Review

Optimizing Mycophenolic Acid Exposure in Kidney Transplant Recipients: Time for Target Concentration Intervention

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Abstract. The immunosuppressive agent mycophenolate is used extensively in kidney transplantation, yet dosing strategy applied varies markedly from fixed dosing ("one-dose-fits-all"), to mycophenolic acid (MPA) trough concentration monitoring, to dose optimization to an MPA exposure target (as area under the concentration-time curve [MPA AUC_{0-12}]). This relates in part to inconsistent results in prospective trials of concentration-controlled dosing (CCD). In this review, the totality of evidence supporting mycophenolate CCD is examined: pharmacological characteristics, observational data linking exposure to efficacy and toxicities, and randomized controlled trials of CCD, with attention to dose optimization method and exposure achieved. Fixed dosing of mycophenolate consistently leads to underexposure associated with rejection, as well as overexposure associated with toxicities. When CCD is driven by pharmacokinetic calculation to a target concentration (target concentration intervention), MPA exposure is successfully controlled and clinical benefits are seen. There remains a need for consensus on practical aspects of mycophenolate target concentration intervention in contemporary tacrolimus-containing regimens and future research to define maintenance phase exposure targets. However, given ongoing consequences of both overimmunosuppression and underimmunosuppression in kidney transplantation, impacting short- and long-term outcomes, these should be a priority. The imprecise "one-dose-fits-all" approach should be replaced by the clinically proven MPA target concentration strategy.

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INTRODUCTION

Graft Loss and Mortality

Outcomes from kidney transplantation remain suboptimal.[1-3] Effective immunosuppressive drugs, along with attention to cardiovascular disease[4] and prophylaxis against infection,[5] have significantly reduced rates of acute rejection (15.4%), graft loss (3.6%), and death (2.8%) in the first posttransplant year for standard risk recipients.[6] However, time to allograft failure remains substantially shorter than typical recipient life expectancy following transplantation, due largely to chronic antibody-mediated rejection.[7-10] Approximately 20% of kidney allograft

recipients have returned to dialysis 5 years after transplantation, increasing to around 50% after 15 years.[11-13] At the same time, drug toxicities remain an important cause of morbidity and mortality from cardiovascular,[14] infectious,[15] and malignant[16,17] diseases.

Immunosuppression and MPA

Immunosuppressant dosing aims for a sufficient biological drug effect to prevent rejection, while minimizing dose-dependent toxicities. Precision dosing requires an understanding of between-subject variability in both the pharmacokinetics (PK) and pharmacodynamics (PD) of the immunosuppressant agents.[18-21]

For all drugs, concentration at site of action (the "biophase") is more directly linked to drug effect than dose.[19,22] For certain drugs, concentrations vary widely between individuals on fixed dosing (FD), due primarily to differences in the extent of absorption (bioavailability) and rate of elimination (drug clearance). If FD leaves an unacceptable proportion of individuals outside the range of safe and effective concentrations,[23] then dosing to a therapeutic range (therapeutic drug monitoring [TDM]) or a target concentration (target concentration intervention [TCI])[24,25] has the potential to both maximize the beneficial effect and minimize toxicities (see Figure 1).

Mycophenolate mofetil (MMF) was initially marketed as a "one-dose-suits-all" drug, despite evidence obtained during drug development supporting concentration-controlled dosing (CCD).[26] It displays wide between-subject variability in PK,[27,28] leading to an over 10-fold range in mycophenolic acid (MPA) exposure (area under the total MPA concentration-time curve from 0 to 12 h [$AUCt_{0-12}$]) with mycophenolate FD. This ranges from <10 to >100 mg/L.h,[29] well beyond the widely proposed therapeutic range of 30–60 mg/L.h.[28-33]

Two randomized controlled trials (RCTs) of CCD in kidney transplantation have demonstrated substantially reduced graft rejection when doses are individualized to
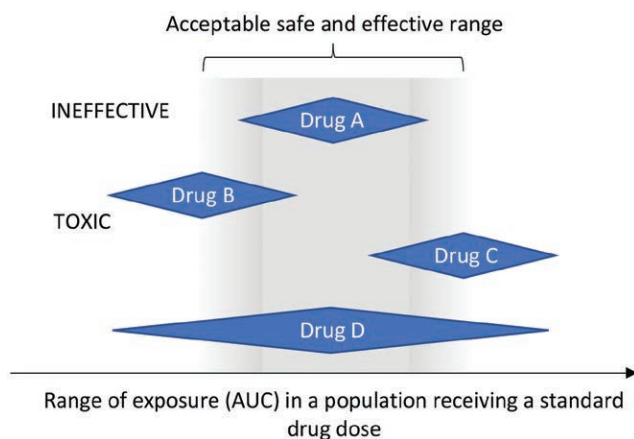
FIGURE 1. An explanation of how drug dosing decisions can be made by examining the relationship between drug exposure (AUC) at a fixed dose and the acceptable range for safe and effective exposure. Drug A can use fixed dosing, as this gives acceptable drug exposure in all. Drug B is being dosed too low—the population dose should be increased. Drug C is being dosed too high—the population dose should be decreased. Drug D shows both overexposure and underexposure on a fixed dose. Some form of dose optimization is required. AUC, area under the concentration-time curve.

a target MPA $AUCt_{0-12}$.[26,34,35] However, 2 decades and numerous publications later, the benefit of CCD over FD remains contentious.[29,36-40] Critically, the 2 largest RCTs, "fixed-dose concentration-controlled trial (FDCC)" and "Opticept," failed to significantly differentiate MPA exposure between treatment arms.[31,41]

To establish a role for CCD, it must first be shown that a measure of systemic exposure is associated with clinical outcomes. Biophase concentrations are rarely available in clinical practice; hence, easily accessible concentrations (eg, blood) are used as surrogate. Depending on the exposure metric (eg, trough or AUC), the matrices (eg, whole blood, plasma, or protein-free plasma for unbound concentrations), and the time-course of drug effect,[19] measured concentrations may or may not predict outcomes. The pharmacokinetic-pharmacodynamic (PKPD) characteristics of MPA,[30] including enterohepatic cycling (EHC),[42] high protein binding,[43,44] and presumed local gut toxicity,[45] may have complicated assessment of the exposure-effect relationship.

For example, although trough concentrations are considered sufficiently well correlated with AUC for many therapeutic drugs,[46,47] the relationship between trough and AUC for MPA is less precise.[48,49] The use of MPA trough concentrations in clinical care is contentious.[30,33,49-51] Despite this, reviews examining the MPA exposure-effect relationship have not distinguished exposure derived from trough concentrations versus AUC_{0-12}. This has likely diluted the relationship between exposure and effect.

Drug concentrations are almost always measured as "total concentration," the sum of unbound drug and drug bound to plasma proteins. However, it is the unbound concentration that is the "effective" concentration, as only an unbound drug can equilibrate across cellular membranes.[43,44,52] While the relationship between unbound and total MPA concentrations is linear in normal physiological states, this is not the case in certain settings, including hypoalbuminemia or severe renal impairment.[33,53]

If an association between a measure of exposure and drug response is shown, the next question is whether using drug concentration to individualize dose, CCD, improves outcomes. Gold standard is the randomized concentration-controlled trial (RCCT), where participants are randomized to 2 or more treatment arms based on target concentration (or exposure) rather than dose size.[24,54-56] This removes confounding influence between PK and PD characteristics[55,56] and allows direct comparison of different exposure targets.

Attention should be drawn to the 2 different methods for CCD: TDM or TCI.[24,25] The concentration-effect relationship is typically monotonic and continuous, approaching an asymptote of maximal effect (Figure 2, curve for beneficial effect).[23,25] For a drug to be clinically useful, the beneficial effect needs to occur at lower concentrations than unacceptable toxicities (Figure 2, toxicity curves). The TDM approach uses a "therapeutic window," a range of concentrations between ineffectiveness and toxicity. However, this entails a false categorization of a continuous covariate (drug concentration) into "subtherapeutic," "therapeutic," and "toxic." Clear thresholds between these 3 categories do not exist,[25] and drug response (both beneficial and toxic) is not the same at the bottom as at the top of such a window (Figure 2). In contrast, the TCI approach targets a specific concentration.[25]
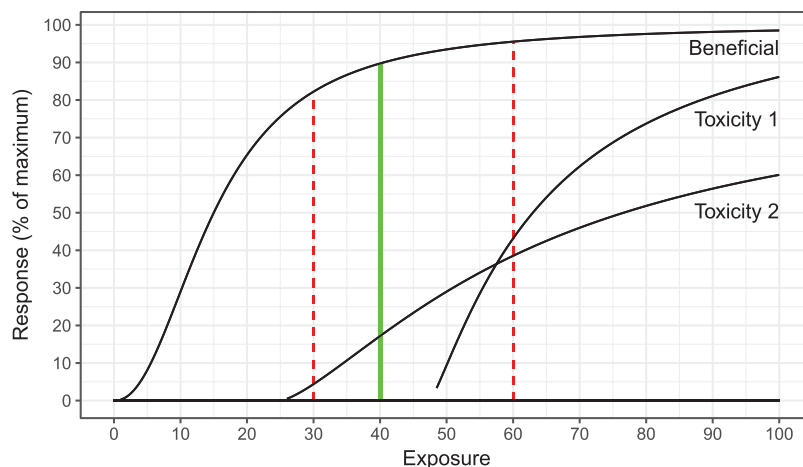
FIGURE 2. Schematic diagram of exposure-effect relationships for hypothetical "DRUG X," with exposure-response curves for benefit (reduction in rejection from the baseline rate), toxicity 1 (infectious risk, including opportunistic), and toxicity 2 (suppression of hematopoeisis). Magnitude of response and likelihood and magnitude of toxicities increase with increasing exposure. From the bottom to the top of the therapeutic range (dashed red lines, 30–60 units), magnitude of beneficial response increases, as do toxicities. The optimal balance of efficacy and toxicities is seen at 40 units (optimal target exposure).

