

Consensus Report on Therapeutic Drug Monitoring of Mycophenolic Acid in Solid Organ Transplantation

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With the increasing use of mycophenolic acid (MPA) in solid organ transplantation, the need for more accurate drug dosing has become evident. Personalized immunosuppressive therapy requires better strategies for avoidance of drug-related toxicity while maintaining efficacy. Few studies have assessed the clinical usefulness of therapeutic drug monitoring (TDM) of MPA in solid organ transplantation in a prospective way, and they have produced opposing results. To provide clinicians with an objective and balanced clinical interpretation of the current scientific evidence on TDM of MPA, a consensus meeting involving 47 experts from around the world was commissioned by The Transplantation Society and held in Rome on November 20 to 21, 2008. The goal of this consensus meeting was to offer information to transplant practitioners on clinically relevant pharmacokinetic characteristics of MPA, to rationalize the basis for currently advised target exposure ranges for MPA in various types of organ transplantation, and to summarize available methods for application of MPA TDM in clinical practice. Although this consensus report does not evaluate the final role of MPA TDM in transplantation, it seeks to examine the current scientific evidence for concentration-controlled dosing of MPA.

Clin J Am Soc Nephrol 5: 341–358, 2010. doi: 10.2215/CJN.07111009

The conflicting results of three recent large randomized studies that examined the clinical benefit of therapeutic drug monitoring (TDM) of mycophenolic acid (MPA) in terms of graft and patient outcome have rekindled the debate on the role of concentration-controlled (CC) MPA dosing in solid organ transplantation. Although a general agreement on the role of TDM of MPA in solid organ transplantation requires further investigation, the need for practical guidelines on mycophenolate mofetil (MMF) dosing has grown in recent years as more and more individualized immunosuppressive drug regimens are considered. To provide clinicians with an objective and balanced clinical interpretation of the current scientific evidence on TDM of MPA, a consensus meeting, commissioned by The Transplantation Society (TTS), was held in Rome on November 20 to 21, 2008. Forty-seven experts from around the

world participated in a 2-day working meeting with the aim of formulating clinical guidelines on the format, the targets, the interpretation, the application, the timing, and the indications for MPA TDM in various types of solid organ transplantation. To accommodate a comprehensive interpretation of data, transplant physicians and surgeons, clinical pharmacologists, and bioanalytical experts were involved in the process. The goal of this consensus meeting was to offer information to transplant practitioners on clinically relevant pharmacokinetic characteristics of MPA, to rationalize the basis for currently advised target exposure ranges for MPA in various types of organ transplantation, and to summarize available methods for application of MPA TDM in clinical practice. Although this consensus report does not evaluate the final role of MPA TDM in transplantation, it seeks to examine the current scientific evidence for the use of MPA on the basis of a CC immunosuppressive strategy.

Participants of the TTS consensus meeting were allocated to different “working groups” on the basis of their expertise and were responsible for systematically evaluating the scientific evidence related to the following topics: Renal transplantation,

Published online ahead of print. Publication date available at www.cjasn.org.

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abdominal transplantation (excluding kidney), thoracic transplantation, pediatric transplantation, analytical methods, and clinical pharmacology and pharmacokinetics. The results of the respective systematic reviews of the literature were analyzed and extensively discussed within the different working groups. Clinical guidelines were then formulated by the working groups and critically reviewed by the entire meeting panel for scientific value and clinical relevance.

Clinical Pharmacokinetic Characteristics of MPA

MMF, the inactive morpholinoethyl ester prodrug of MPA and the enteric-coated mycophenolate sodium salt (EC-MPS), are absorbed from the gastrointestinal tract and presystemically hydrolyzed, resulting in a high MPA bioavailability (>90%) (1,2). MPA is mainly metabolized by UDP-glucuronosyltransferases in the liver, intestine, and kidney into the inactive 7-O-glucuronide (MPAG) metabolite and to a lesser extent into the pharmacologically active acyl-glucuronide (AcMPAG) (1,3,4). Approximately 97 to 99% of MPA and 82% of MPAG are protein bound (1). MPA metabolites are excreted *via* the kidney (1). MPA and MPAG are subject to enterohepatic (re)circulation which can account for up to 10 to 60% of the total dose-interval MPA area under the concentration time curve (AUC) (1). The biliary excretion of MPA/MPAG and distal (re)absorption involve several transport mechanisms, including the multidrug resistance-associated protein 2 (5).

The clinical pharmacokinetics of MPA are characterized by a high between-subject and within-subject variability (6). A >10-fold range in MPA dose-normalized AUC between patients has been observed in heart, renal, and liver transplantation, strengthening the argument for CC dosing of the drug (7). Reasons for between-subject pharmacokinetic variability include differences in albumin concentrations, bilirubin and hemoglobin concentrations, renal and hepatic function (impairment), co-administration of cyclosporine (CsA), comorbidities such as cystic fibrosis, body weight, exposure to concomitant medication, time after transplantation, gender, race, and genetic polymorphisms in drug-metabolizing enzymes (6–10).

MPA exposure is lower early after liver and small bowel transplantation compared with identical MMF dosage in renal transplantation (11). In liver transplantation, this seems to be due to a low bioavailability (mean 48.5%) and a high clearance of MPA (12). This mirrors the experience in hematopoietic stem cell transplantation, for which even greater extremes in bioavailability and clearance are observed (13). Also younger children require relatively higher MMF doses per body mass than older children and adults to achieve comparable MPA exposure (14). The mechanisms underlying these age-related differences are largely unknown but are probably related to developmental changes (known as ontogeny of drug disposition) of the UDP-glucuronosyltransferase enzymes (15,16). For ethnicity, the situation is complex, because MPA pharmacokinetics in patients of African descent are not different from those of white patients, whereas Asian patients reach higher MPA exposure at an equivalent dosage (17).

A clinically important phenomenon observed in all types of

solid organ transplantation is the increase of dose-normalized MPA exposure in the first months after transplantation, especially during the first 3 months (1). This increase in MPA exposure can range from 30 to 50% or even higher (>80%) in children and is multifactorial (1,14). A reduced metabolism of MPA as a consequence of a decrease in the MPA free-fraction as a result of increasing serum albumin levels and improving renal function are among the causes (1,14).

Co-administration of other immunosuppressive agents may influence MPA exposure. This has been clearly shown for CsA with a 30 to 40% lower dose-normalized MPA exposure (and higher MPAG exposure) in patients who received CsA as compared with patients who received tacrolimus or sirolimus (18). The difference in MPA exposure, depending on the concomitant calcineurin inhibitor (CNI), is explained by a pharmacokinetic interaction of CsA with the main MPA metabolite 7-O-MPA glucuronide (7-O-MPAG) (5). CsA inhibits the multidrug resistance protein 2-mediated transport of 7-O-MPAG into the bile, leading to less enterohepatic circulation of MPA and hence lower exposure (5). This interaction also suggests that if CsA dosages are tapered, then MPA exposure significantly increases, in both adult and pediatric recipients, and after complete discontinuation of CsA, MPA concentrations may increase by 50 to 100% (6).

Corticosteroids and rifampicin also seem to decrease MPA exposure in transplant recipients, probably *via* enzyme induction (19,20). Small bowel decontamination and antibiotics such as norfloxacin and metronidazole reduce MPA exposure by affecting its absorption, whereas cholestyramine inhibits the enterohepatic recirculation (21–23). Proton pump inhibitors (*e.g.*, pantoprazole, lansoprazole) reduce hydrolysis of MMF and hence MPA concentrations (24,25).

