Controlled-Dose Versus Fixed-Dose Mycophenolate Mofetil for Kidney Transplant Recipients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Xianding Wang,[1] Xin Qin,[1] Yong Wang,[2] Zhongli Huang,[1] Xiaohong Li,[3] Quantao Zeng,[2] Hao Zeng,[1] Yiping Lu,[1] Li Wang,[1] and Tao Lin[1,4]

Background. Although mycophenolate mofetil (MMF) is recommended at a fixed dose, there is increasing interest in controlled-dose (CD) MMF based on therapeutic drug monitoring. We systematically evaluated published randomized controlled trials (RCTs) on the efficacy and safety of CD versus fixed-dose MMF for kidney transplant recipients.

Methods. The electronic databases Medline, Embase, and Cochrane Library (up to June 2012) were searched to identify relevant RCTs. Two reviewers independently applied the study selection criteria, examined the study quality, and extracted the data. Dichotomous measures were expressed as relative risk (RR) and continuous outcomes were expressed as weighted mean difference, both with 95% confidence intervals (CIs). All statistical analyses were performed using Review Manager 5.1.6.

Results. Four RCTs met our selection criteria and included 1755 de novo recipients. The differences between CD and fixed-dose MMF in treatment failure (RR, 0.95; 95% CI, 0.82–1.10; *P*=0.52), serum creatinine clearance (weighted mean difference, 2.46; 95% CI, −1.15 to 6.07; *P*=0.18), total gastrointestinal adverse events (RR, 1.23; 95% CI, 0.65–2.35; *P*=0.53), diarrhea (RR, 1.08; 95% CI, 0.92–1.25; *P*=0.35), anemia (RR, 1.24; 95% CI, 0.95–1.64; *P*=0.12), leukopenia (RR, 1.12; 95% CI, 0.93–1.35; *P*=0.25), thrombocytopenia (RR, 0.80; 95% CI, 0.47–1.36; *P*=0.41), and malignancy (RR, 0.61; 95% CI, 0.27–1.38; *P*=0.23) were not statistically significant. Furthermore, total infections were more frequent in the CD group (36.0% vs. 30.9%; RR, 1.16; 95% CI, 1.03–1.30; *P*=0.01).

Conclusions. Based on current evidence, CD MMF administration cannot be recommended as routine practice for kidney transplant recipients. Therapeutic drug monitoring for MMF may be targeted toward high-risk recipients, who should be identified in future studies.

Keywords: Area under the curve, Kidney transplantation, Meta-analysis, Mycophenolate mofetil, Therapeutic drug monitoring

(*Transplantation* 2013;96: 361–367)

Mycophenolate mofetil (MMF) is an effective anti proliferative drug and a key component of the current standard immunosuppression regimen for kidney transplant recipients (KTRs) (*1*). After oral administration, MMF is rapidly and almost completely absorbed and converted to the active metabolite mycophenolic acid (MPA) (*2*). Although MMF is recommended at a fixed dose with documented efficacy and safety (*3*), there is increasing interest in the therapeutic drug monitoring (TDM) for MMF (*4*). MPA area under the curve $(AUC)_{0-12\ hr}$ of 30 to 60 mg hr/L is proposed to be the target therapeutic window for KTRs (*5*). However, approximately 35% of KTRs receiving a fixed dose will have MPA AUC outside of the target therapeutic window: 25% are underexposed and 10% are overexposed (*6*). For a fixed dose of 1 g twice daily, MPA exposure can vary by 10-fold between KTRs (*7*). This variability is clinically important because low MPA exposure increases the risk of acute rejection, and overexposure increases the risk of adverse effects (e.g., diarrhea, infection, and anemia) (*8*). Thus, efficacy/safety may be further improved by controlled-dose

The authors declare no funding or conflicts of interest.

