Mycophenolate monitoring in liver, thoracic, pancreas, and small bowel transplantation: a consensus report

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Abstract

Assessing the value of mycophenolic acid (MPA) monitoring outside renal transplantation is hindered by the absence of any trial comparing fixed-dose and concentration-controlled therapy. However, in liver and thoracic transplantation particularly, clinical trials, observational studies with comparison groups, and case series have described MPA efficacy, exposure/efficacy relationships, pharmacokinetic variability, and clinical outcomes relating to plasma MPA concentrations. On the basis of this evidence, this report identifies MPA as an immunosuppressant for which the combination of variable disposition, efficacy, and adverse effects contributes to interindividual differences seemingly in excess of those optimal for a fixed-dosage mycophenolate regimen. Combined with experiences of MPA monitoring in other transplant indications, the data have been rationalized to define circumstances in which measurement of MPA concentrations can contribute to improved management of mycophenolate therapy in nonrenal transplant recipients.
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1. Introduction

Mycophenolic acid (MPA) was first licensed for transplantation in 1995 and rapidly grew in popularity, becoming the second most widely prescribed immunosuppressant in the United States in 2004 [1]. Acting as a noncompetitive selective inhibitor of inosine monophosphate dehydrogenase II, it especially reduces proliferation in rapidly replicating immune cells dependent on de novo purine synthesis (reviewed in Weimert et al [2]). Mycophenolic acid is valuable not only for minimizing the dosage and adverse effects of calcineurin inhibitors (CNIs) and corticosteroids but also as an adjunctive and sometimes single immunosuppressant [3]. Fixed-dosage prescription of myco-

phenolate mofetil (MMF) has been recommended in its product leaflet [4]. In contrast, there is evidence for therapeutic failure or an increased risk of adverse effects outside a therapeutic window for MPA concentrations (this review) as well as a substantial greater than 10-fold interindividual diversity in MPA pharmacodynamics/kinetics (reviewed in Staatz and Tett [5]). Trials of fixed-dosage vs concentration-controlled trials of MPA usage have not been conducted outside renal transplantation [6], but routine monitoring for MPA is increasingly performed.

This review seeks to provide a guide to transplant specialists wishing to optimize MPA therapy using therapeutic drug monitoring in liver, thoracic, pancreas, and small bowel transplantation. It has been compiled by those members of the Transplantation Society Consensus Group on therapeutic drug monitoring of MPA [6] who particularly focused on nonrenal transplantation.

We have examined the literature in 4 areas: (i) MPA efficacy, (ii) exposure/efficacy relationships, (iii) pharmacokinetic/ pharmacodynamic variability, and (iv) studies involving

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MPA monitoring. Mycophenolic acid concentration targets have been devised from this evidence. Most studies involve hepatic and thoracic (especially heart) transplant recipients with only a few in pancreatic/pancreatic islet or in small bowel transplantation. Interestingly, MPA is increasingly used and monitored in bone marrow and stem cell transplantation (eg, Hiwarkar et al [7]), and useful lessons can be learnt because these patients often have low plasma albumin levels and low initial circulating MPA concentrations like those in many abdominal graft recipients.

2. MPA efficacy in liver, thoracic, bowel, and pancreas transplantation

Two formulations of MPA are available: MMF (CellCept; Roche, Nutley, NJ) and enteric-coated mycophenolate sodium (EC-MPS; Myfortic; Novartis, Basel, Switzerland). Only MMF has been studied widely in transplantation, predominantly for treating acute rejection, minimizing steroids, and, most importantly, for CNI-minimizing strategies.

2.1. Acute rejection and maintenance immunosuppression

Compared with azathioprine, MMF lowered the incidence of acute rejection in a ciclosporin (CsA)-based regimen (38.5% vs 47.7%, $P < .03$) during the first 6 months after liver transplant [8]. Mycophenolate mofetil was also used successfully for treating steroid- or T-cell antibody (OKT3)-resistant rejection with 21 of 23 recipients responding, 14 completely [9]. Used in a tacrolimus (TRL) plus steroids immunosuppressive regimen, MMF contributed to an acute rejection incidence of only 6.1% in the first year posttransplant [10].

In a heart transplant multicenter, randomized, controlled trial using a CsA-based immunosuppressive regimen, MMF reduced 1-year mortality compared with azathioprine (6.2% vs 11.4%, $P = .031$). Mycophenolate mofetil also reduced the incidence of acute rejection (45.0% vs 52.9%, $P = .055$) and treatment interventions but was associated with a higher incidence of opportunistic infections, mostly herpes simplex (53.3% vs 43.6%, $P = .025$) [11].

In lung transplant recipients on a CsA-based regimen after antithymocyte globulin induction, MMF was associated with fewer rejection episodes than azathioprine (0.29 ± 0.10 vs 1.53 ± 0.29, respectively; $P < .01$) [12].

2.2. Corticosteroid minimization

Effective immunosuppression was achieved using TRL and MPA in 30 adult de novo liver graft recipients without prophylactic steroids and led to a graft survival of 83.9% at 2 years [13]. When used for corticosteroid replacement, MMF significantly improved plasma cholesterol, lowered plasma glucose and insulin requirements, decreased hemoglobin A1c, and increased bone density [14] in a study of 30 patients with posttransplant autoimmune hepatitis. Significantly

lower rates of hepatitis C virus (HCV) recurrence (18.1% vs 46.0%) and cytomegalovirus infection (5.6% vs 22.2%) were achieved following MMF replacement of corticosteroids in 28 patients on a CNI-based regimen [15]. There was no negative impact on the rates of acute cellular rejection, even with a higher proportion ($P = .015$) receiving preemptive HCV therapy. In contrast, Reggiani et al [16] showed significantly higher rates of acute rejection in the first 10 days after liver transplant with corticosteroid avoidance using TRL plus MMF, but neither an effect on long-term graft outcome nor a reduction in steroid-related adverse effects was observed in their 30 patients.