A reduction in renal function is associated with increased MPA clearance and consequently decreased total MPA exposure as a result of displacement of MPA from plasma protein-binding sites by increased levels of MPAG, especially when creatinine clearance drops below 25 ml/min (10). In contrast, within higher creatinine clearance ranges, a reverse relationship is observed with increased MPA clearance as renal function improves (26).

Only a few data have shown the within-subject variability of MPA exposure parameters. For MPA predose trough concentrations, the mean intraindividual coefficient of variation (CV) ranges from 36 to 62%, whereas a mean intraindividual CV of 30 to 47% (range 18 to 80%) has been described for MPA AUC_{0 to 12 hours} (27). For the enteric-coated MPA formulation, intraindividual CVs for exposure parameters (except maximum concentration) are comparable (28). The relatively high within-subject variability of MPA exposure is an important limitation for the development of useful TDM strategies.

Regarding MPA pharmacokinetics and dynamics, it has been demonstrated that administration of nearly equimolar dosage of EC-MPS and MMF (720 and 1000 mg, respectively) results in a bioequivalent MPA full-dose interval AUC, similar exposure to MPAG and AcMPAG, and similar inosine monophosphate dehydrogenase (IMPDH) inhibition (2,28,29). MPA absorption from EC-MPS is delayed, resulting in a delayed enterohepatic

recirculation and subsequently higher and more variable MPA 12-hour trough concentrations and t_{max} (time to reach maximum plasma concentrations) values (28–30); therefore, MPA trough level monitoring cannot be used as a guide to monitor MPA exposure in patients who are given EC-MPS ($r^2 = 0.02$ for correlation between trough level and dose-interval AUC for EC-MPS and 0.48 for MMF respectively) (30). When MPA exposure is assessed with a full 12-hour pharmacokinetic curve, therapeutic ranges for MPA are similar for the MMF and the EC-MPS formulation. Because of the more variable pharmacokinetic profile, however, the more practical limited sampling strategies (LSSs) or other single concentrations are unlikely to be useful for EC-MPS (30).

How MPA exposure is best measured in clinical practice is still a subject of debate. The advantages and difficulties of the various methods for assessing MPA exposure have been reviewed extensively and are briefly summarized in Table 1 (31–34).

In a number of countries, the patent of MMF has already expired; in others, this will happen within a short period of time. Generic formulations of MMF are now available. Registration of these generic drugs is based on demonstration of bioequivalence. To demonstrate bioequivalence, population means and 90% confidence intervals of AUC and maximum concentration ratios for the generic product and the reference product are determined; however, the relationship between C_{min} (minimum plasma concentration) and AUC may differ between the two products, and LSSs developed for one product may not perform as well when applied to the other product (35). Also, MMF and EC-MPS have been shown to be bioequivalent according to the aforementioned criteria but also require different methods to perform TDM (35). Caution should therefore be exercised while monitoring drug concentrations when substituting for a generic product.

Clinical Application of TDM of MPA

Renal Transplantation

TDM of MPA has been applied to varying extents in renal transplantation programs because its clinical utility for patient treatment is still controversial (36,37). The usefulness of TDM of MPA is determined by several conditions: (1) Is there a relationship between MPA exposure and efficacy and/or toxicity? (2) What are the extent and causes of variability of MPA pharmacokinetics? (3) Can clinical target ranges for MPA exposure be defined? (4) How can therapeutic concentrations be achieved in clinical practice? (5) What is the cost-effectiveness to maintain patients within the therapeutic window? In the past few years, large clinical trials and pharmacokinetic studies of renal recipients have provided new insights in this discussion.

Relationship between MPA Exposure and Acute Rejection.

An association between MPA exposure ($AUC_{0\text{ to }12\text{ hours}}$ or trough concentration [C_0]) and the risk for acute rejection was found in previous studies; after these observational studies, three randomized trials prospectively tested the added value of adjusting dosage on the basis of MPA exposure in CC studies (37,38). The *Adaption de POsologie du MYcophénolate en Greffe Renale* (APOMYGRE) study compared a fixed-dosage (FD) reg-

imen of MMF 2 g/d with a CC regimen based on MPA AUC measurements (target concentrations of $40\text{ mg} \times \text{h/L}$) using a Bayesian estimator in 137 kidney graft recipients who were receiving CsA therapy (39). Patients in the CC group achieved significantly higher MPA exposure within the first 3 months after transplantation and had a significantly lower incidence of biopsy-proven acute rejection (BPAR; 7.7 versus 24.6%; $P < 0.01$) (29). The Fixed Dose–Concentration Controlled (FDCC) study compared an FD regimen of 2 g of MMF with a CC regimen based on abbreviated MPA AUC measurements (target concentrations of 30 to 60 $\text{mg} \times \text{h/L}$) in 901 patients who were treated with CsA or tacrolimus (40). Early MPA exposure correlated inversely with the risk for BPAR: MPA AUC on day 3 versus BPAR in the first month ($P = 0.009$) and versus BPAR in the first year ($P = 0.006$) (40); however, in FDCC, a benefit for a CC approach could not be demonstrated. The Optcept study also compared fixed (2 g) and CC dosing of MMF on the basis of MPA predose trough concentrations (target 12-hour trough concentrations of 1.3 mg/L for the CsA group and 1.9 mg/L for the tacrolimus group) in 720 patients who were on either a standard or a reduced dosage of CsA or tacrolimus (41). Whereas analysis of the intention-to-treat population demonstrated no benefit of TDM, a *post hoc* analysis of 590 patients who were treated with tacrolimus showed that risk for acute rejection was significantly lower ($P < 0.001$) in patients who achieved target MPA trough levels of $>1.6\text{ mg/L}$ (41).

The two largest of the three randomized, controlled trials to examine the value of adjusting MPA dosage on the basis of drug concentrations did not demonstrate a better composite outcome in terms of acute rejection incidence, graft loss, death, and MPA discontinuation. In retrospect, this could be explained, at least in part, by suboptimal aspects of the study design and difficulties in the practical execution of the study protocols (40,41).

Although these studies clearly confirmed the relationship between early MPA exposure and the risk for acute rejection in the first 3 postoperative months when used in conventional CNI-based regimens, less evidence is available for late acute rejection episodes (>3 months), which occur far less frequently. Especially when evaluating the effects of CNI or corticosteroid minimization, withdrawal, or complete avoidance, more data on the association between MPA exposure and late efficacy would be helpful. Hazan *et al.* (42) demonstrated that the risk for acute rejection after CsA withdrawal at 3 months after transplantation was higher in patients with subclinical inflammatory (“borderline”) changes in their prewithdrawal surveillance biopsy or patients with lower MPA exposure ($AUC_{0\text{ to }12\text{ hours}}$: 43 ± 9 versus $58 \pm 22\text{ mg} \times \text{h/L}$; $P = 0.045$). In the Cyclosporine Avoidance Eliminates Serious Adverse Renal toxicity (Caesar) study, in which CsA withdrawal at 6 months after transplantation was explored, the increased risk for acute rejection was also associated with MPA exposure, albeit to a lesser extent (43); however, the Caesar study was not primarily designed to examine the effect of MPA exposure on acute rejection after withdrawal of CsA (43). This *post hoc* relationship needs to be interpreted carefully, because no conclusions can be drawn about which MPA concentration would be needed to prevent acute rejection after discontinuation of CsA. The relationships

