

Therapeutic Monitoring of Mycophenolate Mofetil

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Mycophenolate mofetil (MMF) has become the single most used immunosuppressant in solid-organ transplantation. Despite a well-documented relationship and efficacy (in terms of acute rejection prophylaxis) and exposure to mycophenolic acids (MPA) as measured by area under the curve (AUC), excellent results have been achieved using a fixed-dosage regimen. In the past several years, there has been an increased interest in the utility of monitoring MPA concentrations to both increase efficacy and decrease toxicity, particularly in many current drug minimization protocols.

MMF is morpholinoethyl ester of MPA, a potent and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), isoform 2 (1). MPA originally was discovered from *Penicillium brevicompactum* and related fungi in the late 19th century, and its major activity on IMPDH first was reported in 1969 (2). MPA was developed as an immunosuppressant by Syntex in 1980s to complement existing immunosuppressive agents, including calcineurin inhibitor, azathioprine, and corticosteroids (3). IMPDH became a target for immunosuppression because lymphocytes depend on the *de novo* guanosine nucleotide synthesis pathway for DNA synthesis and cell division (3). Because other cell types, including neurons, depend primarily on the alternative salvage pathway for DNA synthesis, MPA selectively inhibits the proliferation of human T and B lymphocytes. Since the 1990s, when large, double-blind, randomized trials in kidney transplant recipients (4–6) showed the efficacy of MMF in preventing early acute rejection, in combination with cyclosporine (CsA) and prednisone, MMF has been used widely as a part of various combination regimens of immunosuppressive agents. To appreciate fully the complexities and controversies involved in therapeutic monitoring, one must have a substantial understanding of the pharmacokinetics and pharmacodynamics of MPA. This review covers the basic pharmacology of MMF and then discusses the data that are available on the utility of monitoring of MPA concentrations.

Pharmacokinetics

MMF, being a pro-drug of MPA, is absorbed rapidly and completely from the gastrointestinal tract and undergoes extensive presystemic de-esterification to become MPA, the active

moiety. After an oral dose, MMF in the systemic circulation quickly disappears and the plasma concentration of MPA rises rapidly, reaching its maximum concentration within 1 h (7). Food intake can delay the rate of MMF absorption but does not affect the extent. Co-administration of antacids or cholestyramine decreases the extent of absorption by approximately 20 and 40%, respectively (7). Mean apparent half-life ($t_{1/2}$) of MPA in the systemic circulation is approximately 17 h (7).

MPA undergoes enterohepatic circulation; its plasma concentration profile shows a secondary peak at 6 to 12 h after intravenous or oral dosing. The pathway of enterohepatic circulation is depicted in Figure 1, which is composed of processes of MPA metabolism, biliary excretion of its metabolites, de-glucuronidation of the metabolites to MPA, and re-absorption of MPA. The majority of MPA is metabolized in the liver (and possibly by other tissues, including intestine and kidney) through a phase II glucuronidation process (mediated by UDP-glucuronosyltransferases [UGT]). The major metabolite of MPA is the pharmacologically inactive 7-O-glucuronide metabolite (MPAG), which is produced by UGT1A9 (7). In addition to MPAG, two other metabolites—MPA-acyl-glucuronide (AcMPAG) and MPA-phenyl-glucoside (glucoside-MPA)—were isolated in renal transplant patients' plasma (8). AcMPAG, produced mainly by UGT2B7, has shown *in vitro* pharmacologic activity and potentially is responsible for the gastrointestinal toxicity of MPA (9). These glucuronide metabolites are excreted into the bile, a process that is mediated by a canalicular transporter, multidrug resistance-related protein 2, and undergo de-glucuronidation back to MPA by enzymes that are produced by colonic bacteria. MPA then is reabsorbed into the systemic circulation. Blockade of multidrug resistance-related protein 2 by an inhibitor, such as CsA, decreases the biliary excretion of MPAG and increases plasma levels of MPAG. This eventually leads to lower plasma levels of MPA because the glucuronide metabolites no longer can be reabsorbed as MPA as a result of disruption of enterohepatic cycling of MPA (10). The ultimate elimination pathway for the glucuronide metabolites is through the kidney, and >95% of an administered MMF dose eventually is found in the urine as the glucuronide metabolites (7).