In 41 heart transplant patients receiving TRL and MMF, weaning of corticosteroids in 25 (62%) resulted in a lower incidence of infection requiring hospitalization. However, no significant benefits were observed on lipids, blood pressure, hyperglycemia, and body mass index. The authors found that significant predictors of failure to wean steroids included higher rejection grade, B-type natriuretic peptide, and lower dose of MMF [17]. Randomized controlled trials in thoracic transplantation are needed to assess steroid withdrawal in patients on concentration-controlled MMF therapy.

2.3. Renal sparing

Mycophenolate mofetil has been widely used to spare the renal dysfunction commonly associated with CNI. The landmark study of Ojo et al [18] in 69 321 nonrenal transplant recipients showed that at 10 years posttransplant, chronic kidney disease (CKD) stage 4 (glomerular filtration rate [GFR] <30 mL/min) or stage 5 (GFR <15 mL/min) was observed in more than 25% of liver, more than 20% of lung, and more than 20% of heart transplant recipients. The highest incidence of CKD stages 4 to 5 was observed in intestinal transplant recipients: more than 25% at 5 years posttransplant [18]. Interestingly, a recent report in 81 patients (46% with diabetes and 80% with hypertension) examining renal biopsy pathology 5 years after liver transplantation [19] suggests that changes in renal function are not due to CNI nephrotoxicity alone: although only 16% showed signs of CNI toxicity, glomerular disease was present in all cases, and changes frequently characterizing diabetic nephropathy occurred even in those 54% without a clinical diagnosis of diabetes.

Three randomized controlled trials confirmed improved renal function of long-term liver transplant recipients with CKD in whom MMF either replaced CNI or reduced or interrupted CNI therapy [20-22]. Acute rejection incidence was 21% (3 of 14 patients) when CNI was discontinued [20] but did not differ when CNI doses were reduced [21,22]. In numerous observational studies, a common finding is an initial increase in GFR with the introduction of MMF for either CNI taper or complete withdrawal later after transplantation [20,22-36]. Typically, either introduction of MMF was several years posttransplant or study numbers were small or changes in renal function were followed only over the short term. For example, renal function in 42 adult

liver recipients grafted for HCV cirrhosis benefited only for the first 3 months after switching to MMF monotherapy at a mean of 6 years posttransplant [37].

The impact of early intervention was evaluated in the ReSpECT multicenter prospective randomized trial of de novo liver recipients with normal pretransplant renal function. Efficacy and renal function at 1 year posttransplant were compared in 3 groups of patients given either a standard TRL plus corticosteroids regimen or MMF (1 g twice daily) plus corticosteroids plus reduced-dose TRL, or MMF plus corticosteroids plus reduced-dose TRL delayed 5 days under daclizumab induction. Both acute rejection incidence (27.6%, 29.2%, and 19.0%, respectively) and the fall in estimated GFR (23.6, 21.2, and 13.6 mL/min, respectively) benefited from the delay of TRL therapy rather than reduced TRL dosage alone [38].

In pediatric liver recipients, improvements in GFR were greater in children younger than 3 (vs >3) years and when MMF was introduced at less than 5 (vs >5) years posttransplant [39].

Concerns about an increased risk of irreversible rejection during CNI taper or withdrawal [40,41] have been moderated by subsequent widespread experience using slow CNI taper and careful patient observation during introduction of MMF. When CNI minimization or withdrawal is required, corticosteroids [31], sirolimus (SRL) [42-45], or monoclonal antibodies [38,46] may provide supplementary immunosuppression.

In summary, MMF has been shown to be an effective agent enabling CNI minimization, causing beneficial effects on renal function. Full benefit accrues by starting MMF before renal function is markedly decreased. Three groups [47-49] have recently highlighted a likely need for conversion within 3 months of transplant: of 594 liver recipients grouped according to GFR early posttransplant, end-stage renal disease developed by year 5 in 35.5%, 48.8%, and 62.2% with initial GFR greater than 80, 60 to 80, and less than 60 mL/min, respectively. In a randomized controlled trial including long-term heart transplant patients with CKD, the use of MMF and low-dose CsA compared with SRL and low-dose CsA resulted in an improvement in renal function (estimated GFR increased from 48.5 ± 21.4 to 61.7 ± 21.4 mL/min 6 months after CsA dose reduction) without increasing the risk of acute rejection [50].

2.4. MMF for reduction of cardiovascular risk and other immunosuppressant adverse effects

Calcineurin inhibitor–treated liver graft recipients are also at increased cardiovascular risk, with treated hypertension observed in 71% of 77 patients at 5 years after transplantation for acute liver failure—a standardized prevalence ratio of 2.73 compared with the general population [51]. Minimizing doses of CNI [20,22,25,27,32] or corticosteroids [52] with MMF has improved blood pressure and reduced antihypertensive medication, which show an interdependence to benefits on renal function (above) [18]. Calcineurin

inhibitor–induced neurotoxicity has also been reduced with CNI taper and MMF introduction [53] or with SRL and MMF [48].

Barrera-Pulido and colleagues [54] showed small decreases of 11% in mean plasma uric acid and 12% in triglycerides 1 year after switching to MMF monotherapy in 31 adult liver recipients. Significant 28% and 40% reductions in mean triglyceride concentration were noted by Herrero et al [23] and Orlando et al [33], respectively, after CNI minimization using MMF. Wierzbicka et al [55] showed small but significant improvements in serum triglyceride, high-density lipoprotein cholesterol, and apolipoprotein concentrations with CNI minimization using MMF.

In summary, MMF has been shown to be an effective adjunct to CNI-based immunosuppressive regimens, with improvement in renal function and hypertension and reduction in steroid-associated adverse effects. Caution during conversion helps manage the risk of an increased rate of rejection.