Table 1. Monitoring strategies: General characteristics

Exposure Measure	How Assessed	Advantages	Disadvantages
Trough concentration (C_0)	Plasma concentration of MPA measured immediately before dosing	Easy to obtain in clinical practice Requires only single sample	Timing may not be accurate Timing may vary from the “ideal” 12-hour dose interval Not a particularly strong association to full AUC
Single concentration time points (<i>e.g.</i> , C_2 or C_4)	Plasma concentration of MPA measured at the exact time after dosing The single concentration can be used to estimate full AUC (regression equation)	Relatively easy to obtain but requires more patient education Requires only single sample Usually better association to full AUC than trough concentration	Timing may not be accurate Not a particularly strong association to full AUC Can be used with accuracy only in the population in which the regression equation has been developed
Multiple concentration time points (several specific timed points after dosing, also called LSSs)	Plasma concentrations of MPA measured at the exact and predefined times after dosing The resultant concentrations can be used to estimate full AUC (multilinear regression equations)	Relatively easy to obtain but requires more resources Better association to full AUC than single concentrations	Requires longer stay for multiple samples Errors in timing lead to errors in estimations Extrapolations can be used with accuracy only in the population in which the regressions have been developed
Single or multiple concentration time points, for Bayesian analysis	Plasma concentration(s) of MPA measured at the predefined time(s) after dosing The resultant concentrations are used in a Bayesian estimator to model the data (<i>i.e.</i> , calculation of pharmacokinetic parameters and exposure indices)	As above for single or multiple time points Bayesian approach is flexible with respect to sampling times because it can accommodate any time point or deviation from recommended time points Better estimate of individualized AUC	As above for single or multiple time points Mathematically more complex, requires preexisting population pharmacokinetic model and knowledge of covariates Computer model based and requires interpretation for dosing advice
Full AUC ($AUC_{0 \text{ to } 12 \text{ hours}}$, dose-interval AUC)	Plasma concentrations of MPA measured at the exact predefined times after dosing Either the resultant concentrations are mathematically modeled and integrated over time, or the trapezoidal rule is used to give the AUC	As above for multiple time points Best relationship to clinical outcomes	As above for multiple time points Requires patient to be available for the complete dosing interval (12 hours)

between MPA exposure and chronic graft histology, function, or outcome have not yet been investigated prospectively.

Relationship between MPA Exposure and Toxicity. Adverse events related to mycophenolate formulations include gastrointestinal disturbances, hematologic disorders (leucopenia and anemia), and infections. The relationship between MPA exposure and adverse events is weak, and contradictory results have been reported. In a multivariate analysis of 125 patients who were on tacrolimus therapy, a rise in median total MPA predose trough concentration of 1 mg/L within 30 days before the clinical event was associated with an increased risk for anemia (relative risk [RR] 1.62; $P < 0.001$), leucopenia (RR 1.62; $P < 0.001$), diarrhea (RR 1.54; $P < 0.001$), and viral infection (RR 2.71; $P < 0.001$) (44). Adverse events were more common in patients who displayed trough concentrations >3 mg/L (44). In another study of kidney recipients who were receiving CsA or tacrolimus, hematologic adverse events (leucopenia and anemia) were associated with higher MPA concentrations at 30 minutes ($C_{30\text{min}}$) after MMF dosing (45). More recently, in a 5-year follow-up study of 100 patients, MPA exposure >60 mg \times h/L was associated with a higher risk for anemia and leucopenia but not with infections or diarrhea (46).

Because two of the latter studies were in fact retrospective analyses of clinical data and MPA concentrations, careful interpretation of a potential causal relationship between MPA exposure and adverse effects is warranted (44,45). In the three recent prospective, randomized studies (APOMYGRE, FDCC, and Optcept), no correlation between MPA predose trough concentrations or AUC and MMF-related adverse events was observed in the first year after transplantation, despite significant differences in MPA exposure, at least in the APOMYGRE study (39–41). The identification of a clear relationship between MPA exposure and toxicity can be hampered by use of imprecise definitions for adverse events, multicausality of adverse effects, including concomitant drugs, time elapsed between MPA measurement and event, assay used for MPA quantification, and associated toxicity profiles of concomitant immunosuppressive medications. In addition, toxic MPA metabolites have been implicated in the origin of certain MMF-related adverse effects, but recent studies failed to confirm these associations, at least with regard to plasma concentrations of AcMPAG (47).

For a drug that requires TDM, it is important to demonstrate a narrow therapeutic index, a relationship between drug concentrations and clinical efficacy and toxicity, and a intraindividual and interindividual pharmacokinetic and pharmacodynamic variability. For MPA, on the basis of the current data, these requirements are not completely fulfilled, most importantly because of lack of a clear relationship between MPA concentrations and clinical outcome, especially drug-related adverse events; therefore, studies that address the identification of a clear relationship between MPA exposure and toxicity are mandatory.

Targets for MPA Exposure. In 2006, the conclusions of a roundtable meeting on TDM of MMF were published and a therapeutic range for MPA was proposed (37). The Randomized Concentration-Controlled Trial (RCCT) formed the basis

for a target AUC between 30 and 60 mg \times h/L (38). Because of the lack of a clear upper limit cutoff value for MPA exposure delineating the onset of more drug-related adverse effects, a pragmatic approach of not exceeding MPA (AUC) exposure of 60 mg \times h/L was adopted for advising MMF dosing in stable patients. The upper limit of the therapeutic range was defined primarily on the basis of the lack of additional efficacy, whereas only a limited number of studies did seem to suggest more frequent signs of toxicity above 60 mg \times h/L (37). In addition, recommended trough concentration targets (MPA $C_0 \geq 1.3$ mg/L with CsA and MPA $C_0 \geq 1.9$ mg/L with tacrolimus) were derived from the corresponding AUC values, on the basis of the assumption that achieving these trough concentrations would ensure that at least 80% of patients achieved an MPA AUC exposure >30 mg \times h/L (37).

Since 2006, three prospective, randomized, controlled trials have applied these therapeutic range recommendations with success. In the APOMYGRE study, seven of 10 BPAR episodes that occurred in the first 3 months after transplantation were associated with an MPA AUC <30 mg \times h/L whereas three rejection episodes were associated with an AUC between 30 and 45 mg \times h/L (39). No rejection episodes were associated with an MPA AUC >45 mg \times h/L. In the FDCC trial, tacrolimus-treated recipients at high immunologic risk had a 2.5-fold increase in the incidence of acute rejection when the day 3 MPA AUC was <30 mg \times h/L (48). In the Optcept study, MPA trough concentrations ≥ 1.6 mg/L were associated with a lower risk for acute rejection in tacrolimus-treated patients (41).

The therapeutic window of 30 to 60 mg \times h/L remains acceptable in patients who have low to intermediate immunologic risk and are on CNI-based therapy for the first 3 months after transplantation, with the lower limit of 30 mg \times h/L being clearly associated with an increased risk for acute rejection. In addition, other data seem to support a target 12-hour trough MPA concentration range of 1.5 to 3.0 mg/L, but this target window needs confirmation in prospective studies (41,44). The exposure to concomitant immunosuppressive drugs has to be taken into account when considering target ranges for MPA exposure. This was shown by Kuypers *et al.* (49) in a cohort of patients who were on MMF and tacrolimus therapy. There was a trend ($P = 0.07$) toward a higher incidence of BPAR (26.3%) in patients with MPA AUC_{0 to 12 hours} <45 mg \times h/L and tacrolimus AUC_{0 to 12 hours} <150 ng \times h/ml, compared with recipients in whom target AUC_{0 to 12 hours} values for both MPA and tacrolimus were achieved (7.7%).