[1] Department of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, China.
[2] West China School of Clinical Medicine, Sichuan University, Chengdu, Sichuan, China.
[3] Department of Health Statistics, West China School of Public Health, Sichuan University, Chengdu, Sichuan, China.
[4] Address correspondence to: Tao Lin, M.D., Department of Urology, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Chengdu, Sichuan 610041, China.
E-mail: urohuaxi@163.com

X.W. participated in the study concept, research design, performance of the research, data analysis, and drafting of the article. X.Q. and Y.W. participated in the performance of the research, data analysis, and drafting of the article. Z.H. participated in the study concept and research design. X.L. and Q.Z. participated in the data analysis. H.Z., Y.L., and L.W. participated in the research design and article review. T.L. participated in the study concept, research design, and article review.
Received 25 September 2012. Revision requested 19 October 2012.
Accepted 7 February 2013.

ISSN: 0041-1337/13/9604-361
DOI: 10.1097/TP.0b013e31828c6dc7

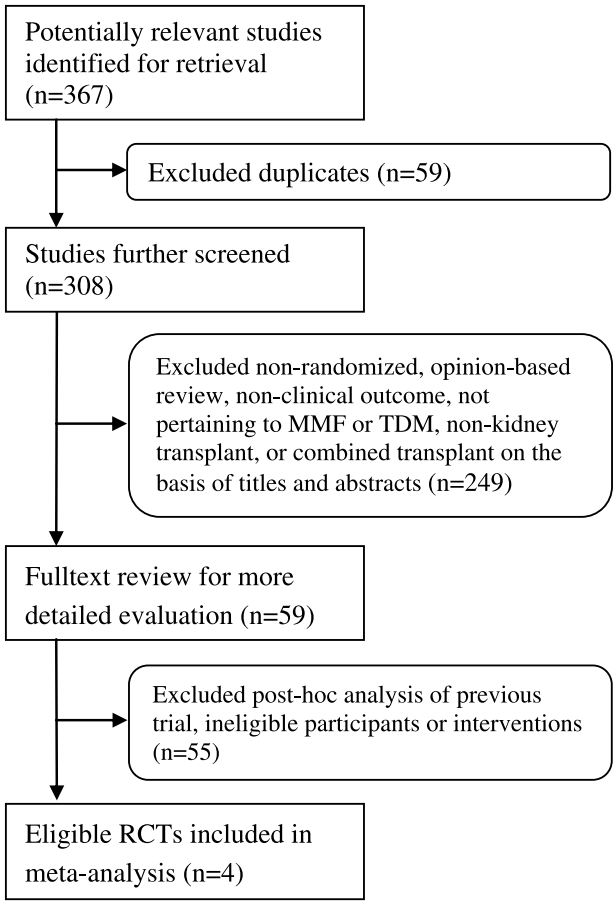

FIGURE 1. Procedure for the search and selection of RCTs included in the systematic review and meta-analysis. RCT, randomized controlled trial.

(CD) administration of MMF based on MPA therapeutic monitoring compared with a fixed-dose (FD) regimen.

Nevertheless, TDM for MMF is not routinely performed in most transplant centers (*9*). A full MPA $AUC_{0-12\ hr}$ measurement is labor intensive, costly, and clinically impractical (*10*). Alternatively, abbreviated AUC monitoring using limited samplings is convenient and may yield acceptable accuracy (*11, 12*). Currently, however, the optimal methodology remains to be elucidated (*13*). Furthermore, data regarding the clinical benefit of TDM-guided MMF dosing are conflicting. The first randomized controlled trial (RCT) regarding CD versus FD MMF, the APOMYGRE study, showed significantly less treatment failure and a lower incidence of biopsy-proven acute rejection in the CD arm. In contrast, another recent RCT, the FDCC study, failed to demonstrate a benefit for TDM-guided MMF dosing (*14*). Thus, more evidence on the validity of the CD MMF approach is needed.

Therefore, our study aimed to systematically evaluate the currently available evidence from RCTs on the outcomes of CD versus FD MMF for KTRs.

RESULTS

Search and Selection

The search and selection flow chart is illustrated in Figure 1. A total of four RCTs, APOMYGRE (*15*), FDCC (*14*), OPTICEPT (*16*), and OPERA (*17*), were finally included in the systematic review and meta-analysis.