2.5. Gastrointestinal (GI) adverse effects of MMF and EC-MPS (Myfortic)

Diarrhea, vomiting, and nausea are frequent complications of MMF therapy, and changes in gastrointestinal (GI) histopathology are frequent in MMF-treated patients [56]. However, there was no evidence of specific damage attributable to MPA in a study of 4 patients with multivisceral transplants by Delacruz et al [57], who highlight the need for specific markers of MPA toxicity.

The combination of MMF with SRL in thoracic transplant recipients has been particularly associated with adverse effects (affecting 30%–76%) and drug discontinuation (8%–75%), mostly secondary to SRL [30,50,58-61].

Studies of EC-MPS introduction in liver transplantation have concentrated on examining its adverse effect profile compared with MMF. In small studies, Nure et al [62] and Robaeys et al [63] showed a reduction in GI symptoms and decreased use of proton pump inhibitors. After switching 19 liver recipients with GI symptoms to EC-MPS from MMF, 42.8% no longer displayed symptoms after 1 month and 15.4% at 9 months [64]. Doria et al [65] also showed an improvement in the incidence of GI symptoms compared with MMF, but noted that a third of the patients discontinued EC-MPS. None of these studies reported or showed any change in the incidence of other adverse effects including rejection. Enteric-coated MPS would appear to offer respite from certain GI adverse effects in a proportion of patients.

3. Exposure-efficacy/toxicity relationship

There are few studies of the exposure-efficacy relationship for MPA in liver transplantation (Table 1) and very few in small bowel or pancreatic transplantation. Briefly, MMF monotherapy was rare, and MMF was used predominantly with CsA and TRL with or without corticosteroids [67], TRL

Table 1
Relationship of MPA exposure to rejection episodes and adverse effects in liver transplant recipients

Study aim	n	Patients/Regimen	MPA exposure and acute rejection	MPA exposure and adverse effects	Author
MMF prophylaxis for acute rejection	10	De novo adult liver graft recipients. ATG + corticosteroids + CNI + MMF MPA C_0 targeted to 1 mg/L	No data	No AEs except leukopenia at MPA C_0 <2 mg/L	Grasser et al [66]
Define MPA C_0 therapeutic range	210	Adult (147) and pediatric (63) liver graft recipients, most late after LTx. MMF ± CNI ± corticosteroids	9/10 adult and 3/3 pediatric episodes at >2.5 mo post-OLT with C_0 < 1 mg/L; relative risk up 4.2-, 2.5-, and 1.6-fold at 0.5, 1.0, and 1.5 mg/L C_0 in adults (P < .05)	For 106 AEs in adults, relative risk of leukopenia, infection, and GI disturbances >3 when MPA C_0 3–4 mg/L (P < .05 for leukopenia)	Tredger et al [67]
Corticosteroid sparing	30	De novo adult liver graft recipients. TRL + MMF vs TRL + MMF + corticosteroids	MPA AUC not significantly different in 9 with and 3 without rejection in week 1 (both mean AUCs <20 mg · h/L)	No data	Reggiani et al [16]
Safety/efficacy of MMF in monotherapy or low-dose CNI	56	Adult liver graft recipients with CNI adverse effects. CNI to MMF alone or CNI + MMF	11 cases; no specific MPA C_0 data in this cohort but "no correlations"	10 cases of leukopenia and diarrhea; no specific MPA C_0 data in this cohort. C_0 > 4 mg/L was avoided.	Bilbao et al [32]
Relating in vivo MPA C_0 and AUC to pharmacodynamics in vitro	15	De novo adult liver graft recipients. TRL + MMF + daclizumab (no steroids)	1 case only. No analysis possible	22 cases of infection, anemia/leukopenia, diarrhea/nausea/vomiting. MPA C_{40min} higher in diarrhea etc (P < .05)	Brunet et al [68]
Conversion from CNI to monotherapy with MMF	42	Adult liver graft recipients with CNI adverse effects at mean 70 mo post-LTx	9 cases—not biopsy confirmed. No significant difference in MPA C_0 vs nonrejectors	7 cases where MPA C_0 data not reported	Orlando et al [33]
Predict AEs from MPA C_0, C_{max}, and AUC	63	De novo adult liver graft recipients TRL + MMF + corticosteroids ± α-CD25 Ab	2 cases, both with MPA C_0 <1 mg/L	52 AEs (including leukopenia, infection, and diarrhea) in patients, where mean C_0, C_{max}, and AUC > no AEs (P < .05). P < .05 for leukopenia alone	Chen et al [69]
Validate and optimize MPA monitoring	304	Adult liver graft recipients up to 5 y post-LTx; MMF ± TRL ± corticosteroids	2 of 72 MMF-treated recipients. Prevented at MPA C_0 >2 mg/L with late monotherapy.	Qualitative data. Serious infections at doses >1.5 g/d. No significant correlations with C_0 in 6 cases of diarrhea/leukopenia	Hwang et al [70]

AE indicates Adverse event; ATG, antithymocyte globulin; C_{20min}, plasma concentration at 20 minutes postdose; C_{40min}, plasma concentration at 40 minutes postdose; α-CD25 Ab, anti-interleukin 2 receptor antibody; LTx, liver transplantation.
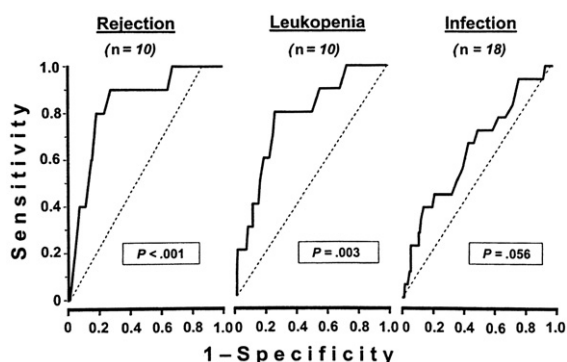
Fig. 1. Receiver operating characteristics curve analysis of plasma MPA concentrations in relation to episodes of acute rejection, leukopenia, and infection. Reproduced from [67] with permission of Wiley Publishing.

and daclizumab [68], and TRL and steroids [69]. The indicators of MPA exposure assessed were predose or trough (C_0) and maximum (C_{max}) plasma concentrations and measured or estimated area under the plasma concentration vs time curve (AUC) over 1 dosage interval.