In humans, the mean contribution of enterohepatic circulation to the overall AUC of MPA was 37% (range 10 to 61%) (11). Considering that the AUC value is determined by both systemic elimination of MPA by the liver and reabsorption of MPA through enterohepatic circulation, the hepatic extraction ratio of MPA (the fraction of MPA that is metabolized during a single pass through the liver) can be estimated to be approxi-

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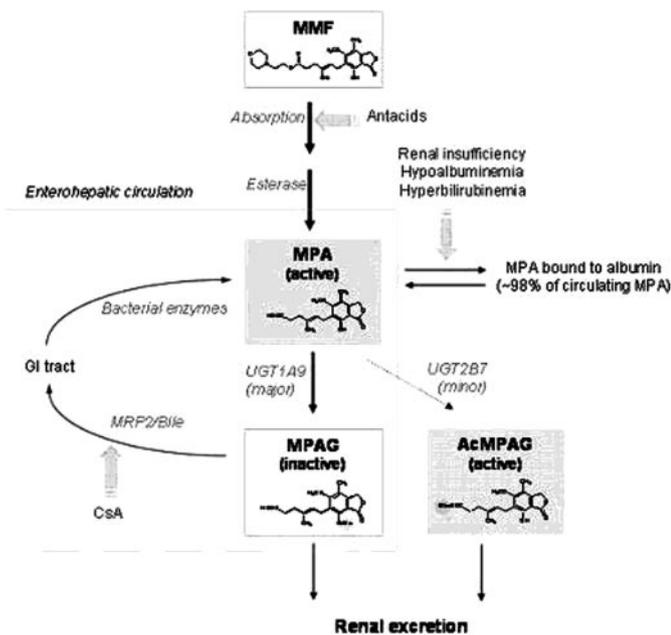


Figure 1. Pharmacokinetic behavior of mycophenolate mofetil (MMF) after oral administration (see text for details). MMF is converted to mycophenolic acid (MPA) presystemically, and then is subsequently metabolized to its glucuronide (Glu) conjugates, MPAG and AcMPAG, by different isoforms of UDP glucuronidyl transferases (UGT) in the liver. Pathways of enterohepatic circulation of MPA *via* the glucuronide conjugate metabolites are shown.

mately 0.3 to 0.7, assuming the liver as a major organ of MPA elimination from the body. This indicates that systemic clearance (calculated by the equation $CL = \text{dose}/AUC_{IV}$, where AUC_{IV} is AUC obtained after intravenous administration of a drug) of MPA can be either restrictive or nonrestrictive. Factors that may influence this include protein binding of MPA, intrinsic enzymatic activity of the liver, and the blood flow to the liver. It should be noted that regardless of whether the drug is of high or low hepatic extraction ratio, oral clearance ($CL_{\text{oral}} = \text{dose}/AUC_{\text{oral}}$, where AUC_{oral} is AUC obtained after oral administration of a drug) always depends on the former two factors (protein binding and intrinsic enzymatic activity) according to conventional theory of pharmacokinetics. In other words, altered AUC_{oral} values of MPA in certain patient populations are likely to reflect changes in protein binding of MPA or UGT enzymatic activities.

MPA is bound extensively to albumin; the range of protein binding is 97 to 99% in patients with normal renal and liver function. *In vitro* studies have shown that although binding of MPA to albumin is constant over the therapeutic MPA concentration range (1 to 60 mg/L), serum albumin concentration can determine the free fraction that is decreased from approximately 3 to 1.5% as the serum albumin concentration increased from 2 to 4 g/dl (12). Because free MPA concentrations determine MPA's immunosuppressive action, factors that alter protein binding can affect the pharmacodynamic effect of the drug. These factors include hypoalbuminemia or renal insufficiency

that occurs in early posttransplantation period. In fact, in renal transplant recipients with chronic renal insufficiency, average free fraction of MPA was more than twice that of patients with normal renal function (5.8 *versus* 2.5%; $P < 0.01$), which subsequently led to an increased incidence of hematologic adverse effect (13,14). Another factor that can alter MPA binding in patients with renal insufficiency is accumulating MPAG (major elimination pathway of MPAG is through the kidney). Significant increase of MPAG in the plasma reduces MPA binding to the albumin; the presence of MPAG at 400 mg/L increased the MPA free fraction by two-fold compared with when 10 mg/L MPAG was present (12).