As far as target therapeutic ranges are concerned, the situation will be different for recipients with high immunologic risk or in situations of CNI minimization/withdrawal, in which higher MPA exposure may be needed. In the Caesar study, patients were randomly assigned to receive either standard CsA therapy or reduced-dosage CsA therapy or reduced-dosage CsA therapy followed by CsA withdrawal at 6 months (43). *Post hoc* analysis of the relationship between MPA AUC_{0 to 12 hours} exposure and risk for acute rejection suggested that higher MPA exposure was required to prevent acute rejection in renal transplant recipients who were withdrawn from CsA or maintained on low-dosage CsA compared with standard-dosage CsA (43).

Strategies for Achieving Therapeutic MPA Concentrations.

For recipients who were on tacrolimus therapy, a starting dosage of 2 g/d MMF guaranteed that 76.2% of patients achieved the target therapeutic range of 30 to 60 mg \times h/L by day 3, whereas, for CsA-treated patients, this amounted to only 51.2% at day 3 (38). In the APOMYGRE study, 73, 69, and 44%, respectively, of CsA-treated patients who were on an FD of 2 g of MMF had an MPA AUC_{0 to 12 hours} <30 mg \times h/L on days 7, 14, and 30 after transplantation (39).

For overcoming this early MPA underexposure, especially in CsA-treated patients, intensified MPA dosing in the early post-operative period is a potential strategy to consider. Clinical studies have been started to evaluate this strategy and will probably provide answers not only in terms of efficacy and toxicity but also concerning the optimal intensified MMF or EC-MPS dosage (3 or 4 g/d MMF or EC-MPS equivalent dose) and the optimal duration of increased dosing (50,51).

Another way to overcome the important between-subject variability of MPA exposure is using carefully timed and executed TDM. As shown in three randomized, controlled studies, this goal is not easily achieved and demands strict adherence to CC dosing guidelines, as the positive outcome of the APOMYGRE study clearly demonstrated (39). Whether achievement of the proposed target therapeutic MPA concentrations will enable clinicians to predict the risk for acute rejection remains to be determined. Acute rejection incidences have gradually declined in recent years, especially in tacrolimus-treated patients, and MPA monitoring that is based on target concentration ranges might not translate into a clinically useful tool with a positive predictive value for what seems to have become a relatively rare clinical event. In addition, TDM has to be compatible with practical hospital outpatient settings and laboratory facilities, be cost-effective, and improve patient outcome to be sustainable. The APOMYGRE study provided important suggestions for future development of MPA TDM: (1) The use of a Bayesian estimator that is based on a LSS of three time points (20 minutes, 1 hour, and 3 hours after MMF dosing) for guiding dosage adjustments was adhered to in >80% of cases. (2) Dosage adjustments enabled clinicians to achieve an MPA AUC_{0 to 12 hours} >30 mg \times h/L in 67% of the patients by day 14 and in 91% at month 1, compared with only 31 and 56% in the FD group, respectively. (3) The mean MMF dosage required in the CC group was 3 g/d during the first 3 months; beyond 6 months, MMF dosages were reduced to a mean of 2 g/d. There was a large distribution of dosages from 1 to 4 g, with 80% of patients needing >2 g/d. (4) A retrospective analysis showed no differences in financial costs between CC and FD groups, with TDM representing only 1% of the total costs (39).

Indications for TDM of MPA. Indications for TDM of MPA were reviewed in a previous consensus meeting and are updated in Table 2 (37). Increasing attention for the role of MPA TDM is required in patients with high immunologic risk because finding the delicate balance between under- and overimmunosuppression in these patients proves to be difficult (48). Patients who are treated with protocols that explore the possibilities of CNI minimization, withdrawal or even complete avoidance, and steroid withdrawal or avoidance regimens

Table 2. Indications for MPA TDM: Target population

Dual immunosuppressive therapy
Reduced-dosage CNI therapy (including delayed introduction of CNI)
CNI switch or withdrawal
Recipients with high immunologic risk
Delayed graft function (renal, hepatic, bowel)
Altered gastrointestinal/hepatic/renal function
Cystic fibrosis
Drug interactions
Noncompliance

might also benefit from intensified TDM of MPA. Dedicated studies are necessary to provide answers to these important questions. The usefulness of MPA TDM in the long-term treatment of transplant recipients is even less documented and could be especially important because persistent strong immunosuppression, in part facilitated by the current lack of a target upper therapeutic exposure limit, can lead to serious complications such as malignancies and BK virus infections.

Liver, Bowel, and Pancreas Transplantation

Randomized, controlled or prospective trials in liver, small bowel, and pancreas transplantation that examine the relationship between MPA exposure and efficacy/toxicity or evaluate the effectiveness of TDM are lacking. MMF was shown to be superior to azathioprine as a supplemental immunosuppressant to CsA and corticosteroids to prevent acute rejection in the first 6 months in liver graft recipients (52). In tacrolimus-treated liver recipients, the addition of MMF also resulted in a trend toward fewer rejection episodes but did not improve graft or patient survival up to 4 years (53). In small bowel transplantation, an acute rejection incidence of 95% was observed with the combination of MMF, tacrolimus, and corticosteroids, with very low MPA exposure, despite an MMF dosage of 82 mg/kg per d (11). There have been no prospective trials on the EC-MPS formulation in liver transplantation, with reports of efficacy and tolerability largely restricted to small series or case reports. One pharmacokinetic study reported molar equivalence of EC-MPS with MMF in liver transplantation and multiple absorption peaks with EC-MPS, which may hamper the development of monitoring strategies (54).

The scientific evidence and data to support the use of TDM in liver, bowel, and pancreas transplantation are very limited and insufficient to advocate TDM for these patients as a strategy to improve clinical outcome. The following summary mainly focuses on the retrospective interpretation of observational data by the Consensus Group, which has formulated opinion-based guidance and has made suggestions for points of interest to include in future prospective studies.

Relationship among MPA Exposure, Acute Rejection, and Toxicity. A relationship between MPA exposure and acute rejection has not been demonstrated prospectively in liver transplantation. To avoid acute liver rejection, three studies suggested a minimum trough level of 1 mg/L during CNI

co-therapy, with a fourth indicating 1.5 mg/L during MMF monotherapy (55–58). Adverse effects of MPA in liver recipients are similar to other transplant indications and are leucopenia (at 12 to 27% frequency), diarrhea (12 to 53%), vomiting and other gastrointestinal sequelae (14 to 24%), and anemia or thrombocytopenia (approximately 10%) (55,56,59,60). Fatal infections/sepsis occurred in approximately 5% of liver recipients, with viral and fungal infections in 4 to 20% at 1.5 g of MMF twice daily (61). Within liver, small bowel, and pancreas transplantation, there are no reports of an association between MPA and cytomegalovirus infection and disease. One randomized, controlled trial showed that MPA did not increase risk for hepatitis C virus re-infection after liver transplantation, but there are no corresponding data on hepatitis B re-infection (62). No specific MPA exposure ranges have been associated with the occurrence of these adverse effects in liver recipients.

Targets for MPA Exposure. A minimum trough level of 1 mg/L during CNI co-therapy and 1.5 mg/L during MMF monotherapy has been proposed to avoid acute rejection, on the basis of the *post hoc* analysis of four clinical trials (55–58) (see Relationship among MPA Exposure, Acute Rejection, and Toxicity). There is less consensus on a corresponding upper limit to avoid adverse effects, although, in two studies, the RR for leucopenia rose significantly during tacrolimus plus MMF therapy when MPA C_0 exceeded 2 mg/L (56,63). With MMF monotherapy, adverse effects occurred when MPA C_0 exceeded 5 mg/L (58). Clinical practice suggests that a target ≥ 1 mg/L is important in the first year after transplantation to minimize rejection, whereas levels should be kept below approximately 3.5 mg/L subsequently to reduce the incidence of adverse effects. Initial intravenous MMF dosing can be considered in liver (and possibly bowel) transplantation to compensate for decreased drug bioavailability early after grafting (12).