3.1. MPA exposure and rejection

Tredger et al [67] considered acute rejection as an indication of failed efficacy and demonstrated an association with MPA C_0 less than 1.0 mg/L in 147 adult liver transplants. The relative risk of rejection (95% confidence intervals) increased 4.2-, 2.5-, and 1.6-fold, respectively, at plasma MPA concentrations of less than 0.5, 1.0, and 1.5 mg/L and receiver operating characteristic (ROC) curve analysis defined a cutoff of 0.85 mg/L in adult liver recipients (Fig. 1). Chen et al [69] only recorded 2 instances of acute rejection in 63 patients, both with MPA C_0 of 0.3 and 0.6 mg/L.

In a pharmacodynamic study, Brunet et al [68] determined the proliferation rate of a human-immortalized uniquely MPA-sensitive T-lymphoblastoid cell line to

MPA in patients' serum. Mycophenolic acid C_0 was significantly negatively correlated ($r = -0.766$) with cell proliferation: concentrations greater than 1 mg/L were associated with a large decrease in proliferation (<30%) in 6 of 7 patients, whereas MPA concentrations less than 1 mg/L were associated with variable decreases (5%–85%).

After heart transplantation, the incidence of acute rejection in the first 6 months was 8.8% in patients with MPA C_0 greater than 2 mg/L and 14.9% with MPA C_0 less than 2 mg/L. A similar trend was observed beyond the first year posttransplant (4.2% vs 11.3%) [71]. Acute rejection incidence was also markedly reduced in heart transplant patients in whom MMF doses were targeted towards a C_0 range of 2.5 to 4.5 mg/L rather than using a fixed-dose regimen (10% vs 67%) [72]. Hesse et al [73] studied the relationship between MPA C_0 and endomyocardial biopsy scores, showing a median MPA concentration of 1.36 mg/L (range, 0.26–6.13) in patients experiencing acute rejection vs 1.76 mg/L (range, 0.49–7.65; $P = .015$) in those without. No comparable relationship was identified using a 2.0 mg/L MPA C_0 cutoff in 2 small series [74,75], but an MPA AUC of less than 30 mg · h/L identified biopsies with (grades 2 and 3) or without (grade 0, $P < .08$, and grade 1, $P < .05$) acute rejection (DeNofrio et al [74] and Billingham et al [76] for definition of rejection grades).

3.2. MPA exposure and adverse effects

In 63 liver transplant recipients, Chen et al [69] showed that relative risks for all adverse effects were significantly increased above cutoffs of 2.0 mg/L, 10.0 mg/L, and 40 mg · h/L for C_0, C_{max}, and AUC, respectively. The specificity and sensitivity of different measurements of MPA exposure varied markedly with the adverse effect considered (Table 2).

3.2.1. Bone marrow toxicity

Chen et al [69] showed C_0, C_{max}, and AUC could all significantly discriminate for leukopenia ($P < .05$) with

Table 2
MPA exposure measurements and their relationship to adverse effects

MPA exposure measurement		Area of ROC curve (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)	P value
C_0	All adverse effects*	0.748 (0.619–0.877)	2 mg/L	52.4	90.5	0.001
	Leukopenia	0.670 (0.534–0.805)		56.5	75.0	0.026
	Diarrhea	0.608 (0.434–0.783)		75.0	22.3	0.198
C_{max}	All adverse effects*	0.692 (0.556–0.828)	10 mg/L	45.2	85.7	0.014
	Leukopenia	0.684 (0.553–0.814)		50.0	82.8	0.013
	Diarrhea	0.538 (0.368–0.708)		43.8	63.8	0.653
AUC_{0-12h}	All adverse effects*	0.695 (0.559–0.831)	40 mg.h/L	71.4	61.9	0.012
	Leukopenia	0.574 (0.428–0.720)		69.6	45.0	0.332
	Diarrhea	0.505 (0.347–0.663)		62.5	42.6	0.950

Abbreviations: AUC_{0-12h}, area under the curve from 0 to 12 hours; C_0, immediate pre-dose concentration; C_{max}, maximum (peak) concentration; CI, confidence interval; ROC, receiver operating characteristic.
Modified from Chen et al [69].
  * All adverse effects include leukopenia, diarrhea, and infection.

cutoffs of 2 mg/L, 10 mg/L, and 40 mg · h/L, respectively. The relative risks were 2.11 for C_0 and C_{max} and 1.67 for AUC. Further details are summarized in Table 2. Tredger et al [67] derived a C_0 cutoff of 2.25 mg/L for leukopenia (Fig. 1).

3.2.2. GI adverse effects

Brunet et al [68] showed significantly elevated mean MPA concentrations at 40 minutes postdose for 6 patients with diarrhea and/or nausea and vomiting compared with symptom-free patients (22.9 mg/L vs 7.4 mg/L). However, corresponding results for C_0, C_{max}, and AUC did not differ significantly [69] (Table 2). Tredger et al [67] also noted no significant association of MPA C_0 with GI adverse effects using ROC curve analysis, although the relative risk rose as MPA concentrations increased.

3.2.3. Infection

Infection is a generic problem associated with immuno-suppression and MPA may not impact similarly on immune responses to bacterial, viral, and fungal infections. Tredger et al [67] defined a C_0 cutoff of 2.85 mg/L using ROC curve analysis for all types of infection (Fig. 1). However, Chen et al [69] showed no significant difference in MPA concentration between those with infection and those without.