Another characteristic feature of MPA is time-dependent pharmacokinetics; overall, the mean $AUC_{0-12\text{ h}}$ of MPA in the early posttransplantation period is approximately 30 to 50% lower for the same dose than in the late posttransplantation period. This change occurs over 3 to 6 mo in kidney transplant recipients (15–17) and also in other solid-organ transplant patients (7). Considering that this temporary increase in oral clearance is shown mainly in transplant recipients with impaired renal function, in whom the free fraction of MPA is increased (18,19), it seems that altered protein binding is partially responsible for the increase in oral clearance in the early posttransplantation period. This was confirmed further in a clinical study that found a 40 to 60% decrease in the MPA free fraction (as the renal function improves) and corresponding changes in $AUC_{0-12\text{ h}}$ over 3 mo after kidney transplantation (20). However, the similar time-dependent pharmacokinetic characteristic of MPA also was shown in other organ transplant recipients, including cardiac transplant, although to a lesser extent (7), which calls for further studies for the mechanism behind this phenomenon.

Pharmacodynamics of MPA

MPA is thought to exert its action by inhibiting the enzyme IMPDH. It is thought that MPH has a greater affinity for isoform 2 rather than the constitutively expressed isoform 1. Studies by Glander *et al.* (21) demonstrated that within the usual pharmacologic range concentration of MPA, MPA concentrations correlate with inhibition of IMPDH. Therefore, on average, at peak concentrations, >70% of IMPDH is inhibited, whereas at standard trough concentrations, <20% of IMPDH is inhibited. Because there is tremendous interpatient variability in both IMPDH concentration and MPA exposure, the relevance of this concentration-dependant inhibition of this enzyme on transplant outcomes has been difficult to assess. Finally, it should be noted that the acyl-glucuronide metabolite also may inhibit IMPDH (22), which may complicate further the assessment of concentration and outcome interpretations.

Ethnic variability exists in the efficacy of MMF when used in renal transplant patients. Black patients were shown to require higher dosages of MMF compared with white patients to achieve a similar extent of prevention from early acute rejection when combined with CsA (23). It is interesting that pharmacokinetic properties of MMF in both groups of patients showed no significant difference (24), suggesting that ethnic variability

lies in pharmacodynamics of MPA. Further mechanistic studies are needed to understand the sources of this variability.

Drug Efficacy Studies

In mid-1990s, three large clinical trials were conducted in kidney transplant recipients to prove clinical efficacy of MMF (4–6). These were the largest prospective, randomized, double-blind trials ever performed in transplantation, using the incidences of acute rejection as a primary end point. The results demonstrated the superior efficacy of MMF (1.0 or 1.5 g twice daily), combined with CsA and steroids, in reducing the rate of acute rejection during 6 mo after kidney transplantation as compared with azathioprine or placebo treatment. Also, they established the safety of MMF in adult renal transplant patients; overall incidence of adverse effects was comparable between groups. The prominent adverse effects of MMF included nausea, vomiting, diarrhea, and hematologic effects, with a high dosage (3 g/d) being associated with increased risk for the adverse effects. Subsequent long-term (1- and 3-yr) follow-up studies reported the similar efficacy and safety of MMF (25–28). In addition, a meta-analysis on >65,000 renal transplant recipients from the US renal transplant scientific registry demonstrated the improved 4-yr patient survival and graft survival by MMF compared with azathioprine (85.6 versus 81.9%; $P < 0.0001$) (29).

Other maintenance immunosuppressants that have been evaluated in combination with MMF include tacrolimus and sirolimus. A randomized, clinical trial in renal transplant patients who were treated with tacrolimus-based triple regimens (tacrolimus/MMF/steroid) demonstrated a significant reduction in the incidence of rejection compared with the double-regimen group (tacrolimus/steroid; 44 to 27%; $P = 0.014$) when MMF was given at a dosage of 1g twice a day for 1 yr after transplantation (30). However, in the first 6 mo of this trial, MMF was discontinued in half of the patients because of gastrointestinal complications or hematologic adverse effects, indicating the need for lower MMF dosages. It was understood later to be because tacrolimus does not inhibit biliary excretion of MPAG, whereas CsA disrupts enterohepatic cycling and intestinal reabsorption of MPA by inhibiting biliary transporters (10,31,32). Subsequent monitoring of MPA levels in renal transplant patients revealed that MPA plasma levels were lower in the CsA-based regimen compared with the tacrolimus combination (33).

In conclusion, MMF is effective in preventing acute rejection and improving graft and patient survival in combination with calcineurin inhibitors (CsA and tacrolimus). Tacrolimus-based treatment requires a lower dosage of MMF compared with a CsA-based regimen to maintain the similar MPA plasma levels.

