 6 months of the study. These patients were evenly distributed across the age groups studied (Table 2). Ninety-two percent of rejection episodes were confirmed by biopsy. Twenty-one percent of patients (15/73) who received antibody induction therapy experienced a rejection. Patients who did not receive in-

Table 3 Summary of creatinine clearance (*ClCr*) by age group and time after transplant. Creatinine clearances (expressed as ml/min per 1.73 m^2) are given as mean values ±SD and range

Time	Parameter	<6 years	6 to <12 years	12 to 18 years
Day 7	Patients in study	32	33[a]	31
	Mean ClCr	102±51.9	98.9±60.4	71.9±52.3
	ClCr range	7.95–222	9.23–302	15.1–147
Month 3	Patients in study	32	32	25
	Mean ClCr	92.8±30.7	92.2±37.5	82.0±26.1
	ClCr range	38.5–156	26.5–193	45.7–143
Month 6	Patients in study	31[a]	30	21
	Mean ClCr	91.4±49.2	89.1±32.8	85.3±23.5
	ClCr range	27.5–310	44.8–205	50.0–139
Month 9	Patients in study	30	28	20
	Mean ClCr	91.0±34.1	97.3±39.6	89.8±41.1
	ClCr range	29.7–180	33.2–208	7.06–165[b]
Month 12	Patients in study	28	27	18
	Mean ClCr	91.3±35.6	88.2±25.8	90.9±26.3
	ClCr range	28.8–189	45.6–150	37.0–134

[a] Data were missing for one patient in this group at this time point

[b] One patient was on dialysis because of graft rejection at this time point, with a serum creatinine value of 12.50 mg/dl

duction therapy had a proportionally higher rejection rate (10/27, 37%).

Between 6 and 12 months after transplantation, an additional four patients experienced their first BPR. At 1 year, five patients experienced graft loss (two had induction therapy) and two patients died (with functioning grafts), resulting in a graft survival rate of 93%. Of five graft losses, three were from patients in Europe, and two were from US patients. Both of the deaths occurred in US patients.

Creatinine clearances, calculated by the Schwartz method [18] as an index of renal function, are shown in Table 3.

Safety and tolerability

Eighty-one of the 100 patients (81%) received the study drug for at least 6 months, and 72 (72%) were on the study drug for at least 1 year. The mean dose of oral MMF through the first year on study drug was balanced across age groups: 524, 551, and 542 mg/m^2 b.i.d. for the groups aged <6 years, 6 to <12 years, and 12 to 18 years, respectively.

All patients experienced at least one AE during the first year (Table 4). Eighty-one patients reported AEs that were deemed by the investigator to be possibly or probably related to the study drug. The proportion of patients reporting AEs was generally similar across age groups for most AEs reported; however, there was a trend toward more frequent diarrhea and leukopenia in the two younger age groups (Table 4).

As mentioned above, ten patients (10%) withdrew from the study because of AEs, and their numbers were balanced across the age groups. The AEs that resulted in premature withdrawal were thrombosis of the renal artery and/or renal vein (two patients), graft thrombosis, Epstein-Barr virus infection, diarrhea (two patients), post-transplantation lymphoproliferative disorder/anemia, anorexia/intermittent abdominal pain, thrombocytopenia, and CMV viremia, all in one patient each. The remaining patient who withdrew because of AEs did so because of diarrhea, decreased appetite, nausea, and abdominal discomfort. In seven of these patients, the AEs resulting in withdrawal were considered by the investigator to be possibly or probably related to the study drug.

Forty-nine patients (49%) experienced AEs that resulted in MMF dose reduction or interruption. The majority of AEs resulting in dose reduction (60%) or dose interruption (66%) had their onset during the first 3 months of treatment. The AEs that most frequently resulted in dose reduction or interruption (in ≥5% of all patients) were leukopenia (22%), diarrhea (13%), sepsis (CMV, infections) (10%), anemia (6%), abdominal pain (5%), and fever (5%). The overall incidence of opportunistic infections (OIs) was 48%; the distribution of OIs was generally similar across age, sex, and racial subgroups, with the exception of mucocutaneous *Candida* infection, which had a higher incidence in the youngest age group. Overall, CMV viremia was the most frequent OI, being reported in 22% of the patients.