Despite reports of in vitro efficacy against hepatitis viral infection (hepatitis B virus [77], HCV [78] for review), corresponding benefits of MPA therapy did not translate to the clinical setting. Jain and colleagues [79,80] found no significant effect of MMF on patient, or graft survival and acute rejection rate or HCV recurrence in 106 patients transplanted for HCV cirrhosis. They hypothesized that either MPA has no antiviral actions or weak antiviral effects counteracted by its own or adjunctive immunosuppressant activity. Likewise, Zmonarski et al [81] in a small study found MMF to be associated with lower B-cell responses to cytomegalovirus, but interpretation of these data was complicated by the use of steroid boluses for antirejection therapy. The steroid-sparing study of Marubashi et al [15] discussed earlier highlights the importance of minimizing steroid use to reduce posttransplant (re)infection rates.

4. Pharmacokinetic data

There are wide variations in MPA concentrations reported with standard MMF dosing in liver transplant recipients. Corresponding studies on pharmacodynamic variability are rare [68]. A variable relationship of MPA concentration with dose, usually weak or sometimes absent, was noted by 66 to 68, 77, 80, and 81. In pediatric liver recipients, Aw et al [82] showed a modest correlation between MMF dose and AUC, but still reported a 9- to 14-fold range in measured C_0, C_{max}, and AUC. Hwang et al [70] reported the relationship between MMF dose and MPA C_0 varied with time posttransplant (coefficient of determination (r^2) = 0.15–0.51) and was weaker than that for TRL, especially in the first month. Sources of variation originate from the process of transplantation and endogenous mediators, pathology, and drug interactions (below). The extent of this variability itself supports the concept of MPA monitoring.

A number of studies have also examined whether drug exposure (AUC) can be accurately estimated from plasma concentrations at single time points. Modest correlations ($r > 0.74$) between C_0 and AUC have been demonstrated in small series of adult liver recipients during TRL coadministration [68,79] and pediatric liver recipients comedicated with TRL or CsA ($r^2 = 0.65$) [83]. In long-term liver transplant recipients, Mardigyan et al [84] described a closer, albeit still modest, correlation of C_2, C_3, and C_4 with MPA AUC ($r^2 = 0.73, 0.69,$ and $0.68,$ respectively) than for C_0 ($r^2 = 0.48$). A contrasting weak association between C_0 and AUC ($r^2 = 0.15$) was demonstrated in one larger adult series (n = 63) [69].

Pharmacokinetic and limited sampling strategies in heart transplant recipients (Table 3) showed that the best surrogate of AUC was C_{12} ($r^2 = 0.64$) in CsA-comedicated patients [88] and C_1 ($r^2 = 0.57$) [89], C_3 ($r^2 = 0.65$) [88], and C_4 ($r^2 = 0.86$) [84] in TRL-treated patients. The dose-adjusted MPA concentration and MPA C_0/AUC ratio were higher in SRL- than in CsA-treated patients ($P < .001$) [85]. In CsA-treated heart transplant patients, an MPA AUC less than

Table 3

Limited sample strategies to estimate the MPA AUC in thoracic transplantation

Organ and time post-Tx	n	Immunosuppression	AUC studied	Best single time point	Abbreviated AUC	Author (reference)
Heart >1 y	9	CsA + MMF	AUC_{0-12h}	C_6 ($r^2 = 0.60$)	–	Mardigyan et al [84]
Heart >1 y	9	TRL + MMF	AUC_{0-12h}	C_4 ($r^2 = 0.86$)	–	Mardigyan et al [84]
Heart >1 y	15	SRL + MMF	AUC_{0-4h}	C_{40} ($r^2 = 0.82$)	$C_0 + C_{40} + C_{120}$ ($r^2 = 0.79$)	Dösch et al [85]
Heart >1 y	47	SRL + MMF	AUC_{0-4h}	C_{75} and C_{120} ($r^2 = 0.64$)		Dösch et al [85]
Heart, first trimester	9	CsA + MMF	AUC_{0-12h}	–	$C_{1.25} + C_2 + C_4 + C_6$ ($r^2 = 0.948$); $C_{1.25} + C_2 + C_6$ ($r^2 = 0.926$)	Baraldo et al [86]
Lung >1 y	19	CsA + MMF (n = 9) TRL + MMF (n = 10)	AUC_{0-12h}	C_{10} ($r^2 = 0.91$)	$C_{0.3} + C_2$ ($r^2 = 0.83$); $C_0 + C_{0.6} + C_2$ ($r^2 = 0.87$)	Ting et al [87] 2006
Heart 9 mo	11	TRL + MMF	AUC_{0-12h}	C_3 ($r^2 = 0.65$)	$C_1 + C_2 + C_4$ ($r^2 = 0.73$)	Wada et al [88]
Heart 9 mo	11	CsA + MMF	AUC_{0-12h}	C_{12} ($r^2 = 0.64$)	$C_0 + C_1 + C_2$ ($r^2 = 0.96$)	Wada et al [88]
Heart >1 y	28	TRL + MMF	AUC_{0-12h}	C_1 ($r^2 = 0.57$)	$C_1 + C_4 + C_8 + C_{10}$ ($r^2 = 0.95$)	Kaczmarek et al [89]

AUC_{0-4h} indicates area under the curve from 0 to 4 hours; AUC_{0-12h}, area under the curve from 0 to 12 hours; C_x, plasma concentration at x minutes postdose; Tx, transplant.

40 mg · h/L MPA correlated with a C_0 of 1.6 mg/L ($r^2 = 0.36$, $P < .01$), whereas in SRL-treated patients, the corresponding MPA C_0 was 2.3 mg/L ($r^2 = 0.61$, $P < .01$) [85].