MMF has made a high impact in the minimization of CNI-induced renal dysfunction (renal sparing) evident as a 30 to 50% reduction in GFR within 6 months of therapy (64). After introduction of MMF, early CNI withdrawal seems to provide more enduring benefit for renal sparing than CNI minimization, provided that it can be achieved safely (65). Isolated reports of an increased incidence and severity of acute rejection after CNI withdrawal emphasize the importance of adequate complementary immunosuppression, particularly in the initial months after transplantation and in those with a history of acute rejection (66). TDM of MPA could, potentially, play an important role in guiding compensatory MMF dosing, but target MPA exposure ranges for CC dosing of MMF in these settings have not yet been validated.

Monitoring MPA Exposure. Monitoring MPA exposure in liver transplantation has predominantly used trough concentration measurements, although additional AUC data exist in some studies. There is evidence to suggest an acceptable correlation between trough and AUC in liver recipients, particularly in relation to achieving therapeutic targets (>1 mg/L for C_0 and $30 \text{ mg} \times \text{h/L}$ for AUC) (67). Nonetheless, the closest correlations ($r^2 > 0.55$) of single time points and AUC were at 1.5, 2.0, and 4.0 hours after dose in liver recipients in the first 14 days after transplantation or at all times between 1 and 8 hours

after dose at 1 year after liver transplantation (68). Examining limited-sampling strategies for AUC determination, Chen *et al.* (69) highlighted deficiencies in predicting AUC using models with only early (<4 hours) time points and showed close correlation ($r^2 > 0.75$) only with three-point models involving samples as late as 4 or 6 hours after dose.

Indications for TDM of MPA. There is insufficient evidence to offer unequivocal guidelines on the requirement for MPA monitoring in liver, small bowel, and pancreas transplantation. On the basis of the interpretation of retrospective clinical data (see Relationship among MPA Exposure, Acute Rejection, and Toxicity), pharmacokinetic data, and *in vitro* and *ex vivo* observations, one rational approach may be to perform MPA monitoring, pending confirmation or refutation by appropriate clinical testing, when there is

- an acute or chronic deterioration in graft function
- onset or change of renal, liver, or bowel (dys)function (including diarrhea, which may be of infective origin rather than being due to MPA)
- a substantial change in serum albumin concentration
- a clinically indicated change of CNI type or dosing
- use of MMF in primary therapy (without CNI) or monotherapy
- a change in the exposure to other interacting medications, in particular oral antibiotics and rifampicin

Thoracic Transplantation

In a multicenter, randomized, controlled trial of 650 heart transplant recipients, use of MMF 3 g/d compared with azathioprine 1.5 to 3.0 mg/kg per d in combination with CsA and corticosteroids resulted in decreased 1-year mortality (6.2 *versus* 11.4%; $P = 0.031$), reduction in treatment for acute rejection (65.7 *versus* 73.7%; $P = 0.026$), and trend toward less severe rejections (more than grade 3A: 45.0 *versus* 52.9%; $P = 0.055$) (70); however, use of MMF was associated with a higher incidence of opportunistic infections, mostly herpes simplex (53.3 *versus* 43.6%; $P = 0.025$) (70). This study confirmed MMF as an effective immunosuppressive drug in heart transplantation and was soon followed by clinical studies that examined the role of CC dosing of MMF in cardiac recipients (see Relationship between MPA Exposure and Acute Rejection and Toxicity). Administration of EC-MPS 1080 mg twice daily in 17 CsA-treated *de novo* heart transplant recipients resulted in MPA exposure (AUC and predose trough concentrations) at 2, 12, and 52 weeks after grafting, comparable with 15 patients who received MMF 1500 mg twice daily in combination with CsA (71).

Despite MMF's being subsequently introduced in lung transplantation, data on the relationship between MPA exposure and clinical outcome or adverse effects in lung recipients are sparse.

Relationship between MPA Exposure and Acute Rejection and Toxicity. In a retrospective analysis of 250 cardiac recipients, the incidence of acute rejection during the first 6 months after transplantation was 8.8% in patients with predose trough MPA concentrations >2 mg/L *versus* 14.9% in recipients with trough MPA concentrations <2 mg/L ($P = 0.05$) (72). A similar

trend in acute rejection episodes was observed in patients who were between 6 and 12 months after transplantation (4.2 *versus* 11.3%; $P = 0.05$), whereas there was no difference in rejection rates according to MPA trough concentrations beyond the first year after transplantation (72). Meiser *et al.* (73) evaluated the incidence of acute rejection in 45 tacrolimus-treated cardiac transplant recipients who were enrolled in a sequential protocol that used an FD of 2 g/d MMF and a CC MMF dosing scheme that targeted predose trough concentrations between 2.5 and 4.5 mg/L. Incidence of acute rejection was 67% in patients who received a fixed MMF dosage compared with 10% in patients who received CC MMF; no rejections occurred with MPA concentrations >3 mg/L (73). In a smaller study that comprised 20 mainly CsA-treated heart recipients, median trough MPA concentrations were 1.36 mg/L (range 0.26 to 6.13) and 1.76 mg/L (range 0.49 to 7.65; $P = 0.015$), respectively, in patients with and without acute rejection according to endomyocardial biopsy (74). Others did not find a relationship between trough MPA concentrations ($>$ or <2 mg/L) and endomyocardial biopsy score (75,76). De Nofrio *et al.* (75) reported an association between an MPA AUC_{0 to 12 hours} <30 mg \times h/L and grades 2 and 3 acute rejection in endomyocardial biopsies.

Targets for MPA Exposure. The present literature suggests a lower incidence of acute cardiac rejection associated with target MPA trough concentrations >2 to 3 mg/L when MMF is combined with tacrolimus. This retrospectively obtained target range, derived from nonrandomized, relatively small studies, needs to be confirmed by larger, prospectively randomized trials. Whether TDM of MPA will improve clinical outcome in thoracic transplantation has not been examined.

Monitoring MPA Exposure. In CsA-treated patients, the coefficient of determination between MPA C₀ and the MPA AUC_{0 to 12 hours} ranges between 0.29 and 0.49 (77,78). In this group of patients, C₆ ($r^2 = 0.60$) and C₁₂ ($r^2 = 0.54$) were reported as the best surrogate sampling points to estimate the dose interval MPA AUC (77,78). In tacrolimus-treated recipients, the coefficient of determination between MPA C₀ and MPA AUC_{0 to 12 hours} ranges between 0.01 and 0.69 (77,78). In this group of patients, C₁ ($r^2 = 0.57$), C₃ ($r^2 = 0.65$), and C₄ ($r^2 = 0.86$) were reported as the best surrogate single time points to predict the full AUC (77,78). MPA C₀ correlated better with the MPA AUC_{0 to 12 hours} in sirolimus-treated patients ($r^2 = 0.61$) compared with CsA-treated patients ($r^2 = 0.36$) (79). In the latter, an MPA C₀ <1.6 mg/L corresponded to an MPA AUC_{0 to 12 hours} <40 mg \times h/L ($r^2 = 0.36$, $P < 0.01$), whereas in sirolimus-treated recipients, an MPA C₀ <2.3 mg/L corresponded to an MPA AUC_{0 to 12 hours} <40 mg \times h/L ($r^2 = 0.61$, $P < 0.01$) (79). LSSs have been evaluated in cardiac recipients, and most studies have provided MPA sampling strategies that comprise three time points within the first 2 hours after MMF dosing, resulting in acceptable predictive algorithms (correlations with MPA AUC_{0 to 12 hours} ranging from $r^2 = 0.79$ to $r^2 = 0.96$) (80–82).