Two patients died, one of hemorrhagic pancreatitis and the other of pulmonary embolus. Neither of these events was deemed by the investigator to be related to MMF. One malignancy (post-transplantation lymphoproliferative disease) was reported approximately 9 months after transplantation and resolved completely after discontinuation of MMF and reduction of other immunosuppressants.

Pharmacokinetic data

Fifty-five patients were included in the pharmacokinetic analysis at day 7. MPA plasma concentrations peaked approximately 1 h post-dose. In the early post-transplantation period (day 7), the mean dose-adjusted MPA maximum concentration (C_{max}) was 12.6±8.3 μg/ml, and the

Table 4 Summary of adverse event (*AEs*) by specific event and age group

Specific adverse event	Number of adverse events (%) by age group			
	<6 years (*n*=33)	6 to <12 years (*n*=34)	12 to 18 years (*n*=33)	Total (*n*=100)
Diarrhea				
All cases	29 (87.9)	23 (67.6)	10 (30.3)	62 (62)
Severe	3 (9.1)	0	0	3 (3)
Possibly/probably related to study drug	13 (39.4)	9 (26.5)	5 (15.2)	27 (27)
Leading to dose reduction or interruption	8 (24.2)	4 (11.8)	1 (3.0)	13 (13)
Premature withdrawals due to AEs	1 (3.0)	1 (2.9)	0	2 (2)
Anemia				
All cases	17 (51.1)	11 (32.4)	9 (27.3)	37 (37)
Severe	5 (15.2)	2 (5.9)	1 (3.0)	8 (8)
Possibly/probably related to study drug	9 (27.3)	4 (11.8)	2 (6.1)	15 (15)
Leading to dose reduction or interruption	4 (12.1)	2 (5.9)	0	6 (6)
Premature withdrawals due to AEs	1 (3.0)	0	0	1 (1)
Sepsis (cytomegalovirus, infections)				
All cases	16 (48.5)	11 (32.4)	8 (24.2)	35 (35)
Severe	1 (3.0)	1 (2.9)	2 (6.1)	4 (4)
Possibly/probably related to study drug	9 (27.3)	8 (23.5)	7 (21.2)	24 (24)
Leading to dose reduction or interruption	3 (9.1)	4 (11.8)	3 (9.1)	10 (10)
Premature withdrawals due to AEs[a]	0	0	2 (6.1)	2 (2)
Leukopenia				
All cases	10 (30.3)	10 (29.4)	4 (12.1)	24 (24)
Severe	3 (9.1)	2 (5.9)	1 (3.0)	6 (6)
Possibly/probably related to study drug	10 (30.3)	8 (23.5)	4 (12.1)	22 (22)
Leading to dose reduction or interruption	10 (30.3)	8 (23.5)	4 (12.1)	22 (22)
Premature withdrawals due to AEs	0	0	0	0

[a] Includes one patient who died of hemorrhagic pancreatitis

mean dose-adjusted MPA $AUC_{0–12}$ was 28.7±10.5 μg h per ml (95% confidence intervals 25.9–31.6). Table 1 lists the mean computed MPA pharmacokinetic parameters by age and time. There were no statistically significant differences ($P>0.05$) in mean MPA plasma concentrations or mean computed parameters among the age groups given MMF suspension, with the exception of the dose-adjusted MPA C_{max} at month 9 in the oldest age group (Table 1). The mean dose-adjusted MPA $AUC_{0–12}$ for all patients was similar to the desired target MPA (27.2 μg h per ml) at day 7, and increased by 90% between day 7 and month 3 and by 11% between month 3 and month 9. A statistically significant difference was noted across the age groups for the mean dose-adjusted MPAG $AUC_{0–12}$ at all time points, with values of this inactive metabolite increasing from the youngest to oldest groups, although large standard deviations were noted in all the groups. In retrospectively defined subgroup analyses, the target MPA $AUC_{0–12}$ was achieved by each age, gender, and ethnic subgroup, although the number of representative patients was limited in some of the subgroups.

No associations were observed between low MPA and MPAG plasma concentrations and the incidence of acute rejection. Similarly, no associations were found between adverse events and pharmacokinetic parameters. MPA and MPAG concentrations calculated from pharmacokinetic AE samples were generally similar to the 12-h pharmacokinetic profile. This study, however, was not designed to formally examine an association of pharmacokinetic and pharmacodynamic parameters.