Therapeutic Drug Monitoring

Since the three major clinical trials proved clinical efficacy of MMF (4–6), MMF has been used widely in a fixed daily dose of 2 g in a CsA-based regimen. Subsequent studies, however, established a strong association of MPA concentration and its pharmacologic effects (especially efficacy, defined as prevention of acute rejection) (34–39). Also, significant (>10-fold)

interindividual variability was found in MPA AUC and pre-dose concentration (C_0) values in transplant patients who received a fixed dose of MMF (33,40). These clinical data supported a need for therapeutic drug monitoring (TDM) of MPA, which is gaining much attention in organ transplantation these days.

Two analytical tools have been used commonly for measurement of MPA plasma levels: HPLC and enzyme-multiplied immunoassay technique (EMIT). EMIT is less specific in measuring MPA than HPLC in that one of the glucuronide metabolites, AcMPAG, cross-reacts with MPA for the antibody used in EMIT. Therefore, MPA concentrations that are obtained by the EMIT method typically are higher than those from HPLC, which is capable of measuring MPA separately from AcMPAG. The overestimation of MPA concentration by using EMIT was reported to be approximately 24 to 35%, the greatest bias seen in kidney recipients early after transplantation (8). The extent of overestimation, in fact, further varies depending on the patients, time elapsed since transplantation, sampling time, and concentration levels of MPA and MPAG (41,42). However, in pediatric renal transplant recipients, the EMIT assay showed a comparable diagnostic efficacy to HPLC for assessing the risk for acute rejection (15), leaving EMIT as an acceptable monitoring tool for MPA. Therefore, either HPLC or EMIT can be used for TDM, although HPLC is a more specific analytical tool for accurate assessment of MPA and the metabolites.

A summary of clinical trials that examined the relationship between MPA levels with clinical outcomes is presented in Table 1. Generally, MPA AUC is a better predictor of clinical events than MPA C_0 , which only weakly correlates with the AUC in most cases (33–36,43).

Randomized, concentration-controlled trials in renal patients who received MMF, CsA, and corticosteroids provided the basis of the currently recommended therapeutic range of MPA $AUC_{0-12\text{ h}}$, 30 to 60 mg·h/L (determined by HPLC), in the early posttransplantation period of CsA-based therapy (36,44,45); the AUC values below this range were associated with an increased risk for development of acute rejection, whereas no further reduction in acute rejection was observed in patients with AUC values >60 mg·h/L (36). It should be noted that this study was limited by the gastric intolerance to the higher dosages of MMF that were needed to reach the targeted levels of 60 mg·h/L. Therefore, because of the time-dependent pharmacokinetics of MPA, attempting to achieve $AUC >60$ mg·h/L in the first few weeks is not well tolerated. This likely is not the case in the long term. A subsequent pharmacokinetic analysis showed that a minimum C_0 of 1.3 mg/L is required to achieve the MPA $AUC_{0-12\text{ h}} >30$ mg/h per L, which was validated later using the clinical data that were obtained from the randomized, concentration-controlled trials (82% of patients on CsA-based regimen with $C_0 >1.3$ mg/L would have an $AUC_{0-12\text{ h}} >30$ mg·h/L) (45). A similar analysis in patients who were on a tacrolimus-based regimen indicated that a higher MPA C_0 of 1.9 mg/L is required to target the therapeutic range of MPA $AUC_{0-12\text{ h}}$ (45); the higher recommended C_0 is because tacrolimus does not affect the enterohepatic cycling of MPA contrary to CsA, leaving intact the secondary peak on the time-concentration profile.

Table 1. Correlation between MMF pharmacokinetics and clinical outcomes in renal transplantation^a