4.1. Transplant-related variables

4.1.1. Type of recipient and donor graft

Tsaroucha et al [90] compared MPA concentrations by type of transplant. In small bowel, liver, and renal recipients receiving MMF, TRL, and steroids, the mean MMF dose required per milligram per liter MPA C_0 was 210.8, 23.4, and 7.9 mg/kg, respectively. These substantially higher dose requirements in bowel recipients might also result from their younger age and shorter interval posttransplant (see below). Braun et al [91] also reported a mean MPA C_0 for liver recipients only 35% of that in kidney transplants.

Jain et al [92] described an impact of donor graft type with a 4-fold higher MPA AUC per 1 g MMF intravenously (IV) in recipients of liver grafts from living rather than deceased donors. A correspondingly lower AUC was noted for the major phenolic glucuronide metabolite (MPAG). The authors suggested that a reduced size living donor graft will have lower metabolizing capacity and reduced glucuronidation activity during regeneration.

4.1.2. Duration posttransplant

Dose-normalized MPA concentrations are also known to increase with duration after transplant. For example, Brunet et al [68] in 15 liver recipients on a standard 1-g twice-daily dose showed a median C_0 of 0.3 mg/L at day 10 and 1.4 mg/L by month 6 posttransplant. Contributing causes appear to be initial reductions in enterohepatic recirculation and bioavailability as well as an initial increase in the proportion of MPA not plasma protein bound (ie, free fraction or MPA$_{ff}$) leading to a temporary increased clearance that normalizes with time. Elevated concentrations of free drug were associated with increased MPA toxicity in a pancreas transplant recipient [93]. Jain and colleagues [28] reported a low bioavailability of MMF (mean, 48.5%, within 1 week of liver grafting). Restoring full bioavailability using IV MMF provided safe antirejection therapy in de novo liver transplantation and additionally conserved renal function [10]. Brunet et al [68] also used IV MMF initially to achieve target MPA concentrations, resuming oral therapy once full oral intake was achieved. Jain et al [79] and Benichou et al [94] showed wide ranges in MPA$_{ff}$ (0.2%–9.8%) within 1 month and at 12 days after liver transplantation, respectively. Pisupati et al [95] showed a progressive decrease in MPA$_{ff}$ from 4.3% to 2.9% to 1.9 % at less than 1 week, less than 2 weeks, and less than 1 month posttransplant, respectively. Benichou et al [94] showed that MPA$_{ff}$ correlated well with the clearance of orally administered MMF and fell significantly as plasma albumin concentrations in liver recipients rose. Free MPA concentrations did not change over time (from 12 to 867 days) after liver transplant. The same authors also showed that MPA$_{ff}$ correlated highly with MPA clearance, and this would be consistent with more

rapid hepatic and renal extraction, and subsequent biliary and urinary excretion. Parallel elevations in MPA$_{ff}$ early after hematopoietic stem cell transplantation have prompted MMF therapy at intravenous doses of 1.5 g 3 or 4 times a day and have provided successful treatment of graft vs host disease [7,96]. Further studies are required to demonstrate whether corresponding intensive therapy might provide successful prophylaxis against acute rejection in those solid organ graft recipients where MPA concentrations less than 1 mg/L otherwise persist early posttransplant.

Mycophenolate undergoes extensive enterohepatic recirculation after hydrolysis of its biliary MPAG conjugate by intestinal bacteria and reabsorption of MPA. Hesselink and Van Gelder [97] estimated that recirculation accounts for 10% to 61% of the MPA AUC. Both the proportion recirculated and systemic MPA concentrations fell markedly after treatment with oral antibiotics, which can eliminate gut flora, particularly after sterilization of the gut in liver transplantation and hematopoietic stem cell transplantation [98]. Recirculated MPA is sometimes evident as secondary peaks in plasma MPA concentrations at 6 to 10 hours postdose. "Trough" MPA samples must not be taken early (<12 hours postdose) for this reason. Secondary peaks are very rare in the initial period after liver transplantation but occur in approximately 50% of patients by 1 month [79,95]. Mycophenolic acid AUC increased approximately 3-fold during this period, the apparent oral clearance decreased and the percentage of the dose appearing in the urine as MPAG was halved, although glucuronidation capacity was unchanged [95]. Cyclosporine also decreased recirculated MPA concentrations [99] (see below), but this may not abolish the secondary (recirculated) MPA peak in pediatric liver recipients [100].

4.2. Endogenous mediators: pharmacogenomics, circadian rhythm, and ontogeny

Genetic polymorphisms in metabolism, circadian rhythm, and ontogeny also contribute to interindividual variability in pharmacokinetics, although the majority have been defined in renal transplant recipients. UDP-glucuronosyltransferase (UGT) 1A9 is the isoform catalyzing 55%, 75%, and 50% of MPAG production by the liver, kidney, and intestinal mucosa, respectively [101]. There is a 17-fold variation in expression of UGT1A9 mediated via polymorphisms in the promoter (T-275A and C-2152T) and coding region of the gene (T98C [UGT1A9*3]) [102,103]. The 2 promoter variants have been associated with high UGT activity and significantly lower MPA exposure after renal transplantation in a dose-dependent manner [104].

Polymorphisms in another UGT isoform, UGT2B7, are related to variability in the production of MPA acyl glucuronide (AcMPAG) [101] but seemingly only during SRL comedication. [105]. Additional variability originates from polymorphisms in the hepatic transporters, multiple drug-associated resistance protein 2 (MRP2, now known as

ABCC2) and particularly organic anion transporter protein 1B3 (OAT1B3). The common T334G polymorphism in the OATP1B3 gene *SLCO1B3* is associated with reduced MPAG uptake into cells transfected with the 334GG variant. Patients show increased circulating concentrations of MPAG and lower concentrations of MPA per gram of MMF dose in 334G homozygous or heterozygous carriers reflecting decreased MPA enterohepatic recirculation [106-108]. Again, variation appears comedication dependent, with Picard et al [108] showing an effect in renal transplant recipients receiving MMF with TRL or SRL but not CsA.