There are 2 distinct advantages to TCI.[24,25,57] First, it promotes determination of the optimal point of balance between benefit and toxicity, a more precise goal consistent with the concentration-effect relationship. Second, the required dose can be calculated directly from the target concentration and clearance.[24] This could be by proportional dose adjustment from an estimate of AUC or by maximum a posteriori Bayesian estimation (MAPBE).[58-61] The latter involves estimation of an individual's PK characteristics using a limited sample of concentrations and a population PK model (Bayesian prior).[20,62]

Given controversies regarding the benefit of CCD, and an ongoing need to improve immunosuppressant precision in kidney transplantation,[2] a systematic literature review was performed. The aim was to provide an updated perspective on the MPA concentration-effect relationship and a critical analysis of exposure and effectiveness in the RCTs of CCD.

Literature Review Methodology

A systematic literature search was undertaken to identify studies in kidney transplant recipients:

1. Assessing the relationship between MPA exposure and beneficial effects.
2. Assessing the relationship between MPA exposure and toxicities.
3. Assessing benefit of mycophenolate CCD by RCT.

To assess the exposure-effect relationships, only studies using estimates of MPA AUC_{0-12} were included. This was to clarify the strength of association based upon the more reliable measure of drug exposure. MPA AUC_{0-12} is estimated by full PK profiling (numerous samples over the entire dosing interval), or from a more limited number of samples (limited sampling strategy [LSS]), using multilinear regression equation[49] or MAPBE.[60]

For studies involving MMF, estimates of MPA $AUCt_{0-12}$ were included whatever the method. In contrast, for studies involving mycophenolate sodium, only prolonged sampling profiles were included (to at least 8 h postdose), as shorter LSS' have not been shown to adequately predict exposure[63,64] due to slow absorption of mycophenolate sodium.

For outcomes, the relationship between MPA $AUCt_{0-12}$ and rejection, hematological toxicity and infection were assessed. The relationship between MPA $AUCt_{0-12}$ and gastrointestinal toxicities was not examined as the mechanism is thought due to direct toxicity from MPA metabolites in the gut via EHC,[45,65,66] thus indirectly linked to plasma MPA concentrations.

Due to low patient numbers without prespecified power calculation in a significant number of studies, the likelihood of type II errors, particularly for toxicities,[67] was considered high. Thus, in addition to reporting the number of articles where statistical significance was met ($P < 0.05$), the number showing an association or trend was reported. While it might be argued that these articles do not meet sufficient statistical standards, it would be erroneous to suggest that they support the null hypothesis of no association.

Studies were examined altogether, and after separation into concurrent calcineurin inhibitor (CNI) usage (if >75% use of specific agent by cohort or if separate data given). This is because concurrent CNI impacts MPA exposure.[31] Cyclosporine inhibits the EHC of MPA, reducing dose-normalized MPA exposure, particularly in the initial posttransplant period with high cyclosporine concentrations.[31,68,69] When tacrolimus is used, the initial reduction in dose-normalized exposure is less, while MPA $AUCt_{0-12}$ above 60 mg/L.h is more common.[31,70-72]

Electronic databases were searched up to January 25, 2019. Medline (Ovid) and Embase (Ovid) databases were searched using the following thesaurus or keywords:

Population: "kidney transplantation";
Intervention: "mycophenol*," "pharmaco*," "drug monitoring";
Outcomes: "drug effects," "rejection," "survival," "mortality" or "survival rate," "severity of illness index," "treatment outcome or treatment failure," "infection," "anemia," "leucopenia," "lymphopenia/lymphocytopenia/lymphocyte depletion," "diarrhea," "IMP dehydrogenase," and "adverse outcome."

In addition, PubMed was searched using keywords "mycophenol*" and "transplant*," from 2013 onward, to identify e-pubs not yet indexed in Medline. Results were

limited to the English language and merged with the references from Staatz and Tett.[66,73] Finally, additional references were sourced through searching of reference lists of relevant retrieved articles.

Duplicate entries were identified and removed. Remaining articles were then screened for relevancy, first through perusing of their title and abstract, then if these appeared suitable, through a full-text examination.

RESULTS

A total of 6029 unique articles were identified through the literature search. This was reduced by title review to 476 articles and by abstract review to 104 articles. Following full-text review, a total of 36 publications were identified as appropriate and included in the systemic review.

Evidence for an Exposure-response Relationship for Reduction of Acute Rejection

Twenty-seven cohorts were identified that assessed the relationship between MPA $AUCt_{0-12}$ and rejection, comprising 3794 individuals. Study features and findings are summarized in Table 1.

A statistically significant relationship between MPA $AUCt_{0-12}$ and rejection was evident in 20 of the 27 cohorts (comprising 3382 of 3794 individuals, 89.1%).[26,31,35,41,74,77-79,81,83-87,89,91-93,95-98] An additional 3 studies showed a trend in favor of this association (5.7% of individuals),[80,90,94] leaving only 4 cohorts (5.1% of individuals) without association.[75,76,82]

For cyclosporine cotreated transplant recipients, 12 of 16 cohorts (comprising 1181 of 1518 individuals, 77.8%) reported a statistically significant association between MPA exposure and acute rejection.[26,35,74,77-79,81,83,86,87,92,95,96] Of the remaining 4, 2 (18.1% of individuals) reported a trend between MPA exposure and acute rejection.[89,90] Only 2 cohorts reported no relationship (4.2% of individuals).[76,82] One of these negative cohorts involved 31 recipients receiving antithymocyte globulin, a lymphocyte-depleting agent with more potent immunosuppressive effects. Rejection occurred in 4 of 31 participants (12.9%), 3 of the 4 having a lower MPA $AUCt_{0-12}$ than those without rejection (without application of a statistical test) following dose reduction for leukopenia.[76]

For tacrolimus cotreated transplant recipients, 7 of 11 cohorts (comprising 1373 of 1696 individuals, 81.0%) revealed a statistically significant association.[41,85,89,91,93,97,98] Two further cohorts reported a trend (11.9% of individuals).[80,94] This left 2 cohorts (7.2% of individuals).[75,88] One reported twice the rate of AR with MPA $AUCt_{0-12}$ below 70 mg/L.h, without application of a statistical test.[88] The other involved 51 transplant recipients (2.7% of individuals) who received high target tacrolimus concentrations by today's standards: 10–20 ng/mL in the initial 2 weeks and then 5–15 ng/mL thereafter.[75] Rejection occurred in 3 of 51 recipients (5.8%), with no relationship to MPA exposure.

Evidence for an Exposure-response Relation for Reduction of Immunosuppressant Toxicity

Twenty-two cohorts involving 3225 kidney transplant recipients were identified that assessed the relationship between MPA $AUCt_{0-12}$ and hematological or infectious toxicities. Study features and findings are summarized in Table 2.

Only 9 of 22 cohorts reported a statistically significant association between MPA exposure and toxicities, comprising 1097 individuals (34.0% of the 3225 individuals).[75,76,80,91,92,94,99,102,104,105] A further 2 cohorts (3.1% of individuals) supported a trend towards this association.[74,84] Eleven of 22 cohorts (62.9% of individuals) reported no association.[26,31,34,35,78,79,81,82,96,100,101,103]

In cyclosporine cotreated cohorts, only 2 of 11 studies reported a statistically significant association between exposure and toxicities (comprising 9.1% of 1065 individuals),[76,92] along with a trend in 1 study (3.0% of individuals).[74]

However, the association was far more consistent in cohorts cotreated with tacrolimus (6 relevant cohorts involving 502 individuals). A statistically significant association was reported in 5 of the 6 cohorts (comprising 481 of 502 individuals, 95.8%).[75,80,91,94,99,105] There was just 1 cohort that did not report any relationship with toxicities (4.2% of individuals).[100]

There were 3 publications where unbound MPA concentrations were measured alongside total drug concentrations,[79,82,102] comprising 375 individuals. All 3 reported a statistically significant association between unbound exposure (MPA $AUCu_{0-12}$) and toxicities. Of these, 2 of the 3 studies concurrently failed to show an association between total concentrations (MPA $AUCt_{0-12}$) and toxicities.[79,82]

Evidence for CCD and Improved Clinical Outcome

Five RCTs of mycophenolate CCD were identified. Study features and findings are summarized in Table 3.

All used the MMF formulation. Three used a TCI strategy: the multitarget RCCT published in 1998,[26,34] "APOMYGRE" published in 2007,[35] and "OPERA" published in 2011.[106] Two used a TDM strategy: the FDCC, published in 2008[31] and "Opticept" published in 2009.[41]

MPA Dose Individualization Using TCI

All 3 TCI trials optimized mycophenolate dose using MAPBE. Two showed a statistically significant and clinically important benefit. A third trial, with 2 distinct interventions in the treatment arm, neither supported nor refuted benefit of TCI.

Multitarget RCCT

The first trial[26,34] was the only RCCT, with more than one target-exposure arm.[55] One hundred and fifty recipients were randomized to 3 separate target MPA $AUCt_{0-12}$ arms: 16.1 mg/L.h (low target), 32.2 mg/L.h (medium target), or 60.6 mg/L.h (high target). Though concentration targets were exceeded in later posttransplant periods (due to so-called "time-dependant clearance"),[68,69] the trial was successful in separating treatment arms into 3 distinct MPA exposure groups (see Figure 1, trial publication).[26] In each arm, within-group PK variability was reduced from 40%–50% to almost 30%.[26]

The primary end point, biopsy-proven acute rejection (BPAR) at 6 months, was less frequent with increasing exposure target: 27.5%, 14.9%, and 11.5% in low, medium, and high AUC target arms ($P = 0.043$, low versus medium/high target groups)[34] The requirement for treatment with muromonab-CD3 or antithymocyte globulin (reflecting more severe rejection) also numerically

TABLE 1.