Study	No. of Patients	Follow-Up Time	Calcineurin Inhibitors	TDM	MPA Parameters	Assay Method	Clinical Outcomes
Borrows <i>et al.</i> (55)	121	1 yr	Tacrolimus	Fixed dosage	C ₀	EMIT	>1.60 mg/L is associated with low rejection rates; >2.75 mg/L is associated with hematologic toxicity and diarrhea
Cattaneo <i>et al.</i> (48)	46	9 mo	CsA	Fixed dosage	AUC _{0-12h} , C ₀	HPLC	AUC >40 mg·h/L or C ₀ >1.5 mg/L is associated with better renal functions; there was a negative correlation between free MPA levels with hematocrit levels
Hale <i>et al.</i> (36)	156	6 mo	CsA	Dosage adjustment by Bayesian estimation	AUC _{0-12h}	HPLC	AUC of 15 and 25 mg·h/L showed 50 and 75% maximal achievable efficacy, respectively
Kiberd <i>et al.</i> (50)	94	3 mo	CsA	Fixed dosage	AUC _{0-12h} , C ₀	HPLC	AUC of 22 mg·h/L was a threshold for prediction of acute rejection episodes
Kuypers <i>et al.</i> (20)	22	1 yr	Tacrolimus	Fixed dosage	C ₀	HPLC	C ₀ of MPA (total or free) and its metabolites did not correlate with clinical efficacy or toxicity
Mourad <i>et al.</i> (46)	51	— ^b	Tacrolimus	Fixed dosage	AUC _{0-12h} , C ₀	EMIT	AUC of 38 mg·h/L was a threshold for toxicity (sensitivity 83%; specificity 60%)
Oellerich <i>et al.</i> (35)	— ^b	6 mo	CsA	Fixed dosage	AUC _{0-12h} , C ₀	HPLC	AUC of approximately 30 to 60 mg·h/L seems to be a reasonable target for early posttransplantation period
Pawinski <i>et al.</i> (33)	33	3 mo	CsA or tacrolimus	Fixed dosage	AUC _{0-12h} , C ₀	HPLC	AUC of 27.5 mg·h/L and C ₀ of 1.1 mg/L were threshold values for prediction of acute rejection episodes
Pillans <i>et al.</i> (39)	27	1 mo	CsA	Fixed dosage	AUC _{0-12h} , C ₀	HPLC	AUC <30 mg·h/L was associated with increased incidence of rejection; no association was found between the incidence of acute rejection and C ₀
van Gelder <i>et al.</i> (44)	154	6 mo	CsA	Dosage adjustment by Bayesian estimation	AUC _{0-12h} , C ₀	— ^b	Incidence of acute rejection in low, intermediate, and high MPA concentration groups (16, 32, and 60 mg·h/L, respectively) were 28, 15, and 12%, respectively
Weber <i>et al.</i> (34)	54	6 mo	CsA	Fixed dosage	AUC _{0-12h} , C ₀	HPLC	AUC of 33.8 mg·h/L differentiates acute rejection (sensitivity 75%; specificity 64%)

^aAUC, area under the curve; C₀, predose concentration; CsA, cyclosporine; EMIT, enzyme-multiplied immunoassay technique; MMF, mycophenolate mofetil; MPA, mycophenolic acids; TDM, therapeutic drug monitoring.

^bNot reported.

Although the relationship between the MPA exposure and clinical efficacy is clear, it has been difficult to establish a similarly strong association between the pharmacokinetic parameters of MPA and drug-related toxicity. Mean AUC_{0-12 h} that were reported for renal transplant patients who experienced toxicities of MPA ranged from 48 ± 19 to 67 ± 30 mg·h/L (45), indicating significant overlap in the therapeutic and toxic ranges of MPA AUC_{0-12 h} values. According to a recent report that examined the efficacy of low-dosage (500 mg twice daily) MMF in combination with tacrolimus, the threshold MPA AUC value to predict drug-related toxicities was 37.6 mg/h per L (sensitivity 83%; specificity 60%), a value that is very close to the lower limit of AUC target for optimum efficacy (45). High plasma protein binding of MPA, which is perturbed easily by various factors, including blood albumin levels or renal functions, may be responsible for this phenomenon. In reality, therapeutic monitoring of MPA mostly involves measuring concentrations of total MPA (both protein-bound and free form), although pharmacologic activity of MPA depends on free concentrations of the drug (12). Because of significant protein binding and variability therein, even at the similar MPA level,

the concentrations of free MPA, in fact, may vary dramatically. For example, in patients with chronic renal failure, total MPA AUC values were comparable to those in stable patients, whereas free MPA AUC values rose as much as five-fold, placing the patients at increased risk for drug-related toxicity (47). Accordingly, in renal transplant recipients, high free but not total MPA AUC values were associated with an increased risk for the MMF-related toxicities, including leukopenia and/or infections (34,48). Therefore, it should be noted that under circumstances of altered protein binding, total MPA levels are difficult to assess because of variable free MPA levels.