The UGT isoenzymes also exhibit changes in activity during the day and with age. Satoh et al [109] reported that MPA AUC during the day was 10% larger than at night. Filler et al [110] demonstrated that children younger than 2 years required twice the MMF dose of adolescents suggesting early enhanced UGT activity consistent with changes in drug metabolic activity described in childhood [111]. It is not clear whether a reduced size adult graft will assume its pediatric host's characteristics after transplantation.

4.3. Impact of bowel, liver, and renal dysfunction

Bowel dysfunction appears to reduce MPA absorption resulting in the widely noted low concentrations during episodes of diarrhea and after small bowel transplantation [90]. Liver dysfunction has complex effects on MPA kinetics, although cirrhosis affects neither MPA absorption nor MPA plasma protein binding or pharmacokinetics [112]. Brunet and colleagues [68] showed no correlation between liver function and MPA C_0 or AUC. However, in a series of 8 liver graft recipients, Jain and colleagues [79] reported that MPA AUC correlated with serum bilirubin and C_0 with albumin concentration. The former effect may relate to impaired hepatic MPAG production, transport, and biliary excretion during cholestasis [79,112] and results in increased urinary MPAG concentrations [79]. The latter correlation of MPA C_0 with albumin is in agreement with Chen et al [69]. Renal dysfunction impairs the excretion of MPAG in urine [113], and there appears to be some compensatory increase in biliary MPAG excretion [79]. Nonetheless, systemic MPAG concentrations rise and displace MPA from plasma albumin. This increases MPA_{ff} and MPA clearance in the short term, decreasing MPA total concentrations [114,115].

4.4. Drug interactions

Drug interactions with MPA affect its absorption, distribution, metabolism, and elimination. Much of the documented evidence emanates from studies in renal transplantation but is likely to apply to all solid organ transplantation. In brief, MPA enterohepatic recirculation appears to be reduced by cholestyramine [116] and oral antibiotics, especially ciprofloxacin, amoxicillin, clavulanic acid [117], norfloxacin, and metronidazole [118]. Borrows and colleagues [119] showed MPA C_0 fell by a mean of 46% within 3 days of starting antibiotics in renal graft recipients

but rebounded spontaneously to 79% of the original C_0 during 2 weeks of continuing therapy or completely normalized after 3 days of cessation. Pantoprazole (40 mg), a proton pump inhibitor, reduced both the rate and extent of MPA absorption in 22 stable heart transplant recipients [119]: mean C_{max} and AUC were 41% and 25% lower, respectively.

Cyclosporine inhibited the intrahepatic MPA transport into bile by MRP2 (ABCC2) and reduced MPA recirculation and MPA C_0 [120]. Mycophenolate mofetil dose requirements to achieve identical MPA C_0 were correspondingly greater with CsA than with TRL comedication (eg, 84 in pediatric liver recipients). Steroid taper caused MPA exposure to rise, probably via a diminishing induction of UGT enzymes [121]. A converse fall in MPA concentrations was achieved through rifampicin induction [104,122]. Valproate was shown to decrease MPA C_{max} and AUC in 3 patients [123]. Rosiglitazone was shown to increase MPA concentrations [124]. Perez et al [125] reported no interaction between valganciclovir and MPA in liver recipients, but acyclovir and ganciclovir may compete with MPAG for renal elimination [114]. A recent in vitro report suggests that *Ginkgo biloba* extracts may be inhibitors of intestinal UGTs at concentrations used commonly in herbal remedies for dementia and mental dysfunction [126], and in vivo confirmation of their potency is awaited.

4.5. EC-MPS pharmacokinetics

In common with findings in renal transplantation [127], the absorption of MPA after EC-MPS administration was erratic in both adult and pediatric liver graft recipients with a wide variation in AUC and often multiple peaks ([128], censored, unpublished data, respectively). For a single dose of EC-MPS in the 21 adults, there was a good correlation between AUC and individual time points at 5, 8, and 12 hours postdose ($P < .05$) [128] and no effect of CNI comedication. Equimolar doses of EC-MPS [128] and MMF [79] yielded similar AUC, t_{max}, C_0, and half-life values, but C_{max} was higher with EC-MPS. Bioequivalence of EC-MPS with MMF was also demonstrated in heart transplant recipients comedicated with CsA [129]. Corresponding studies in renal graft recipients converted from MMF showed a higher MPA C_0 with EC-MPS (2.40 vs 1.83 mg/L) [127], and de Winter et al [130] warned that estimation of MPA AUC_{0-12} with limited sampling strategies for EC-MPS was likely to result in biased and imprecise results.

5. Studies evaluating MPA monitoring

5.1. Suggested targets

It is important to point out that there are no randomized controlled trials to assess the benefit of therapeutic drug monitoring in nonrenal transplant. In liver transplantation, C_0 has predominated over abbreviated AUC as a monitoring technique, perhaps because of its practical benefits. Target ranges for both C_0 and AUC approximate those initially