A summary of studies that have examined the relationship between MPA exposure and beneficial outcomes

Reference	Population	Concurrent therapy	Daily dose MPA	Effect metric	Exposure method
Takahashi et al[74]	32 Adults, first grafts, living or deceased donor	No induction CsA Steroids	1–3.5 g	Immunosuppressive effects (freedom from rejection) shown in patients with MPA $AUCt_{0-12}$ >40 mg/L.h Strong association between MPA $AUCt_{0-12}$ and BPAR, $P < 0.001$.	12 h AUC at 1, 2, and 3 wk
Hale et al[26] and van Gelder et al[34]	150 Adults, first or second graft, deceased donor	No induction CsA Steroids	TCI	90% efficacy at an MPA $AUCt_{0-12}$ of 40 mg/L.h BPAR 27.5%, 14.9%, and 11.5% in low, medium, and high target groups ($P = 0.043$, low vs medium/high target). Strong association between MPA $AUCt_{0-12}$ and BPAR, $P < 0.0001$	12 h AUC days 3, 7, and 11, then 2 h LSS with MAPBE of full AUC days 21 and 28, then 4 weekly
Mourad et al[75]	51 Adults, deceased donor	No induction Tac Steroids	1 g	Significant association not seen Rejection in 3/51 participants (5.8%). High tacrolimus concentration target (C_0 10–20 ng/mL initial 2 wk, then 5–15 ng/mL)	12 h AUC at 2 wk, 3 mo, and for cause
Mourad et al[76]	31 adults, deceased donor (living donor N = 3)	ATG CsA Steroids	2 g	Significant association not seen Rejection in 4/31 participants (12.9%), of whom 3/4 had numerically lower MPA $AUCt_{0-12}$ than nonrejectors after dose reduction for leukopenia	12 h AUC at 2 wk, 3 mo, and for cause
Pillans et al[77]	27 Adults	No induction CsA Steroids	2 g	MPA $AUCt_{0-12}$ <30 mg/L.h associated with twice the rejection rate (4/14, 29%, compared to 8/13, 62%) Significant difference in MPA $AUCt_{0-12}$ between nonrejectors (35.1 ± 2.18 mg.L/h) and rejectors (27.6 ± 1.98 mg.h/L), $P = 0.02$	6 h AUC on days 3–5
Cattaneo et al[78]	46 Adults, first deceased donor graft	No induction CsA Steroids	2 g	Higher CrCl at 6–9 mo after transplantation if MPA $AUCt_{0-12}$ >40 mg/L.h: 85.7 mL/min (± 23.2) vs 64.5 mL/min (± 17.5), $P < 0.05$, with significant correlation between MPA $AUCt_{0-12}$ and CrCl ($P < 0.01$)	Estimated full AUC from 2 h LSS (MLR equation), at 6–9 mo after transplantation
Weber et al[79]	54 Children, first or second graft, living or deceased donor	No induction CsA Steroids	600 mg/m²	Best ROC threshold 33.8 mg/L.h, relative risk BPAR 41% if below, 14% if above. MPA $AUCt_{0-12}$ strong discriminator for AR, $P = 0.009$	12 h AUC days 7 and 21, 3 mo, and 6 mo
Kuypers et al[80]	100 Adults, first or second graft, deceased donor, excluded if CIT > 36 h or DCD donor	IL2RB (31%) Tac Late steroid withdrawal	1–2 g	For thresholds of MPA $AUCt_{0-12}$ = 45 mg/L.h and Tac $AUCt_{0-12}$ = 150 ng/mL.h, BPAR seen in 7.7%, 15%, 18.2%, and 26.3% ($P = 0.09$), for groups with (1) both drugs above threshold, (2) Tac below threshold, (3) MPA below threshold, and (4) both below threshold respectively ($P = 0.09$ across the four cohorts, $P = 0.07$ for dual above vs dual below threshold)	12 h AUC LSS day 7, 4 h LSS at 3, 6, and 12 mo, 2 h LSS at 6 wk (MLR equations)
Kiberd et al[81]	94 Adults, first graft	IL2RB (76.6%) CsA Steroids	2 g	Optimal ROC threshold for rejection = MPA $AUCt_{0-12}$ 22 mg/L.h (24.9 mg/L.h if IL2RB used) Strong association between MPA $AUCt_{0-12}$ on day 3 ($P = 0.007$), or average days 3, 5, and 7 and rejection.	Estimated full AUC from 4 h LSS on days 3, 5, and 7 (MLR equation)
Atcheson et al[82]	42 Adults Tac used in participants with higher PRA (N = 10)	IL2RB CsA (76%) Steroids	2 g	Significant association not seen	6 h AUC on day 5

TABLE 1. (Continued)

Reference	Population	Concurrent therapy	Daily dose MPA	Effect metric	Exposure method
Hazzan et al[83]	108 Adults, first deceased donor graft, PRA <30%, no AR during first 3 m; randomized at 3 m to MPA or CsA withdrawal (N = 54)	ATG CsA Steroids	2 g	In CsA withdrawal group: odds ratio AR based on MPA $AUCt_{0-12}$ at 3 mo, by Cox multivariate analysis, 0.89 (0.82 to 0.99) per 5 mg/L.h, $P = 0.028$. For entire group, odds ratio 0.79 (0.64 to 0.98) per 5 mg/L.h, $P = 0.033$ If BPAR/SCAR and an MPA $AUCt_{0-12}$ >50 mg/L.h observed at 3 mo (dose not adjusted prior), CsA or MPA withdrawal appeared safer	12 h AUC at 3 mo
Okamoto et al[84]	67 Adults, living donor (deceased donor N = 2)	IL2RB (37.3%) CsA (52%) Steroids	TDM	Significantly higher MPA $AUCt_{0-9}$ in those free of rejection, $P = 0.04085$	9 h AUC at 2 and 4 wk
Satoh et al[85]	30 Adults first graft, living donor, no DGF	No induction Tac (initial target 15–20 ng/mL) Steroids	2 g	MPA $AUCt_{0-12}$ <40 mg/L.h in 71.4% of rejectors vs 26.1% of nonrejectors. Risk ratio for acute rejection 1.06 (1.01–1.11, $P = 0.04$) for daytime MPA $AUCt_{0-12}$ and 1.09 (1.01–1.18, $P = 0.021$) for nighttime MPA AUC_{0-12}.	12 h AUC on day 28
Kuriata-Kordek et al[86]	26 Adults, deceased donor grafts	No induction CsA Steroids	Not stated	MPA $AUCt_{0-4}$ <20 mg/L.h associated with increased risk rejection. Significantly higher MPA $AUCt_{0-4}$ in nonrejectors, mean (SD) 11.4 ± 7.23 mg/L.h vs 34 ± 26.8 mg/L.h, $P = 0.01$	4 h AUC
Pawinski et al[87]	51 Adults	No induction CsA Steroids	2 g	MPA $AUCt_{0-12}$ of 24.1 mg/L.h 77.8% sensitivity and 91.7% specificity for discriminating rejectors from nonrejectors	Estimated AUC from 2 h LSS (MLR equation) at 1 wk and 2 mo and 3 mo
Le Meur et al[35]	137 Adults first or second graft, exclusion PRA >50%	IL2RB CsA Late steroid withdrawal	2 g or TDM	Of 10 rejection episodes in first 3 mo, 7/10 associated with MPA $AUCt_{0-12}$ <30 mg/L.h, 3/10 associated with MPA $AUCt_{0-12}$ 30-45 mg/L.h, none with MPA $AUCt_{0-12}$ >45 mg/L.h.	Estimated AUC from 3 h LSS using MAPBE, days 7, 14, and months 1, 3, 6, and 12
Kagaya et al[88]	71 Adults, first living donor graft	No induction Tac Steroids	1–2 g	Significant association not reported. Acute rejection rate 33% with MPA $AUCt_{0-12}$ <70 mg/L.h vs 13%–17% if MPA $AUCt_{0-12}$ >70 mg/L.h (no statistical test performed).	12 h AUC on day 28
van Gelder et al[31,89]	901 (839 Adults and 62 children), living or deceased donor. Exclusion PRA >50% within 6 mo, CIT >48 h. "High-risk" subpopulation, one or more of: DGF, second or third graft, PRA >15%, >3 HLA mismatches, or African descent	Induction (46.4%) CsA (54.2%) Steroids	2 g or 600 mg/m^2 or TDM	Day 3 MPA AUC_{0-12} <30 mg/L.h identified 79% of individuals suffering BPAR in the following 3 mo; associated with BPAR at mo 1 ($P = 0.009$) and mo 12 ($P = 0.006$). Low MPA $AUCt_{0-12}$ on day 10 showed trend to increased BPAR in the first mo ($P = 0.0655$). For entire cohort, higher BPAR in those with a day 3 MPA $AUCt_{0-12}$ <30 mg/L.h (18.8% vs 13.3%, $P = 0.018$). For tacrolimus cohort, substantially higher BPAR in "high-risk" individuals with MPA $AUCt_{0-12}$ <30 mg/L.h on day 3 (23.9% vs 10.4%, $P = 0.012$), while MPA $AUCt_{0-12}$ not associated with BPAR in low-risk individuals. Excluding DGF from the "high-risk" tacrolimus cohort, significance remained: 14.2% vs 5.5%, $P = 0.017$.	Estimated AUC from 2 h LSS (MLR equation) on days 3 and 10, wk 4, and mo 3, 6, and 12