Maintenance of adequate MPA levels is important in the early posttransplantation period for its full immunosuppressant activity. A recent study reported that in liver transplant patients, the consistent pharmacologic activity of MPA was shown from patients' sera only when MPA AUC or predose concentration was within the recommended range listed previously (49). Also, in kidney transplant patients who were on CsA-based therapy, MPA AUC on day 3 was predictive of later incidence of acute rejection ($P = 0.007$) (50), suggesting the importance of adequate MPA exposure, as early as posttrans-

Table 2. Current recommendation on TDM of MMF in transplantation (45)^a

Initial dosing	CsA-based regimen: start MMF at 1.5 g twice daily, and then adjust dosage on the basis of TDM Tacrolimus-based regimen: start MMF at 1 g twice daily
Frequency of monitoring and dose adjustment	Days 3 and 7 and once during days 10 to 14 after transplantation Week 3 or 4 (optional) Occasions of substantial changes in immunosuppressant regimen Occasions that require evaluation of clinical events, such as drug-related toxicity or rejection
Assay considerations	Either HPLC or EMIT is acceptable for monitoring MPA target concentrations using EMIT are higher (as a result of cross-reactivity with AcMPAG)
Target concentrations (HPLC)	MPA AUC 30 to 60 mg·h/L in the first 30 d after transplantation MPA C ₀ CsA-based regimen: ≥1.3 mg/L tacrolimus-based regimen: ≥1.9 mg/L Special populations calcineurin inhibitor-sparing regimen a higher end of MPA target concentrations range is required altered protein binding: free drug MPA concentration can be higher ^b renal impairment high bilirubin
Dosage adjustment ^c	AUC based: $\text{New dose} = \frac{\text{old dose} \times \text{target MPA AUC}}{\text{measured MPA AUC}}$ C ₀ based: $\text{New dose} = \frac{\text{old dose} \times \text{target C}_0}{\text{measured C}_0}$

^aData are summary of reference (45). AcMPAG, MPA-acyl-glucuronide.

^bBecause of extensive protein binding of MPA, free drug MPA concentration can be higher, although the total MPA concentration is within the target range. Therefore, under circumstances of altered protein binding, total MPA levels are difficult to assess.

^cThis recommendation is under assumption of dosage linearity in MPA pharmacokinetics, which may not exist in all cases.

plantation day 3, for prevention of acute rejection. Therefore, TDM of MPA would play a significant role in improving its efficacy, especially in the early posttransplantation period. Recently, a computer simulation for TDM of MPA revealed that a concentration-controlled MMF dosing regimen could achieve a therapeutic concentration faster than a fixed-dosage regimen does (51).

Despite the strong association between MPA AUC_{0-12 h} and clinical outcomes, there has been increasing questioning on whether the implementation of TDM of MPA would provide clinical benefits that are substantial enough to justify the time and expense. For example, accurate measurement of MPA AUC_{0-12 h} requires multiple blood samples during the dosing interval, which can be expensive and clinically impractical. Abbreviated sampling strategies therefore were suggested to estimate full MPA AUC_{0-12 h} by using a smaller number of sampling time points and various regression methods (20,43,52). Alternatively, a method of maximum *a posteriori* probability Bayesian estimation was developed for dosage adjustment on the basis of MPA AUC_{0-12 h} (53,54). The Bayesian

estimation uses a patient's own data in addition to a population-based pharmacokinetic model to estimate the MPA dosage that will produce desired values of pharmacokinetic parameter, such as AUC_{0-12 h} of 30 to 60 mg·h/L. As a result, Bayesian estimation is considered more robust and accurate compared with using regression models, although the use of Bayesian estimation in common practice may be limited because of requirement of appropriate computer software. In any case, various limited sampling strategies would provide benefit in decreasing the time and the cost that are involved with TDM of MPA and thus have been incorporated into large-scale, concentration-controlled clinical trials that currently are ongoing (45).

As an effort to optimize MMF therapy in transplantation, a roundtable meeting was held in December 2004, where guidelines on the application of TDM to MMF therapy were updated (a summary of the revised recommendation is shown in Table 2). Also, multiple clinical trials currently are ongoing to determine whether TDM of MPA would lead to improved efficacy and reduced toxicity. These studies ultimately will investigate the advantage of therapeutic MPA monitoring in renal trans-

plant recipients by comparing fixed-dosage *versus* concentration-controlled MMF therapy. They include a multinational trial that was initiated in 2003, FDCC Trial; a second large, randomized trial, the OptiCept Trial, initiated in the United States in 2004; and the APOMYGRE trial, in which maximum *a posteriori* probability Bayesian estimation is used for MMF dosage adjustment (54). It is hoped that these studies will clarify the role of TDM in increasing the therapeutic potential of MMF and better define therapeutic windows for MPA pharmacokinetic parameters.

Disclosures

None.

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