Discussion

This study demonstrates the efficacy, safety, and pharmacokinetics of MMF (600 mg/m^2 b.i.d.) in pediatric patients. The incidence of biopsy-proven rejection was similar across the three age groups and compares favorably with rejection rates observed in adult renal transplant patients at 6 months post-transplantation [8, 9, 10]. The majority of rejection episodes were borderline or grade I in severity, following the Banff criteria. The overall patient survival rate was 98%, and graft survival (excluding death) was 95% at 12 months.

US Registry data show that 12-month graft survival rates in children have been improving. The current rate (85%–94%) is similar to that observed in adults (83%–94%). European Registry data show that 12-month graft survival rates in children have slightly improved from the late 1980s (61%–78%) to the late 1990s (66%–81%). These rates are now similar to those of adults in Europe (75%–83%), with the exception of poorer graft survival rates in the youngest patients (<3 years of age). Higher rates of vascular thrombosis account for the increased graft loss in these patients [19].

Acute rejection has been reported to develop in 40–70% of pediatric renal recipients treated with a cyclosporine/azathioprine regimen, the majority occurring during the first 3 months post-transplantation.

Two deaths occurred among patients in this study; neither death was considered related to MMF. The overall patient survival rate of 98% was comparable to that reported among MMF-treated adult renal transplant recipients (94.5%–96.4%) [8]. All patients experienced at least one AE, as would be anticipated during the postoperative period in chronically ill children who are receiving intensive immunosuppressive therapy. The overall level of immunosuppression, as well as the AE profiles of the particular immunosuppressant drugs used, may contribute to the types of AEs reported. For most AEs, the types of events reported and the proportion of patients experiencing them were similar among the pediatric age groups and also similar to those observed in adult patients. However, certain adverse events (including diarrhea, anemia, leukopenia, and sepsis such as CMV and infection) showed a trend toward higher incidence among younger pediatric patients. Diarrhea is not an uncommon side effect of immunosuppression, occurring in 41% of patients given cyclosporine and corticosteroids [20]. Additionally, the greater incidence of diarrhea in younger patients may be related to the increased susceptibility of this population (further augmented by immunosuppressive therapy) to viral gastroenteritides [21], which are clinically manifested predominantly as diarrheal illness. Nonetheless, in our study, despite the need for dosage reduction due to diarrhea in some patients, only two patients were withdrawn from the study for reasons that included diarrhea.

Among the hematological AEs, anemia was reported most frequently in the youngest age group, while the incidence of leukopenia was greater among the youngest and middle age groups. In addition to the potential impact of renal dysfunction on the development of anemia in this renal transplant population, the incidence of anemia in the present study may be increased by other contributing factors, including inadequate dietary iron intake [22], blood loss due to phlebotomy, administration of immunosuppressants, and a bone marrow-suppressive effect of superimposed infections [22, 23]. Furthermore, the youngest patients may experience an increased incidence of anemia and leukopenia related to their greater susceptibility to infection (particularly viral) due to the absence of prior natural immunity. Most episodes of anemia and leukopenia in this study were successfully managed with modifications in study drug dosing. Only one patient needed to withdraw from the study because of anemia (<6 years old group), and none were withdrawn because of leukopenia.

The overall immaturity of the pediatric immune system, combined with administration of immunosuppressants, may account for the increased occurrence of sepsis in the younger age group [21]. Although sepsis (CMV, infections) occurred more frequently in the youngest age group, the incidence that was considered probably or possibly related to MMF was similar for the three age groups, as was the proportion of patients for whom this AE led to dose reduction or interruption. Only two patients were withdrawn from the study because of sepsis (both from the oldest age group). There were no withdrawals due to sepsis among the youngest age group, in which the incidence was greatest.

The pharmacokinetic data confirmed that the 600 mg/m^2 b.i.d. dosage (up to 1 g b.i.d.) of oral MMF suspension achieved an MPA AUC_{0-12} in the early post-transplantation period similar to that in adult renal transplant patients receiving 1 g b.i.d. Also similar to adult renal transplant patients, the pediatric patients had an increase (1.9-fold) in MPA AUC_{0-12} and C_{max} between day 7 and month 3, with a minimal increase (1.1-fold) between months 3 and 9.

In conclusion, administration of MMF 600 mg/m^2 b.i.d. is effective in the prevention of acute rejection, provides predictable pharmacokinetics, and is associated with an acceptable safety profile in pediatric renal transplant recipients.

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