TABLE 1. (Continued)

Reference	Population	Concurrent therapy	Daily dose MPA	Effect metric	Exposure method
Gaston et al[41]	720 Adults, first or second, living donor or deceased donor graft	ATG (43%) and IL2RB (32%) Tac (81.9%) Steroids	2 g or 600 mg/m² or TDM	For tacrolimus subgroup (N = 590): Low MPA trough associated with time to BPAR, risk ratio 0.322 ($P < 0.0001$) and risk ratio 0.390 ($P < 0.0001$), 6 and 12 mo, respectively. Optimal cutoff ≥1.6 µg/mL by ROC analysis. Low MPA $AUCt_{0-12}$ also associated with BPAR at 6 mo ($P < 0.0002$) and 12 mo ($P < 0.0001$). Not tested for CsA subgroup (too small).	Estimated AUC from 3 h LSS on days 3, 10, and 30 and mo 3, 6, and 12
Kuypers et al[90]	16 Adults, CsA withdrawal arm of CEASER trial, first grafts, excluded if depleting induction, CIT >30 h, PRA >20% within 6 mo	ILR2B CsA late withdrawal (6 m) Steroids	2 g	In the cohort with cyclosporine withdrawal at 6 mo for whom PK data were available (N = 16), no rejection in those with day 7 MPA AUC_{0-12} > 44.2 mg/L.h	12 h AUC on day 7 and mo 3, 7, and 12
Gourishankar et al[91]	126 Adult, deceased or non-HLA-identical living donor graft, excluded if CIT >30 h, PRA >25% within 6 mo, polyclonal anti-T-cell therapy	IL2RB (85%) Tac Steroids	2 g or initial 3 g for 5 d, then 2 g	Lower rejection with day 5 MPA $AUCt_{0-12}$ >30 mg/L.h (15.5% vs 50%, $P = 0.0047$). Significant difference in rejection-free survival remained with exclusion of suspected and borderline AR cases ($P = 0.0002$, log-rank test of Kaplan-Meier survival distributions)	12 h AUC days 3 and 5
Sommerer et al[92]	66 adults, eGFR >20	IL2RB CsA Steroids	720–2880 mg (MPS)	MPA $AUCt_{0-12}$ lower in those with acute rejection episodes [median 28 mg/L.h (7–45) vs 40 mg/L.h (16–130), $P < 0.01$]. Significance remained in multivariable regression that included other PK (dose, Cmax) and PD (IMPDH enzyme activity curve) parameters.	12 h AUC, 1 profile per patient, day 14 (10–56) posttransplant
Barraclough et al[93]	120 adults, living or deceased donor	IL2RB Tac Steroids	2 g	Median (IQR) day 4 MPA $AUCt_{0-12}$ lower in rejecters: 19.6 mg/L.h (17.1, 27.1) vs 31.1 mg/L.h (24.6, 41.3), $P = 0.004$. Optimal ROC cutoff for predicting rejection 23 mg/L.h (sensitivity 80%, specificity 75%). By multivariable regression (including adjustment for DGF), a 0.2 change in odds of rejection for a 12.2 mg/L.h (SD) increase in MPA $AUCt_{0-12}$ ($P = 0.04$).	Estimated AUC from 4 h LSS (MLR equation) on day 4 and mo 1
Fu et al[94]	183 Adults, living related donor grafts, PRA <10%. First graft in 99%, >80% had 1–3 HLA mismatches.	No induction Tac Steroids	TDM vs FD (nonrandomized)	In TDM group, rejection in 8/101 (7.9%). MPA $AUCt_{0-12}$ <30 mg/L.h in 3/8 with rejection, and 30–40 mg/L.h in 5/8 with rejection. No rejection seen in those with MPA $AUCt_{0-12}$ >40	Estimated AUC from 4 h LSS (MLR equation) on days 3, 7, 14, and 30
Daher Abdi et al[95,96]	490 Adults, pooled from APOMYGERE (N = 128, first or second graft, PRA <50%), OPERA (N = 221, first graft, recent PRA 0%, CIT <36 h) and routine care (N = 141)	IL2RB (minority Thymo) CsA (79.6%) Late steroid withdrawal (most)	2 g or TDM	Optimal "threshold" MPA $AUCt_{0-12}$ >35 mg/L.h in the first days, increasing to >41 mg/L.h by 6 mo. Strong association MPA $AUCt_{0-12}$ and rejection, $P = 0.0081$. Subsequently followed to 2 y (N=222, 57.5% CsA and 42.5% Tac), significant association shown between MPA exposure and the composite of acute rejection, graft loss, and death.	Estimated AUC from 3 h LSS using MAPBE on days 7 and 14 and mo 1, 3, 6, and 12

Reference	Population	Concurrent therapy	Daily dose MPA	Effect metric	Exposure method
Ding et al[97]	58 Adults, expanded criteria deceased donor grafts	ATG induction Tacro Steroids	1440 mg/d (MPS)	On multivariable regression analysis, odds ratio for BPAR was 0.842 (95% CI, 0.784 to 0.903, $P = 0.021$) if MPA $AUCt_{0-12}$ at 1 wk $\geq$30 mg/L.h vs <30 mg/L.h	Full PK profile at wk 1 and mo 1
Peng et al[98]	209 Adults, first graft, deceased donation after circulatory death. Excluded if PRA $\geq$20%, WIT >60 min, CIT >18 h	Induction with ATG (69%) or IL2RB (31%) Tacro Steroids	Initial dose MPS 2160 vs 1440 mg/d	Day 7 MPA $AUCt_{0-12}$ significantly lower in rejectors vs nonrejectors: mean ± SD = 33.5 ± 20.2 mg/L.h vs 55.7 ± 30.6 mg/L.h, $P = 0.006$	Full PK profile day 7

AR, acute rejection; ATG, antithymocyte globulin; AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; BPAR, biopsy-proven acute rejection; C_0, trough concentration; CIT, cold ischemia time; CsA, cyclosporine; CrCl, creatinine clearance; DCD, donation after cardiac death; DGF, delayed graft function; HLA, human leukocyte antigen; IL2RB, interleukin-2 receptor blocker; IQR, interquartile range; LSS, limited sampling strategy; MAPBE, maximum a posteriori Bayesian estimation; MLR, multilinear regression equation; MPA, mycophenolic acid; MPS, mycophenolate sodium; PRA, panel reactive antibody; PK, pharmacokinetics; ROC, receiver operating characteristics; SCAR, subclinical acute rejection; Tac, tacrolimus; TCI, target concentration intervention; TDM, therapeutic drug monitoring, Thymo, thymoglobulin; WIT, warm ischemia time.

decreased with increasing exposure targets—13.7%, 6.4%, and 3.9%, respectively—failing to reach statistical significance though in small numbers.[34]

By logistic regression analysis, the relationship between randomly assigned MPA $AUCt_{0-12}$ and rejection was highly significant ($P < 0.001$).[26] Increasing MPA $AUCt_{0-12}$ was associated with a reduction in the probability of BPAR by 50%, 75%, and 90% at MPA $AUCt_{0-12}$ values of 15, 25, and 40 mg/L.h, respectively.[26] The association between rejection and trough MPA total concentration was also significant, though weaker ($P < 0.01$). With doses adjusted to randomly assigned exposure targets, the association between MMF dose and BPAR was not significant ($P = 0.082$).[34]

For toxicities, there was a significant relationship between serious adverse events or death and increased MMF dose ($P < 0.001$), but no significant relationship was found with total MPA AUC_{0-12}, peak or trough concentration.[34]

APOMYGRE

The second RCT ("APOMYGRE") randomized 137 renal transplant recipients to FD MMF (2 g/d) or TCI to a target MPA $AUCt_{0-12}$ of 40 mg/L.h.[35] The primary outcome, treatment failure, was a composite of acute rejection, death, graft loss, and MMF withdrawal at 12 months.

TCI improved MPA exposure. At day 14 (the first postadjustment MPA $AUCt_{0-12}$), the proportion of patients above an MPA $AUCt_{0-12}$ of 30 mg/L.h was 68.3% versus 30.2% in TCI versus FD groups, with no difference in proportion above 60 mg/L.h (1.6% in each). At the next MPA $AUCt_{0-12}$ assessment (month 1), proportions were 90.8% versus 55.5%, respectively, with MPA $AUCt_{0-12}$ above 60 mg/L.h in 13.8% versus 4.7%.

Treatment failure occurred in 47.7% versus 29.2% in the FD versus TCI arms, respectively ($P = 0.03$). This was entirely due to differences in rejection (BPAR in 24.6% versus 7.7%, $P = 0.01$). TCI led to early dose escalation in underexposed individuals, with 82% of recipients taking between 2.5 and 4 g/d MMF at month 1, as well as

individualized dose reductions, with MMF dose below 2 g/d in 6% at 1 month, 26% at 3 months, and 48% at 6 months. These are low MMF doses with concomitant cyclosporine (some below 1 g/d), without apparent negative impact given overall superiority of the TCI arm.