In lung transplant patients who are on CsA or tacrolimus, MPA C₈ or C₁₀ correlates better with the MPA AUC_{0 to 12 hours} compared with C₀, whereas LSSs that use only two MPA sam-

pling points within the first 2 hours after MMF dosing (C₀ + C₂ and C₀ + C_{1.5}) constitute the best compromise between clinical feasibility and predictive performance ($r^2 = 0.82$ and $r^2 = 0.79$, respectively) (82,83).

Pediatric Transplantation

According to the North American Pediatric Renal Trials and Collaborative Studies Registry in 2008, mycophenolate in some form seems to be used in approximately 80% of pediatric renal transplant recipients at discharge from US hospitals (84). This popularity of mycophenolate reflects its proven efficacy in reducing risk for acute renal rejection and its safety and tolerability profile. The incidence of acute rejection is markedly lower, ranging from 15 to 35%, in patients who received MMF compared with those who received either azathioprine or no antimetabolite in combination with a CNI and corticosteroids (85–89). MMF has also been found to improve 5-year outcome in pediatric renal transplant recipients and prolong half-life of the graft (90).

Relationship among MPA Exposure, Acute Rejection, and Toxicity. Studies on the pharmacokinetic/pharmacodynamic relationship to determine the target drug exposure are scarce in pediatric solid organ transplantation. The first study on MPA pharmacokinetics in pediatric renal allograft recipients showed that MMF dosages of 23 and 30 mg/kg yielded MPA exposure (AUC_{0 to 12 hours}) in the same range as derived from adult studies of approximately 30 mg \times h/L (91). Closer analysis of the pharmacokinetics indicated that pediatric MMF dosage could be determined more accurately when calculated on the basis of body surface area and that this target could be achieved using a starting dosage of 600 mg/m² per dose (1200 mg/m² per d) in patients on concomitant CsA therapy (91). This body surface area–related MMF dosing leads to a comparable MPA exposure over the entire pediatric age range (14). The recommended MMF dosage in conjunction with tacrolimus or without a concurrent CNI is 900 mg/m² per d in two divided doses (92); however, recent data indicate that the recommended MMF dosage of 1200 mg/m² per d in conjunction with CsA leads to MPA underexposure early after transplantation in approximately 60% of patients, indicating a need for a higher initial MMF dosage for optimal immunosuppressive activity (14). For achieving adequate MPA exposure in the majority of patients, an initial MMF dosage of 1800 mg/m² per d in conjunction with CsA and 1200 mg/m² per d in conjunction with tacrolimus for the first 2 to 4 weeks after transplantation has been suggested (14,93).

Whereas the efficacy of MMF in preventing acute rejection is comparable in pediatric *versus* adult patients, the adverse effect profile seems to be slightly different, especially in children who are younger than 6 years (94). When MMF needs to be reduced or discontinued (in approximately 13 to 16% of pediatric recipients), the reasons are usually gastrointestinal (*e.g.*, nausea, upper abdominal pain, diarrhea) and hematologic (*e.g.*, leucopenia, anemia) (94,95). It was assumed that temporary discontinuation of MMF had no effect on acute rejection; however, this may not be the case, particularly in patients who are treated with a steroid-free reg-

imen. Patients who were maintained on suboptimal MMF dosing, receiving <75% of the 600 mg/m² per dose for ≥1 month, seemed to have an almost five times higher risk for developing acute cellular rejection (rate of 55%) compared with patients who were on optimal MMF dosages (96). The free MPA-AUC is a significant risk factor for leucopenia or severe infections at values >0.4 mg × h/L (97); therefore, monitoring of the free MPA-AUC may be advantageous in patients who show the symptoms mentioned here.

Targets for MPA Exposure. The currently recommended therapeutic window for MPA exposure in conjunction with full-dosage CNI therapy in the initial period after pediatric renal transplantation to minimize risk for acute rejection is an AUC_{0 to 12 hours} of 30 to 60 mg × h/L (HPLC) or 37 to 70 mg × h/L (enzyme multiplied immunoassay technique [EMIT]) (98). Predose plasma concentrations should be between 1.0 and 3.5 mg/L (HPLC) or 1.3 and 4.5 mg/L (EMIT) (98); however, these therapeutic ranges have not been validated in patients several years after transplantation. In addition and in view of the cost and effort involved in performing TDM, more evidence for the validity of a dosage individualization approach is needed. This is particularly important with respect to developing optimal dosing strategies in the context of steroid- and/or CNI-sparing protocols, because MMF has become the main long-term immunosuppressant in many centers.

Monitoring MPA Exposure. In general, the MPA AUC_{0 to 12 hours} is more strongly correlated with acute rejection than the predose plasma concentration and is therefore selected as the pharmacokinetic parameter for drug monitoring by most investigators; however, because determination of AUC_{0 to 12 hours} is impractical to perform in routine clinical practice, a LSS for monitoring MPA is recommended (37,99). An algorithm based on three pharmacokinetic sampling time points during the first 2 hours after MMF dosing (estimated AUC_{0 to 12 hours} = 18.6 + 4.3 × C₀ + 0.54 × C_{0.5} + 2.15 × C₂) has been validated for the estimation of MPA exposure (99). This algorithm is able to predict the full MPA AUC_{0 to 12 hours} with a low percentage prediction error (10.7%) and an acceptable coefficient of determination ($r^2 = 0.72$) in children who receive CsA and steroids as co-medication (99). In addition, the equation's r^2 and percentage prediction error values were comparable among different pediatric age groups, indicating reliable application to the entire age range of children and adolescents (99). Furthermore, receiver operating characteristic curve analysis demonstrated that this abbreviated profile is of clinical value because it is able to differentiate between rejecters and nonrejecters with a comparable prognostic sensitivity (66.7%) and specificity (61.9%) (99).

For pediatric patients who are on MMF in conjunction with tacrolimus or no CNI, a different algorithm for estimating MPA exposure on the basis of a LSS should be used (estimated AUC_{0 to 12 hours} = 10.0 + 3.95 × C₀ + 3.24 × C_{0.5} + 1.01 × C₂) (100). Various other algorithms for a LSS in pediatric recipients have been published with comparable results (101-104).

Indications for TDM of MPA. Indications for TDM of MPA in pediatric recipients are similar to adult patients (see Indications for TDM of MPA and Table 2).

Analytical Methods to Measure MPA Concentrations

Methods that are in use to measure MPA are HPLC with either ultraviolet detection or mass-spectrometric (MS) detection or an EMIT assay (105-107). Two other platform assays have emerged. One is the cloned enzyme donor immunoassay, which is not available in all parts of the world; the other is an enzyme inhibition assay (108-110). There is also a particle-enhanced turbidimetric inhibition immunoassay, which has not yet entered commercial production (111).

The performance characteristics of these assays are summarized in Table 3. The choice of which assay to use will depend on a number of factors: Apparatus and expertise available in the laboratory, sample load, and whether the assay is to be used for total or unbound (free) concentrations of MPA or MPA metabolites. In general, laboratories that have a small number of samples to analyze or receive samples only infrequently and that are providing a routine TDM service will tend to use the platform assays. Those with a large sample load and those with research interests are likely to use a chromatographic technique. Differences between chromatographic and immunoassays in measured concentration of MPA is due to interference by the acyl glucuronide, AcMPAG, in immunoassays and to differences in calibration of various assays (112).