defined in renal transplantation (1–3.5 mg/L and 30–60 mg · h/L, respectively) [131] and apply to the studies summarized in Table 1. Grasser et al [66] targeted greater than 1 mg/L MPA in 10 de novo liver recipients receiving a regimen including MMF for prophylaxis against rejection. Mild rejection was diagnosed in 3 patients and responded to increased immunosuppression. Adverse effects other than leukopenia were experienced when MPA C_0 rose above 2 mg/L. The same cutoff prevented acute rejection in the large cohort of 304 liver recipients treated with CNI and MMF by Hwang et al [70]. Tredger et al [67] analyzed greater than 2100 MPA C_0 concentrations in 230 (147 adults and 83 children) liver graft recipients largely receiving CNI and MMF at more than 3 months posttransplant. They obtained a normal range of 0.3 to 5.2 mg/L for MPA defined on the basis of 95% confidence intervals for those exhibiting no recognized adverse events. However, because of the significantly increased risk of rejection (at <1.0 mg/L) and adverse effects (at 3–4 mg/L), a therapeutic range of 1.0 to 3.5 mg/L was defined as providing the best combination of specificity and sensitivity. The same therapeutic range was verified by Hiwarkar et al [7] for use in HSCT. Jacobsen et al [132] noted a higher incidence of engraftment at MPA concentrations of greater than 1 mg/L also in HSCT. Mycophenolic acid C_0 concentrations were also significantly higher in the 52 liver recipients with adverse events described by Chen et al [69], whereas Hwang et al [70] associated serious infections with high MMF doses. In contrast, some authors have reported no distinction between MPA exposure and treatment outcomes. For example, Bilbao et al [32] and Orlando et al [33] showed no differences between MPA C_0 in those with and without acute rejection, whereas Reggiani and colleagues [16] showed no corresponding difference in MPA AUC, although all AUCs were less than 20 mg · h/L.

There is considerable debate in the therapeutic drug monitoring literature as to the ideal monitoring method for MPA, and a fuller discussion appears in the pharmacokinetics review in this issue. Good correlations (r) and coefficients of determination (r^2) between C_0 and AUC have been achieved in small series of adult liver recipients during TRL coadministration [69,79,133] and in pediatric liver recipients comedicated with TRL or CsA ($r^2 = 0.65$) [83]. In a larger series (n = 63), however, Chen et al [69] showed $r^2 = 0.154$ between AUC and C_0. A more significant relationship of AUC with C_8 ($r^2 = 0.82$) was apparent in adult liver recipients receiving TRL ($r^2 = 0.46$ for C_0) [84], and the authors suggested C_2 as a convenient monitoring time ($r^2 = 0.73$). In heart transplant recipients, the association between MPA C_0 and AUC was closer in SRL-treated ($r^2 = 0.61$) than in CsA-treated ($r^2 = 0.36$) patients [85], but correlations ranged from 0.01 to 0.69 in those comedicated with CsA and TRL [84,88].

5.2. Recent monitoring data

There are no long-term prospective studies of concentration-controlled vs fixed-dose prescribing of MMF in liver

transplantation, but a recent single-center study reported improved management of variable MPA pharmacokinetics using MPA monitoring with benefits to acute rejection (<10% incidence) and minimizing adverse effects [70]. Mycophenolic acid C_0 was monitored for 4 months during TRL/MMF therapy following basiliximab induction in 82 de novo liver recipients. The target therapeutic range was 1 to 2 mg/L, and MMF was stopped in patients where C_0 consistently failed to reach 0.5 mg/L after 1g MMF twice daily ("poor absorbers"). Serum albumin infusions were used to raise serum concentration to greater than 30 g/L and achieve therapeutic total MPA concentrations. An acute rejection incidence of less than 10% was achieved, and adverse effects associated with high MPA concentrations were controlled by MMF dose reductions [70].

5.3. Measuring MPA metabolites

The relationships of MPA metabolites to posttransplant outcomes are little studied. In an audit of MPAG concentrations during routine MPA monitoring, there was no discernable value beyond confirming the lack of drug in samples with undetectable concentrations of MPA (Brown et al, unpublished data). Mycophenolic acid acyl glucuronide has immunosuppressive activity [134] but showed low (<5%) cross-reactivity with the recombinant IMPDH assay [135] and appeared unimportant for the development of GI adverse effects [136]. It may be important in the development of drug-protein adducts [137], but the clinical significance of these is presently unknown.

5.4. Summary and recommendations

Based on the accumulative evidence presented above, it is clear that the literature lacks fixed-dose vs concentration-controlled trials to definitively support MPA monitoring in liver, heart, lung, bowel, or pancreas transplantation. However, such trials are unlikely to be performed now. On the basis of the other published work, there is strong evidence supporting interindividual pharmacokinetic variability of MPA in the order of 10-fold or more. There is also evidence from some larger cohort studies of associations of greater risk from acute rejection at lower and MPA-related adverse effects at higher MPA exposure: collectively, these suggest that acute rejection is more likely at concentrations less than 1 to 2 mg/L (μg/mL) and adverse effects at concentrations 3 to 4 mg/L or greater. Therapeutic MPA concentrations should be targeted between these limits. However, studies involving smaller numbers of patients do show variable results. Successful clinical management was facilitated when targeting C_0 between these limits in one large cohort of liver recipients [70]. Generally, the evidence using MPA C_0 is stronger than for AUC monitoring in liver / bowel/pancreas transplantation. There is insufficient evidence to make recommendations for monitoring MPA during EC-MPS therapy.

On this basis, we propose that specialists consider monitoring MPA C_0 (or AUC) early after introduction of MMF and regularly until the required stable exposure is achieved at a constant appropriate dosage. Where these suggestions are adopted, samples for routine MPA monitoring should be separated within 12 hours of collection to minimize instability and the plasma stored at 4°C or lower before analysis [138]. Subsequently, it is suggested [6] that MPA is monitored when there is

- an acute or chronic deterioration in graft function;
- a change in renal, liver, or bowel dysfunction (including diarrhea);
- a substantial or progressive change in serum albumin concentration;
- a clinically indicated change in the type or dose of CNI;
- MMF monotherapy or MMF use as the main immunosuppressant supplemented by low-dose TRL, CsA, or SRL (with or without corticosteroids); and
- a change in the exposure to other interacting medications, in particular oral antibiotics, proton pump inhibitors and rifampicin;
- a change in the brand or formulation of MMF prescribed.

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