Of acute rejection episodes in the first 3 months, 70% were associated with an MPA $AUCt_{0-12}$ <30 mg/L/h, while the remaining 30% occurred in those with an MPA $AUCt_{0-12}$ between 30 and 45 mg/L.h. Trial design dictated that dose adjustment was capped at 1g/d at a time; however, MAPBE predicted need for >1g/d dose increase for 70% of individuals based on day 7 AUC and 33% based on day 14 AUC. Thus, if larger dose increments had been allowed, the benefit of TCI may have been even greater.[107]

The TCI dosing in APOMYGRE cost <1% of total yearly costs (hospital and treatment) after a renal transplant. This can be compared with the marginal cost saving in preventing a single transplant failure of 8% of total yearly costs.[108]

OPERA

The third RCT, "OPERA," was not a pure TCI trial. It involved 247 kidney transplant recipients considered to be at a low risk of rejection (primary allograft, panel reactive antibody at transplantation of 0%, cold ischemia time <36 h).[106] Randomization was to either MMF 2 g/d (FD) or an MMF optimization arm with 2 aspects: an empiric increased dose of 3 g/d for 10 days following transplantation ("dose intensification"), followed by TCI to a target MPA $AUCt_{0-12}$ of 40 mg/L.h. Steroids were withdrawn on day 7 in both arms.

The optimization arm received significantly higher dose and MPA exposure for the first 6 weeks after transplantation ($P = 0.001$ at week 2; $P = 0.002$ at week 6). MPA $AUCt_{0-12}$ was >30 mg/L.h in 66% versus 38% of optimization versus FD patients at week 2 (due to "dose intensification") and 81% versus 62% at week 6 (due to TCI). Doses ranged from 1 to 4 g/d in the TCI arm, with significantly reduced within-group AUC variability.[106]

The primary outcome, BPAR (including subclinical rejection) at 3 months, was lower than expected, with no

TABLE 2.

A summary of studies that have examined the relationship between MPA exposure and toxicity

Reference	N	Concurrent therapy	Daily dose MPA	Adverse event against total MPA	Adverse event against unbound MPA
Takahashi et al[74]	32	No induction CsA Steroids	1–3.5 g	CMV infection in 2 of the 3 subjects with MPA $AUCt_{0-12}$ >90 mg/L.h	Not tested
Hale et al 1998[26] and van Gelder et al[34]	150	No induction CsA Steroids	TCI	No significant association between adverse events and MPA $AUCt_{0-12}$ Significant relationship between mean MMF dose and premature withdrawal due to adverse events ($P < 0.001$)	Not tested
Cattaneo et al[78]	46	No induction CsA Steroids	2 g	Significant association not seen	Not tested for MPA $AUCu_{0-12}$ $P < 0.05$, inverse correlation hematocrit with unbound MPA trough concentration and fraction; inverse correlation leukocyte count with unbound MPA fraction
Mourad et al[75]	51	No induction Tac Steroids	2 g	Significantly higher MPA $AUCt_{0-12}$ in those with adverse effects (composite hematological/ GI side effects): 48.4 ± 18.5 vs 36.0 ± 10.8 mg/L.h, $P = 0.0006$	Not tested
Mourad et al[76]	31	ATG CsA Steroids	1 g	Significantly higher MPA $AUCt_{0-12}$ in those with adverse effects (composite hematological/ GI side effects): 62.1 ± 21.1 vs 39.8 ± 15.3 mg/L.h, $P = 0.0005$	Not tested
Weber et al[79]	54	No induction CsA Steroids	600 mg/m²	No significant association	Increased risk of leukopenia and infections with MPA $AUCu_{0-12}$ > 0.4 mg/L.h, sensitivity 92.3% specificity 61%. Significant association between MPA $AUCu_{0-12}$ and leukopenia/infections, $P = 0.007$
Kiberd et al[81]	94	IL2RB (76.6%) CsA Steroids	2 g	No significant association	Not tested
Kuypers et al[80,99]	100 at 1 y 56 at 3 y 43 at 5 y	IL2RB (31.3%) Tac Late steroid withdrawal	1–2 g	Significantly higher MPA $AUCt_{0-12}$ in patients with (1) Leukopenia, at 3 mo: $AUCt_{0-12}$ 61.4 ± 30.9 vs 42.3 ± 25.3 mg/L.h ($P = 0.01$), and at 12 mo: $AUCt_{0-12}$ 84.4 ± 45.6 vs 44.2 ± 21.9 mg/L.h ($P = 0.04$) (2) Anemia at 3 mo: $AUCt_{0-12}$ 49.4 ± 28.9 vs 37.5 ± 19.4 mg/L.h ($P = 0.03$), and at 12 mo: $AUCt_{0-12}$ 61.1 ± 31.9 vs 42.3 ± 21.3 mg/L.h ($P = 0.01$) Followed to 5 y, ongoing finding of significantly higher MPA $AUCt_{0-12}$ in patients with: (1) Leukopenia: $AUCt_{0-12}$ 59.7 ± 31.0 vs 46.5 ± 26 mg/L.h ($P = 0.004$) (2) Anemia: $AUCt_{0-12}$ 56.2 ± 32.5 vs 45.6 ± 24.7 mg/L.h ($P = 0.005$)	Not tested
Satoh et al[100]	21	No induction Tac Steroids	2 g	No significant association between MPA $AUCt_{0-12}$ and viral infections MPA $AUCt_{0-12}$ of patients with and without viral infections was 61.5 ± 30.3 and 50.4 ± 31.6 mg/L.h, respectively.	Not tested
Atcheson et al[82]	42	IL2RB CsA (76%) Steroids	2 g	No significant association	Significantly higher MPA $AUCu_{0-6}$ in individuals with 1 or more hematological or infectious events (33% CMV, 17% MRSA bacteremia, 17% UTI, 33% wound infection/ cellulitis): 1.9 ± 0.3 vs 1.1 ± 0.1 mg/L.h, $P = 0.0043$

TABLE 2. (Continued)

Reference	N	Concurrent therapy	Daily dose MPA	Adverse event against total MPA	Adverse event against unbound MPA
Okamoto et al[84]	67	IL2RB (37%) CsA (52%) or Tac Steroids	TDM	Trend to higher MPA $AUCt_{0-9}$ among patients with infectious AE (CMV infection N = 12, varicella N = 2, GI toxicity N = 1): MPA $AUCt_{0-9}$ 39.2 ± 22.8 vs 30.1 ± 8 mg/L.h, $P = 0.08772$	Not tested
Pawinski et al[101]	33	No induction CsA Steroids	2 g	No significant association	Not tested
Armstrong et al[102]	279	Induction (46.4%) CsA (54.2%) Steroids	2 g or 600 mg/m² or TDM	Association seen between total MPA $AUCt_{0-12}$ and leukopenia, thrombocytopenia, $P = 0.023$	Association seen between MPA $AUCu_{0-12}$ and leukopenia/ thrombocytopenia, $P = 0.004$
Le Meur et al[35]	137	IL2RB CsA Late steroid withdrawal	2 g or TDM	No significant association	Not tested
van Gelder et al[31]	901	Induction (46.4%) CsA (54.2%) Steroids	2 g or 600 mg/m² or TDM	No significant association	Not tested
Gourishankar et al[91]	126	IL2RB (85%) Tac Steroids	2 g (3 g for 5 d in half)	MPA $AUCt_{0-12}$, on day 5 significantly associated with anemia ($P = 0.0369$), not with other adverse events	Not tested
Sommerer et al[92]	66	IL2RB CsA Steroids	720–2880 mg (MPS)	Patients with infections had significantly higher MPA $AUCt_{0-12}$: median (range) 65 mg/L.h (37–130) vs 37 mg/L.h (7–120), $P < 0.005$	Not tested
Daher Abdi et al[95,96]	490	IL2RB (minority thymoglobulin) CsA (79.6%) Late steroid withdrawal (most)	2 g or TDM	No significant association with CMV disease	Not tested
Sobiak et al[103]	61	No induction stated CsA (45.9%) or Tac (39.3%) Steroids	Not stated	In the late posttransplant period (>6 mo), no significant association between MPA $AUCt_{0-4}$ and anemia, leucopenia, or thrombocytopenia	Not tested
Born-Duval et al[104]	240	Thymoglobulin (77.5%) or IL2RB (22.5%) CsA (53.7%) or Tac (44.2%) Steroids (late with-drawal if low risk)	Not stated	On multivariable analysis, 3-month MPA $AUCt_{0-12}$ >50 mg/L.h significantly associated with sustained BKV viremia (AHR 3.6, $P = 0.001$), and PyVAN (AHR 3.01; $P = 0.05$) Recommendation: a target MPA $AUCt_{0-12}$ of 40 mg/L.h, rather than 50 mg/L.h or more. Lower target of 20 mg/L.h in cases of sustained BKV	Not tested
Fu et al[94]	183	No induction Tac Steroids	TDM vs FD (nonrandomized)	TDM group had lower MPA $AUCt_{0-12}$ at day 30 (54.1 ± 9.7 vs 61.4 ± 18.9, $P = 0.004$), along with fewer infections at 12 mo (16.8% vs 31.7%, $P = 0.018$) Of 43 patients developing infectious complications, 55.8% had MPA $AUCt_{0-12}$ >60 mg/L.h, 37.5% had MPA $AUCt_{0-12}$ of 30–60 mg/L.h and 7% had MPA $AUCt_{0-12}$ <30 mg/L.h	Not tested
Kiang et al[105]	21	Induction not stated Tac Steroid free	MMF 2 g/d	Significant inverse association between MPA $AUCt_{0-12}$ at 1-month and ANC ($P < 0.05$) For dose-normalized MPA $AUCt_{0-12}$, significant inverse association with ANC at 1, 3, and 12 mo (all $P < 0.05$)	Not tested

AE, adverse event; AHR, adjusted hazard ratio; ANC, absolute neutrophil count; ATG, antithymocyte globulin; AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; BKV, BK virus nephropathy; CMV, cytomegalovirus; CsA, cyclosporine; FD, fixed dosing; GI, gastrointestinal; Hb, hemoglobin; IL2RB, interleukin-2 receptor blocker; LSS, limited sampling strategy; MPA, mycophenolic acid; MPS, mycophenolate sodium; MRSA, methicillin-resistant *Staphylococcus aureus*; N, number; Tac, tacrolimus; TCI, target concentration intervention; TDM, therapeutic drug monitoring.

significant difference between treatment arms.[106] The optimization arm did not tolerate therapy as well, with significantly more dose reductions for adverse events (58.7% versus 42.2%, $P = 0.009$). Although lacking statistical significance, all toxicities associated with MPA were numerically higher in the optimization arm. Finally, there was a trend toward increased BPAR in the optimization arm (24.6% versus 14.9%, $P = 0.06$).