The enzyme inhibition assay does not seem to be significantly affected by metabolite interference. Results from two studies based on the use of this assay for measuring MPA in samples from patients who were receiving MMF have been in good agreement with results from chromatographic assays (109,110).

On average, from proficiency testing data, agreement between the various methods for blinded samples that contain known concentrations of MPA is good; however, the issue of calibrator accuracy should always be kept in mind, especially for centers that use chromatographic techniques, because most prepare their own calibrators. Accuracy of calibration is an important factor for long-term consistency of results and for pooling of data from multiple centers in clinical studies.

There is a clear advantage to the use of chromatographic assays when there is a need to measure the metabolites of MPA. Attention has mostly focused on the measurement of the phenolic glucuronide as the major metabolite of MPA and the metabolite that can displace MPA from its protein binding sites and the acyl glucuronide for its possible role in the adverse effects of MPA (113). The phenolic glucuronide is available commercially, whereas the acyl glucuronide is not.

The lower limit of assay sensitivity that is achievable using MS detection is hardly a necessity for measuring total MPA concentrations but useful when measuring MPA free-fraction (114). HPLC-ultraviolet assays can be calibrated to the low concentrations needed to measure the free fraction (<2% of total concentrations) but are generally less robust at these concentrations than HPLC-MS assays (115,116).

Table 3. Summary of method performance for the measurement of MPA

Method	HPLC-UV or UPLC-UV; HPLC-Fluorescence	HPLC-MS	EMIT (Siemens)	IMPDH-Based Enzyme Inhibition Assay (Roche)	CEDIA (Microgenics)	PETINIA (Siemens)
Analytical platforms	No limitations	Single or triple quadrupole with ESI or APCI detection	Validated applications for Cobas Mira and Viva systems	Validated applications for Cobas Integra 800/400, Cobas c501/c301	Validated applications for Hitachi, Modular, Olympus AU series, MGC 240, Beckman Synchro LX20 and DxC 600, and Furono CA 90	Validated applications for the Dimension systems
Specificity of the method for MPA	High if validated appropriately	High if validated appropriately. Potential problems: fragmentation of metabolites and the internal standard MPAC in the ion source to produce MPA; ion suppression	Overestimation by approximately 25%, partly explained by cross-reactivity with AcMPAG	Trend to overestimate MPA concentrations at concentrations close to the LLOQ (approximately 10% at 0.5 mg/L); no clinically relevant overestimation as a result of AcMPAG	Overestimation by approximately 36%, partly explained by cross-reactivity with AcMPAG	Overestimation by approximately 25%, partly explained by cross-reactivity with AcMPAG
Assessment of metabolite concentrations	Allows differentiation between MPA and its metabolites	Allows differentiation between MPA and its metabolites	Concentration-dependent cross-reactivity with AcMPAG, no differentiation between MPA and metabolite concentrations possible	Not possible to measure metabolite concentrations with this technique	Concentration-dependent cross-reactivity with AcMPAG, no differentiation between MPA and metabolite concentrations possible	Concentration-dependent cross-reactivity with AcMPAG, no differentiation between MPA and metabolites possible
Method imprecision over the therapeutic concentration range	<5 to 10% (mostly 5 to 7% at a concentration of 1 mg/L)	<5 to 10% (mostly 5 to 7% at a concentration of 1 mg/L)	<5 to 10% (6 to 8% at a concentration of 1 mg/L)	<5 to 10% (3 to 10% at a concentration of 1 mg/L)	<5 to 10% (5 to 10% at a concentration of 1 mg/L)	<5 to 10% (5 to 7% at a concentration of 1 mg/L)

Method accuracy (comparability with a validated reference method)	Reference method	Reference method	Slopes: 1.01 to 1.10; intercepts: -0.09 to 0.24; $r^2 = 0.89$ to 0.99	Slopes: 1.01 to 1.17; intercepts: -0.17 to 0.06; $r^2 = 0.95$ to 0.99	Slopes: 0.975 to 1.180; intercepts: -0.24 to 0.45; $r^2 = 0.83$ to 0.93	$Y(\text{PETINIA}) = 1.12(\text{HPLC-UV}) - 0.24; r^2 = 0.98$
LLOQ	Mostly <0.25 mg/L	Mostly <0.1 mg/L	0.2 mg/L	0.3 mg/L	0.3 mg/L	0.2 mg/L
Method linearity (sufficiency in regard to therapeutic concentrations)	Yes, mostly up to 50 mg/L	Yes, mostly up to 50 mg/L	Only for C_0 ; linearity up to 12 mg/L. For C_{max} and for LSS, sample dilution needed	Only for C_0 ; linearity up to 12 mg/L. For C_{max} and for LSS, sample dilution needed	Only for C_0 ; linearity up to 10 mg/L. For C_{max} and for LSS, sample dilution needed	Yes, linearity up to 50 mg/L
Assessment of unbound MPA concentrations	Possible	Possible	Only after modification	No	No	No
Turnaround time sufficient for dosage adjustment	Yes	Yes	Yes	Yes	Yes	Yes
Around-the-clock availability	In general, no	In general, no	Yes	Yes	Yes	Yes
Need for specialist expertise	Yes	Yes	No	No	No	No
Published experience in PK/TDM studies	Yes	Yes	Yes	Yes	No	No

Method accuracy data are a guide only, because comparison of the published data is complicated by use of a variety of different statistical approaches. Data for PETINIA are preliminary; the method is due to be released in Europe during 2009. C_{max} , maximum concentration; LLOQ, lower limit of quantification; PETINIA, particle-enhanced turbidimetric inhibition immunoassay; PK, pharmacokinetic; UPLC, ultraperformance liquid chromatography; UV, ultraviolet.

Although HPLC with MS detection is often described as the gold standard technique, it is not without some problems (117). Among these are suppression of ionization by components in the sample matrix, leading to falsely lowered results, and in-source fragmentation of the phenolic glucuronide, leading to falsely elevated results. There is no commercial source of a stable isotope-labeled form of MPA for use as an internal standard in the assay. Assay validation in line with international recommendations is essential for all of the chromatographic techniques, irrespective of method of detection.

For standardization of analysis of MPA, an EDTA plasma sample has been recommended as the sample matrix (118); however, a heparinized plasma sample can be used with most analytical methods, although the matrix used should conform to the package inserts of platform assays, or data should be generated specifically to show the suitability of a matrix. During and after blood collection, storage and sample handling procedures should be standardized. Plasma concentrations of MPA have been shown to be stable and remain constant up to at least 8 hours at room temperature, 96 hours at 4°C, and 11 months at –20°C (118). Samples in which there is a very high concentration of the acyl glucuronide can result in falsely elevated MPA concentrations. Patients with compromised elimination of glucuronides, such as those who have recently received a kidney transplant and have delayed function, can have high concentrations of this metabolite, sometimes higher than the parent compound. The acyl glucuronide is unstable at neutral or alkaline pH, with a loss of approximately 25% after 12 hours and approximately 40% after 24 hours at room temperature (119). There are protocols that can be used to overcome the preanalytical problem (119–122).

In summary, if sample analysis can be performed within 12 hours of collection and the presence of MMF in the sample can be excluded, then sample storage in a refrigerator at 4°C is acceptable. If this is not possible, then samples should be frozen immediately after collection. For clinical trials that involve a large number of samples and extended storage, acidification of plasma should be considered for measurement of total MPA concentrations.

Thus, methods for measuring MPA are divided between chromatographic and platform assays. The choice of technique is heavily dependent on resources available and intended use of the assay. Laboratories must ensure that they use an appropriate technique and that their results are in agreement with accepted peer values.