Given the initial substantive difference in dose between treatment arms, the independent impact of subsequent TCI cannot be objectively assessed in this low-risk steroid withdrawal protocol.

TABLE 3.

RCTs of concentration-controlled dosing and clinical outcome

Reference	N	Population	Concurrent therapy	Trial type	Outcome and comments
Hale et al[26] and van Gelder et al[34]	150	Adults, first or second graft, deceased donor	No induction CsA Steroids	Multitarget RCCT 3 target MPA $AUCt_{0-12}$ arms: 16.1, 32.2, or 60.6 mg/L.h	BPAR 27.5%, 14.9%, and 11.5% in low, medium, and high target groups ($P = 0.043$, low vs medium/high target) By logistic regression, strong association between MPA $AUCt_{0-12}$ and BPAR ($P < 0.001$) Significant association between increasing MMF dose and serious adverse events or death ($P < 0.001$)
Le Meur et al[35]	137	Adults, first or second graft, exclusion PRA >50%,	IL2RB CsA Late steroid withdrawal	RCT, TCI to an MPA $AUCt_{0-12}$ of 40 mg/L.h vs 2 g/d	Treatment failure in 47.7% vs 29.2% ($P = 0.03$), FD vs TCI arms, respectively BPAR in 24.6% vs 7.7% ($P = 0.01$), FD vs TCI arms, respectively Cost neutral[38]
van Gelder et al[31]	901	Adults (children N = 62), living or deceased donor. Exclusion PRA >50% CIT >48 h	Induction (46.4%) CsA (54.2%) Steroids	RCT, TDM to an MPA $AUCt_{0-12}$ of 30–60 mg/L.h vs 2 g/d	No benefit seen Lack of substantive dose adjustments in treatment arm leading to similar mean MPA $AUCt_{0-12}$ and proportion in range between treatment arms Unable to test benefit of optimizing MPA exposure
Gaston et al[41]	720	Adults (>13 y age), first or second graft, living or deceased donor. Exclusion PRA >50% CIT >48 h	Induction (75%, ATG in 43%) Tac (80%) Steroids	3 arm RCT: (A) MMF TDM to a trough MPA >1.3 or 1.9 µg/mL (if CsA or Tac, respectively) + "reduced" CNI vs (B) MMF TDM (as above) + "standard" CNI target vs (C) 2 g/d + "standard" CNI target	Noninferiority met for MMF TDM and "reduced" CNI vs 2 g/d and "standard" CNI Higher mean MMF dose group A than both groups B and C, though insufficient to improve MPA exposure Unable to test benefit of optimizing MPA exposure
Le Meur et al[106]	247	Adults, first living or deceased donor graft, PRA 0% (current), CIT <36 h	Cyclosporine Steroids (withdrawn day 7)	RCT, dose optimization (3 g/d MMF for 10 d then TCI to a target MPA $AUCt_{0-12}$ of 40 mg/L.h) vs 2 g/d	Optimization arm (dual intervention) had significantly higher MMF dose and MPA exposure for the first 2 wk (empiric), which continued for the subsequent 4 wk (TCI driven) No benefit seen on BPAR/SCAR at 3 mo Dose optimization associated with significantly more dose reductions ($P = 0.009$) and a trend to inferiority on 12-month BPAR (14.9% vs 24.6%, $P = 0.06$, FD vs dose optimization, respectively) Unable to independently assess benefit of TCI

ATG, antithymocyte globulin; AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; BPAR, biopsy proven acute rejection; CIT, cold ischemia time; CNI, calcineurin inhibitor; CsA, cyclosporine; DGF, delayed graft function; FD, fixed dosing; IL2RB, interleukin-2 receptor blocker; MMF, mycophenolate mofetil; MPA, mycophenolic acid; N, number; NS, not significant; PRA, panel reactive antibodies; RCT, randomized controlled trial; RCCT, randomized concentration-controlled trial; SCAR, subclinical acute rejection; Tac, tacrolimus; TCI, target concentration intervention; TDM, therapeutic drug monitoring.

MPA Dose Individualization Using TDM

Fixed Dose Concentration-controlled Trial

"FDCC" was the largest of the RCTs, with 901 kidney transplant recipients randomized to either FD of 2 g/d or CCD.[31] Although designed to achieve a target MPA $AUCt_{0-12}$ (45 mg/L.h), actual implementation used a TDM approach.[31] Exposure within 30–60 mg/L.h was considered acceptable. Clinicians could also choose a different target concentration for individual patients based on their assessment of immunological risk, as long as this fell within the 30–60-mg/L.h range.[31] Finally, only MPA $AUCt_{0-12}$ values were provided. The decision to

adjust dose, and by how much, was left to the individual clinician.

The TDM approach in FDCC was unsuccessful in improving MPA exposure. There was "nonadherence to required early dose increments" by clinicians, with an overall lack of substantive dose changes. Consequently, "mean MPA AUC values, and the proportion of patients achieving AUC values within the therapeutic range," were similar in the TDM and FD groups. Outcomes were also the same: treatment failure in 25.6% versus 25.7% ($P = 0.81$) and BPAR in 14.9% versus 15.5%, in the TDM and FD groups, respectively. However, with minimal difference in exposure between the 2 groups,

differences in outcome "could not be expected, and were not observed."[31]

As the CCD procedure was unsuccessful in differentiating MPA exposure between the 2 arms, a conclusion regarding method effectiveness of CCD cannot be drawn.[56,109,110] This contrasts with the TCI trials, which clearly demonstrated that MPA exposure can be effectively controlled, leading to outcome benefits.[26,34,35]

Opticept

The second TDM trial, "Opticept,"[41] was the only RCT of CCD using trough MPA concentrations. Seven hundred and twenty participants were randomized to 3 treatment arms with 2 intervention variables: MMF dosing strategy (TDM versus FD), and CNI therapeutic range ("standard" versus "reduced"). Group C was the control arm: FD mycophenolate and "standard" CNI. Group A was the primary intervention arm: MMF TDM and "reduced" CNI. Group B was halfway between: MMF TDM and "standard" CNI. The primary outcome was noninferiority of group A compared with C, based upon treatment failure at 12 months (a composite of BPAR, graft loss, loss to follow-up, or withdrawal).

MMF dose optimization was by TDM, to achieve MPA trough concentrations ≥ 1.3 or ≥ 1.9 µg/mL, alongside cyclosporine or tacrolimus, respectively. Dose individualization for MPA was according to clinician judgement rather than a centralized PK-guided calculation.

TDM led to significantly higher MMF dose in group A compared with groups B and C. The reason for dose difference between groups A and B—noting that both were TDM arms—was not made clear. Most importantly, however, as with FDCC, dose adjustments were insufficient to attain planned exposure, with "little differentiation among treatment groups in MPA exposure." In tacrolimus-cotreated patients (81.9% of total participants), MPA trough concentrations were "identical at all time points with or without monitored dosing."

The primary outcome end point was achieved: noninferiority of Group A (MMF TDM + "reduced" CNI) against Group C (MMF FD + "standard" CNI).[41] In fact, there was numerically less rejection and treatment failure in the intervention arm, group A, despite lower CNI exposure, while outcomes in groups B and C were identical. Specifically,

treatment failure occurred in 55 (22.6%), 67 (28.3%), and 67 (27.9%) subjects in groups A, B, and C, respectively ($P = 0.13$ for A versus B and $P = 0.18$ for A versus C). BPAR occurred in 15 (6.2%), 23 (9.7%), and 23 (9.6%), respectively ($P = 0.17$ for group A versus C). The occurrence of adverse events was similar across treatment groups.

As with FDCC, lack of differentiation in exposure to MPA between treatment arms means that method effectiveness of CCD was not tested.

DISCUSSION

The consequences of both underimmunosuppression or overimmunosuppression, with potentially preventable morbidity and mortality, remain prevalent after kidney transplantation.[1-3] For mycophenolate, the dosing strategy applied varies markedly, from "one-dose-suits-all" (FD),[111] to trough concentration monitoring,[40] to TCI to an estimated MPA $AUCt_{0-12}$ target.[112]

This review demonstrates that mycophenolate FD consistently leaves a proportion of individuals with MPA underexposure associated with rejection (see Table 4). In addition, a link has been shown between MPA exposure and both hematological and infectious toxicities, more apparent with tacrolimus cotherapy or when unbound MPA is measured (see Table 4).

The link between MPA $AUCt_{0-12}$ and rejection is considered "definitive."[113] Five prospective RCTs of mycophenolate CCD have been performed. When critically analyzed, these trials show that CCD using TCI leads to effective control of MPA exposure and to improved clinical outcomes.

The 1998 multitarget RCCT randomly assigned participants into 1 of 3 exposure targets,[26,34] the pharmacological gold standard for unbiased assessment of the exposure-response relationship.[55,56,114] It was hailed at the time as a landmark demonstration of science-based drug development based on clinical trial simulation.[114,115] Increasing exposure target significantly reduced BPAR.[26] With random assignment of participants to exposure targets, the association between MPA exposure and BPAR was highly significant, while that between MPA dose and BPAR was not.[26]

In "APOMYGRE,"[35] the TCI approach was superior to FD, with a 39% reduction in treatment failure. This

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TABLE 4.
Summary table of observational exposure-effect data

	Total		Significant association		Trend		Neither significant association nor trend	
	Cohorts	N	Cohorts	N (% of total)	Cohorts	N (% of total)	Cohorts	N (% of total)
MPA $AUCt_{0-12}$ vs acute rejection								
All cohorts	27	3794	20/27	3382 (89.1)	3/27	217 (5.7)	4/27	195 (5.1)
Cyclosporine cotherapy	16	1518	12/16	1181 (77.8)	2/16	274 (18.1)	2/16	63 (4.2)
Tacrolimus cotherapy	11	1696	7/11	1373 (81.0)	2/11	201 (11.9)	2/11	122 (7.2)
MPA $AUCt_{0-12}$ vs toxicities								
All cohorts	22	3225	9/22	1097 (34.0)	2/22	99 (3.1)	11/22	2029 (62.9)
Cyclosporine cotherapy	11	1065	2/11	97 (9.1)	1/11	32 (3.0)	8/11	936 (87.9)
Tacrolimus cotherapy	6	502	5/6	481 (95.8)	0/6	0 (0)	1/6	21 (4.2)
MPA $AUCu_{0-12}$ vs toxicities	3	375	3/3	375 (100)				

AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; MPA $AUCu_{0-12}$, AUC for unbound mycophenolic acid concentration.

involved initial individualized dose escalation followed by individualized dose reduction, with overall superiority and no increase in toxicities. In addition, TCI was cost neutral.[108]

In "OPERA," TCI was effective in maintaining MPA exposure target and reducing within-group PK variability, beyond the initial "dose intensification" period. Notably, 3 other trials of MPA "dose intensification" (without subsequent TCI), in standard or higher-risk recipients, revealed either a significant reduction in rejection[98,116] or strong trend,[91] showing that this intervention alone can impact outcomes. In contrast, OPERA revealed no efficacy benefit at 3 months (and less tolerance). This suggests that intensified dose (3 g/d for 10 d) followed by TCI is not beneficial in a preselected low-risk early steroid withdrawal population. The trend to higher rejection at 12 months in the dose optimization arm is also of interest: perhaps more dose reductions secondary to toxicities might have contributed?[106] Regardless, it is impossible to assess impact of increased precision in MPA exposure (by TCI) independent of the substantive dose difference in the initial phase.

Thus, 2 TCI trials (the multitarget RCCT[26,34] and APOMYGRE[35]) reveal a statistically significant and clinically important benefit of TCI. This is not refuted by the subsequent OPERA trial.

The TCI trials, with effective control of MPA exposure, contrast with the 2 trials using TDM to individualize exposure. In FDCC[31] and Opticept,[41] TDM without consistent dosing advice did not reliably achieve target MPA exposure (nor even differentiate MPA exposure between treatment arms). As a result, both trials failed to show a clinical benefit of CCD.

A "dose optimization feedback loop" is recommended for RCCTs to maximize probability of target concentration attainment.[55,56] A centralized system provides the clinician with a probability-based dose prediction that they can immediately use. Without this, CCD relies on the individual clinician having the time, and the experiential knowledge, to determine new doses themselves.

The clinical pharmacology community has long advocated active PK-guided dosing to a concentration target (TCI) in clinical care.[24,25,117-119] TCI is more pharmacologically rational than TDM,[23,117,120] although to the authors' knowledge, the 2 have never been directly compared in terms of clinical outcomes. The RCTs of mycophenolate CCD, while not head-to-head, provide an indirect but noteworthy comparison.

The question arises as to why TCI and PK-guided dosing appear necessary to improve MPA exposure, contrary to other immunosuppressant drugs where TDM suffices. It may relate to clinician experience with CNIs, where doses are generally increased cautiously, perhaps reflecting the lesser precision of trough concentrations and desire to avoid overshoot. For MPA, however, concentration attainment may require greater than proportional dose adjustment.[112,121] In addition, TDM leaves the dose unchanged if drug exposure lies anywhere within the broad therapeutic window set for MPA, contrasting the TCI trials showing benefit where active intervention to reach an optimal target was used, even if the measured value was within 30–60 mg/L.h.

Assessing the actual exposure achieved in CCD trials is critical. The Elite-Symphony trial[6] reported superiority of low-dose tacrolimus over low- or standard-dose cyclosporine. However, while the target exposure in the tacrolimus arm was 3–7 ng/mL, the actual concentrations achieved were higher. Mean trough concentrations were above 7 ng/mL for the first 8 weeks (with almost 50% of individuals above the therapeutic range for this period).[6,122] By 12 months, mean (SD) tacrolimus concentration was 6.4 ± 2.4 ng/mL, and at 3 years, 6.5 ± 2.3 ng/mL.[6,123] This trial supports excellent outcomes out to 3 years posttransplant[123] with the achieved tacrolimus trough concentrations. However, the results from the Elite-Symphony trail cannot be used to support the intended 3–7-ng/mL therapeutic range (outcomes achieving this have not been given). Equally, it is erroneous to assert that a trial of CCD with minimal difference in exposure between arms (because concentrations were not well controlled) proves the lack of benefit of CCD.

In 2013, Wang et al[124] published a systematic review and meta-analysis of RCTs of mycophenolate CCD versus FD, concluding that the evidence was not supportive. However, whilst the result of this meta-analysis was technically correct, "an analysis is only as good as the data on which it was based." Meta-analysis of the RCTs without careful consideration of the trial methodologies and exposures achieved has led to misinterpretation of the strength of the evidence.

First, Wang et al[124] excluded the original multitarget RCCT[34,125] due to lack of FD comparator.[124] While this trial design does not test the degree of benefit of CCD over FD, it remains the most robust method for determining the causative relationship between exposure and effect.[24,54-56,114,126] In this case, it revealed a highly significant relationship between MPA exposure and BPAR,[26,34] with MPA exposure values spanning those seen in a population on FD. Second, Wang et al[124] included RCTs that, as has been shown in this review, cannot be used to support or refute benefit of CCD. Not accounting for these critical differences in trial methodologies and exposures achieved led Wang et al[124] to a conclusion that we reject in this review.

Only 2 RCTs have been able to independently test the benefit of CCD.[26,34,35] Both reported clear benefit, using TCI to a target MPA $AUCt_{0-12}$ of 40 mg/L.h. Together, they confirm MPA $AUCt_{0-12}$ as a valid biomarker of drug exposure linked causally with drug effect.[54,55] No subsequent RCTs have refuted this finding.

The link between exposure and toxicities has proven difficult to establish, particularly in cyclosporine cohorts. This is not because MPA has a "wide therapeutic index," as dose-dependent toxicities remain prevalent with FD.[26,35,127-130] Rather it relates to issues with the exposure metric in certain settings.

The use of total MPA concentration as surrogate for unbound concentration fails in certain pathophysiological states. Hypoalbuminemia (≤31 g/L) leads to a reduction in total MPA without changing unbound MPA concentration,[33,131,132] potentially missing toxic unbound concentrations if only total MPA concentrations are measured (Figure 3).

Severe renal impairment (creatinine clearance <25 mL/min) leads to reduced excretion of the major MPA metabolite, MPA-glucuronide (MPAG). This leads to an increase in both total and unbound MPA concentrations, presumed due to EHC and reactivation of accumulating MPAG.[53,133] However, with cyclosporine cotherapy, EHC is inhibited,
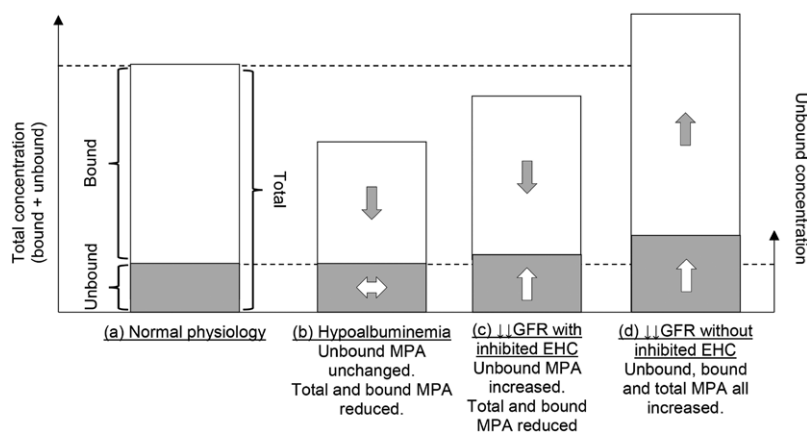
FIGURE 3. The relationship between the "effective" unbound MPA concentration and total concentration in normal physiological state and relative change (at steady state) in several pathophysiological states. (A) Normal physiology, (B) hypoalbuminemia, (C) severe renal impairment with inhibited EHC (eg, due to CsA), and (D) severe renal impairment without inhibited EHC (eg, Tac used instead of CsA). CsA, cyclosporine; EHC, enterohepatic cycling; GFR, glomerular filtration rate; MPA, mycophenolic acid.

significantly reducing reactivation of MPAG to MPA. Greater MPAG accumulation also increases displacement of MPA from albumin (hence a decrease in total MPA), with unbound concentration unchanged or elevated.[53] Again, although for cyclosporine cohorts only, toxic unbound concentrations may be missed if only total MPA concentrations are measured (Figure 3).[53]

MPA exposure is higher overall alongside tacrolimus in the initial period,[31,70-72] further explaining better correlation with toxicities in such cohorts (a greater prevalence of overexposure).