Another possibility is to monitor the pharmacodynamic effect of MPA by measuring activity of the target enzyme IMPDH (7). The advantage of using this pharmacodynamic measure is that, in contrast to MPA concentrations, it does take into account interindividual differences in response to the drug. Glander *et al.* (123) developed an HPLC method that measures the rate of xanthine monophosphate production by peripheral blood mononuclear cells under controlled *in vitro* conditions, assuming that this reflects the target immunologic cells involved in graft rejection. Recently, this assay was further optimized (124). Typically, considerable interpatient variability in IMPDH activity combined with relatively small intraindividual

variability has been found, and part of the variability is related to a polymorphism in the IMPDH type II gene (125). In a preliminary study, correlations between preoperative IMPDH activity and posttransplantation outcome were shown, but larger studies are needed to evaluate better the added value of IMPDH activity monitoring for patient treatment (126).

Conclusions

TDM of MPA that is based on LSSs is preferred in solid organ transplantation compared with drug dosing that is based on single MPA (trough) concentrations. LSSs provide a good estimation of the MPA dose-interval AUC, which is associated with early postoperative efficacy (avoidance of acute rejection) but less clearly with drug-related toxicity. Using LSSs can improve early graft outcome in terms of acute rejection, although avoidance of drug-related adverse events has not been shown. Whether TDM of MPA will be required for maintenance immunosuppressive therapy is not clear; therefore, the general routine use of MPA TDM in solid organ transplantation cannot be recommended on the basis of the available evidence. This analysis of data suggests that specific patient populations might benefit from prolonged CC MPA dosing, including patients who are at increased immunologic risk; patients who are undergoing minimization or withdrawal of immunosuppressive therapy; and patients who are experiencing altered renal, hepatic, or bowel function. In terms of graft outcome and patient survival, no direct evidence is available to suggest a possible benefit of MPA TDM.

Acknowledgments

The Transplantation Society (TTS) Consensus Group on TDM of MPA includes the following: Dirk R.J. Kuypers, Department of Nephrology and Renal Transplantation, University Hospitals of Leuven, Belgium; Yannick Le Meur, Department of Nephrology, Centre Hospitalier Universitaire La Cavale Blanche, Brest, France; Dario Cattaneo, Unit of Clinical Pharmacology, “Luigi Sacco” University Hospital, Milan, Italy; Richard Borrows, University Hospital Birmingham, England; Christine E. Staatz, School of Pharmacy, University of Queensland, Brisbane, Australia; Susan E. Tett, University of Queensland, Faculty of Health Sciences, Brisbane, Australia; David W. Holt, Bioanalytics, St. George’s–University of London, London, England; Alexander A. Vinks, Division of Clinical Pharmacology, Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio; Lutz T. Weber, Pediatric Nephrology, University Children’s Hospital, Ludwig-Maximilian’s University, Munich, Germany; Bruno Meiser, Department of Cardiac Surgery, Ludwig-Maximilians-University of Munich, Munich, Germany; Bryce Kiberd, Dalhousie University, Halifax, Nova Scotia, Canada; Masatomo Miura, Department of Pharmacy, Akita University Hospital, Akita, Japan; Shigeru Satoh, Division of Renal Replacement, Therapeutic Science Department of Urology, Akita University School of Medicine, Akita, Japan; Pierre Marquet, INSERM U850, Department of Pharmacology-Toxicology, University Hospital of Limoges, Limoges, France; Jens Goebel, Department of Nephrology and Hypertension and Kidney Transplantation, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio; Michael Oellerich, Department of Clinical Chemistry/Central Laboratory, University Medical Center Göttingen, Göttingen, Germany; Mary H.H. Ensom, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada; Marcelo Cantarovich, Multi-Organ Transplant Program, McGill Uni-

versity Health Center, Montreal, Quebec, Canada; Rowan G. Walker, Department of Nephrology, Royal Melbourne Hospital, Melbourne, Australia; Nigel W. Brown, Liver Pathology, Institute of Liver Studies, King's College Hospital, London, England; Michael J. Tredger, Institute of Liver Studies, King's College Hospital and King's College London School of Medicine, London, England; Maria Shipkova, Central Institute of Clinical Chemistry and Laboratory Medicine Klinikum Stuttgart, Stuttgart, Germany; Burkhard Tönshoff, Pediatric Nephrology, University Children's Hospital, Heidelberg, Germany; Leslie M. Shaw, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; Franck Saint-Marcoux, INSERM UMRS 850, Department of Pharmacology and Toxicology CHU Limoges, Limoges University Hospital, Limoges, France; Elias David-Neto, Renal Transplant Unit, Hospital das Clínicas—University of São Paulo School of Medicine, São Paulo, Brazil; Robert Ettenger, Department of Pediatrics, Division of Pediatric Nephrology, Mattel Children's Hospital at UCLA, Los Angeles, California; Guido Filler, Department of Pediatrics, Division of Nephrology, University of Western Ontario, London, Ontario, Canada; Eileen Tsai, Department of Pediatrics, Division of Pediatric Nephrology, Mattel Children's Hospital at UCLA, Los Angeles, California; Bernd Zimmerhackl, Department of Pediatrics, Medical University Innsbruck, Innsbruck, Austria; Jeremy Chapman, Centre for Transplant and Renal Research, University of Sydney, Sydney, Australia; Teun van Gelder, Departments of Hospital Pharmacy and Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands; Roy D. Bloom, University of Pennsylvania Health System, Philadelphia, Pennsylvania; Robert S. Gaston, University of Alabama at Birmingham, Birmingham, Alabama; Mercè Brunet, Hospital Clinic i Provincial, Barcelona, Spain; Ashok Jain, University of Rochester Medical Center, Department of Surgery, Division of Solid Organ Transplantation, Rochester, Minnesota; Mark Pescovitz, Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana; Pierre Wallemacq, Department of Clinical Chemistry, Laboratory of Toxicology and Therapeutic Drug Monitoring, Université Catholique de Louvain, Brussels, Belgium; Josep M. Grinyo, Hospital Universitari de Bellvitge, Barcelona, Spain; and Klemens Budde, Department of Nephrology, Campus Charité Mitte, Berlin, Germany.

We thank The Transplantation Society for the support of this Consensus Meeting on MPA TDM. We are grateful to Ms. Filomena Picciano (Director of Society Operations TTS) and Ms. Catherin Parker (Project Manager TTS) for their support.

Disclosures

D.R.J., T.v.G., and B.M. have received honoraria and lecture fees as well as a research grant from F. Hoffmann-La Roche Ltd. D.C. has received travel grants and lecture fees from Hoffmann La Roche Ltd. R.B. has received an unrestricted educational grant from F. Hoffmann La Roche Ltd. A.A.V. has received a research grant from Roche Laboratories, Inc. Jens Goebel has received research grant support from Roche Laboratories, Inc. M.H.H.E. has received a research grant from F. Hoffmann La Roche Ltd. M.C. has received research support, travel grant, honoraria, or lecture fees from Astellas, Hoffman LaRoche, Genzyme, Isotechnika, Novartis, and Wyeth. R.W. has received honoraria for serving on national and international advisory boards for Roche and Novartis. B.T. has received grant support, travel support, and lecture fees from Roche, Astellas, Novartis, and Wyeth. L.M.S. has received research grant funding and lecture fees from Hoffman La Roche. M.O. has received lecture fees from and participated in clinical trials for F. Hoffmann La Roche. E.D.-N. has received study grants from Novartis, Wyeth, and Jansen-Cilag. K.B. has received research grants and/or honoraria from Roche, Novartis, Wyeth, Astellas, LifeCycle Pharma, Pfizer, and Bristol Myers Squibb.

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