Finally, although not examined in this review, MPA-induced gastrointestinal side effects are thought related to local toxicity from metabolites undergoing EHC.[45,65,66] This puts the biophase at a site distal to the plasma compartment, explaining greater difficulty correlating exposure with effect.

After the initial multitarget RCCT, it was noted that "the efficacy of MMF is primarily related to MPA AUC, whereas tolerability is more dependent on the dose of MMF. The apparent discrepancy between these findings cannot readily be explained."[26,34] We now have a plausible explanation: issues using total to predict unbound MPA concentrations in certain settings, and an indirect link between plasma concentration and amount of drug in the gut for GI toxicity.

To summarize, complicated PKPD characteristics and challenges in CCD have clouded understanding of the exposure-effect relationship of MPA in kidney transplantation. This has contributed to failure to recognize the better outcomes when dose optimization is based on PK-guided TCI[25] compared with TDM and individual clinician-based dose adjustment. Only if MPA target exposure is effectively achieved are benefits seen.

It is of course noteworthy that the 2 RCTs that effectively tested mycophenolate CCD, showing benefit of TCI, were in cohorts concurrently receiving cyclosporine. Nowadays, tacrolimus use predominates in many centers, along with induction antibody therapy ("quadruple therapy": induction, steroids, MPA, and CNI). In addition, rejection rates are low.[6,111]

However, the validity of MPA $AUCt_{0-12}$ as a biomarker for drug exposure, causally linked to drug effect, will still apply with different drug combinations or populations, although exposure target may differ. Second, precision dosing aims to maximize benefits and minimize toxicities: in contemporary cohorts, there remains MPA underexposure associated with rejection,[41,89,91,93,97,98] dose-dependent toxicities,[129,130,134] and overexposure associated with toxicities,[80,94,99,104,105] highlighting a potential value of TCI.

The MPA $AUCt_{0-12}$ target of 40 mg/L.h in the initial posttransplant period, based on the method effective RCTs, can reasonably be extrapolated to tacrolimus cohorts based on 2 lines of evidence. First, this approximates the typical (mean or median) MPA $AUCt_{0-12}$ seen in the initial posttransplant week in tacrolimus cotreated cohorts on 2 g/d dosing (ie, this is the exposure the typical patient receives).[31,91,135] Continuing 2 g/d, typical MPA $AUCt_{0-12}$ then increases to over 50 mg/L.h by week 4[31,91,135] and to 60 mg/L.h by month 3,[91,135] presumably due to higher serum albumin and glomerular filtration rate[53,68] ± reduction in steroid dose.[136]

This target also aligns with the observational data that exist, at least for recipients at increased risk. A substantial increase in rejection rates has been reported with an initial MPA $AUCt_{0-12}$ <30 mg/L.h and 1 of the following: >3 human leukocyte antigen mismatches, panel reactive antibody >15%, repeat transplant, delayed graft function, or African American descent;[89] if concurrent underexposure to other immunosuppressants[93] or for expanded criteria donation.[97,98] Elsewhere, similar rejection "thresholds" have been reported in contemporary regimen.[41,91] Rapid and effective target concentration attainment could ameliorate this risk in such individuals.

MPA underexposure in the immediate posttransplant week may not be detrimental in low-risk recipients.[89,106] However, the authors would caution against concluding that early AUC estimation is unnecessary in this group. While a target of 40 mg/L.h may not be required in the immediate posttransplant period, identification of high exposure (ie, 60–100+ mg/L.h) provides an opportunity for early individualized dose reduction. Supporting benefit of such a strategy, reduced infection was reported in a nonrandomized MMF CCD trial alongside tacrolimus in the first posttransplant month.[94]

In the maintenance phase, "incomplete efficacy, patient intolerance, and side effects" to antiproliferatives remain an issue,[2] although infrequency of hard outcomes makes it harder to show quantitative associations. Importantly, Daher Abdi et al[95,96] used joint modeling to link longitudinal changes in MPA exposure with outcomes at 1 (490 subjects) and 2 years posttransplant (222 subjects), pooling cohorts from APOMYGRE, OPERA, and clinical care. Robust association was reported between MPA $AUCt_{0-12}$ and hazard of rejection at 1 year ($P = 0.0081$), with suggestion to maintain exposure above a "threshold" of 37 mg/L.h at 1 month posttransplant, above 40 mg/L.h by month 3, and above 41 mg/L.h by month 6 and onward.[95] Out to 2 years (excluding the OPERA cohort), all subjects having received induction therapy, MMF, CNI (42.5% tacrolimus), and steroid withdrawal after 3 months, a significant association was shown between MPA exposure and the composite of acute rejection, graft loss and death at 2 years (with each 1 mg/L.h increase in MPA $AUCt_{0-12}$, there was a 4% hazard reduction).[95]

In contemporary "quadruple therapy" regimen with steroid continuation, equivalent data to support a maintenance phase MPA exposure target do not yet exist (although presumably a lower target than for steroid withdrawal cohorts would suffice). Furthermore, there has been a trend to empiric reduction of the population dose of mycophenolate in the first few months in such regimens (to 1.5 g/d, and eventually 1 g/d if low risk),[111] due to an increase in toxicities including BK virus nephropathy.[137,138] Nevertheless, an association has been reported between MPA dose reduction and rejection in steroid continuation cohorts.[134,139] In addition, multivariable analysis of 240 kidney transplant recipients has revealed an association between an MPA $AUCt_{0-12}$ >50 mg/L.h at 3 months posttransplantation and both sustained BK viremia ($P < 0.0001$) and polyomavirus-associated nephropathy ($P = 0.013$) over the subsequent 2 years.[104] Just as targeted dose reductions occurred in the TCI arm of APOMYGRE, TCI in contemporary regimens has the potential to more effectively reduce BK virus disease and other toxicities than the current trend to empiric population dose reduction,[111] while avoiding iatrogenic underexposure in those with already low MPA exposure on initial FD.

Finally, the impact of tacrolimus exposure on subclinical inflammation and de novo donor-specific antihuman leukocyte antigen antibody (dnDSA) formation has been reported in recent years.[140-145] In contrast, while some studies have linked the use of mycophenolate to reduced dnDSA formation,[146,147] the impact of MPA dose or exposure on dnDSA formation is largely absent. Torres et al[141] linked tubulointerstitial inflammation in low-risk recipients with combination of low tacrolimus concentrations and reduced MMF dosing, while Filler et al[148] reported a significant association between minimum MPA trough concentrations and dnDSA formation in pediatric renal transplant recipients.

This review provides strong evidence favoring MPA TCI in kidney transplantation. However, there is an urgent need to better define target concentration beyond the initial phase in steroid continuation regimens, and to correlate MPA exposure with dnDSA formation. This could first involve prospective collection of MPA exposure, both for total and unbound MPA, within contemporary steroid continuation drug regimen. PKPD time to event analyses could then be performed, like that by Daher Abdi et al,[95,96] to link the time course of exposure with dnDSA formation and clinical outcomes. As a final definitive step, an RCT of FD versus TCI to an AUC target, with surrogate endpoints including dnDSA, would be of benefit.

There is in addition a need for consensus on practical aspects of MPA TCI. Frequent AUC estimation has been suggested in cyclosporine-cotreated cohorts: "in the first week after transplant, then each week for the first month, each month until month 3, and subsequently every 3 months up to 1 year."[33] This is due to a 30%–50% increase in dose-normalized exposure over the first 3 months, to avoid overshooting target. However, without the dose-dependent inhibitory effect of cyclosporine on EHC, the change in exposure over the first 3 months appears less substantial in tacrolimus-containing regimens,[121,149] and thus a lesser frequency should suffice.

Access to methods for MPA TCI is also required, by broadening access to MAPBE,[112,150] or using acceptably precise LSS methods for estimation of MPA $AUCt_{0-12}$, for example, multilinear regression equation equation validated in an equivalent population[49] or extended sampling for trapezoid estimation.[63] To reduce practical burden of repeated blood sampling, validation of new technologies enabling precise dried blood spot testing is needed.[151]

Finally, more data are needed to determine optimal unbound MPA exposure in the initial posttransplant weeks to allow interpretation of MPA exposure in the setting of significant hypoalbuminemia or delayed graft function.[33] In addition, the use of intracellular concentrations of MPA in peripheral lymphocytes[152] or pharmacodynamic measurement of Inosine-5'-monophosphate dehydrogenase activity[153,154] could in theory offer an alternative to systemic exposure estimation, though to date clinical value has not been shown.

The consequences of inefficacy and toxicities from current immunosuppressive agents remain significant, due to between-subject PKPD variability as well as individual patient susceptibilities. Expectations are for "slow, painstaking, stepwise improvements in outcomes from the techniques we have … and careful honing of new methods with better efficacy than old ones."[155] Increasing precision with MPA by individualizing dose to a target concentration (TCI) provides such an opportunity.

CONCLUSION

MPA $AUCt_{0-12}$ is a valid biomarker of drug exposure, more directly linked to drug effect than mycophenolate dose. FD leads to both overexposure and underexposure and off-target toxicities. Along with the overwhelming observational evidence, 2 adequately designed and executed trials[26,34,35] have tested the benefit of dosing to a target MPA exposure, revealing statistically significant and clinically important benefit. No subsequent evidence refutes these findings.

There remains a need for consensus on frequency of exposure estimation in the early phase; to increase access to estimation methods that balance precision and practicality; to better define exposure targets in the maintenance phase; and to better define the exposure-effect relationship for the unbound concentration. These should be seen as

a priority, given ongoing prevalence of immune-mediated graft loss and life-limiting toxicities. The imprecise one-dose-suits-all approach with mycophenolate should come to end and be replaced by the scientifically based and evidence-proven TCI approach.

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