Included Trials

The four eligible RCTs, representing a total of 1755 de novo KTRs, were reported in English-language journals and published over 4 years (between 2007 and 2011). All RCTs were multicenter trials. APOMYGRE and OPERA were conducted in France; FDCC in Europe, South America, Canada, Asia, and Australia; and OPTICEPT in the United States. APOMYGRE, FDCC, and OPERA had two study arms: CD versus FD MMF. OPTICEPT had three study arms: group A, CD MMF with reduced calcineurin inhibitor (CNI) levels; group B, CD MMF with standard CNI levels; and group C, FD MMF with standard CNI levels. In our meta-analysis, only KTRs in groups B and C were included. APOMYGRE and OPERA included only adult KTRs, whereas FDCC and OPTICEPT included both pediatric and adult KTRs. The general study characteristics of the four RCTs are summarized in Table 1. The methodology of pharmacokinetic measurement of MPA exposure is listed in Table 2.

Quality of Included Trials

Overall, the quality of the included trials was moderate. APOMYGRE, FDCC, and OPERA had a Jadad score of three, whereas OPTICEPT had a score of two. OPTICEPT did not report a method of allocation concealment. All four RCTs reported completeness of follow-up and an intention-to-treat (ITT) analysis.

Treatment Failure

Treatment failure was defined as any one of the following events (whichever was reached first): acute rejection, graft loss, death, or MMF discontinuation. Based on the four RCTs, the pooled proportion of KTRs reaching the composite endpoint of treatment failure was 28.1% (246 of 877) and 29.3% (257 of 878) over the follow-up period in the CD and FD groups, respectively. The meta-analysis showed that the incidence of treatment failure in the CD group was not different from that in the FD group (relative risk [RR], 0.95; 95% confidence interval [CI], 0.82–1.10; P=0.52; I^2=44%; Fig. 2A).

Additionally, there was no significant between-group difference for any component of treatment failure (Table 3). There was significant heterogeneity among the trials for acute rejection (I^2=65%). We first performed a sensitivity analysis by removing OPTICEPT, which had a lower quality score and used MPA trough concentrations to adjust MMF doses (the remaining three RCTs used limited sampling methods), but subsequent analysis showed that heterogeneity still existed (I^2=77%). Then, we hypothesized that the heterogeneity may have been caused by APOMYGRE. First, its sample size was the smallest among the four RCTs (130 of 1755). Second, MMF dose adjustments were calculated by a computer program to reach the target MPA AUC, whereas, in the other RCTs, dosing adjustments were left to the discretion of the investigators. After removing APOMYGRE, there was no more heterogeneity (RR, 1.10; 95% CI, 0.90–1.35; P=0.35; I^2=0%).

TABLE 1. General study characteristics of eligible trials included in the systematic review

Trials	No. KTRs	Induction/maintenance immunosuppression	Intervention	Main outcomes	Follow-up duration
APOMYGRE 2007	130	IL2-RA/CsA+MMF±Pred	CD: target MPA AUC of 40 mg hr/L; FD: MMF 2 g/d	Acute rejection, death, GI AEs, graft function, graft loss, hematologic AEs, infection, MMF discontinuation, treatment failure	12 mo
FDCC 2008	901	Multiformity/CNI+ MMF+Pred	CD: target MPA AUC of 45 mg hr/L; FD: MMF 2 g/d for adults and 1.2 g/m^2/d for pediatrics	Acute rejection, death, GI AEs, graft loss, hematologic AEs, infection, malignancy, MMF discontinuation, treatment failure	12 mo
OPTICEPT 2009	477	Multiformity/CNI +MMF±Pred	CD: target MPA trough level ≥1.3 mg/L (CsA) and ≥1.9 mg/L (FK); FD: MMF 2 g/d for adults and 1.2 g/m^2/d for pediatrics	Acute rejection, death, GI AEs, graft loss, hematologic AEs, infection, malignancy, MMF discontinuation, treatment failure	2 yr
OPERA 2011	247	IL2-RA/CsA+ MMF±Pred	CD: target MPA AUC of 40 mg hr/L; FD: MMF 2 g/d	Acute rejection, death, GI AEs, graft function, graft loss, hematologic AEs, infection, MMF discontinuation, treatment failure	12 mo

AEs, adverse events; AUC, area under the curve; CD, controlled-dose; CNI, calcineurin inhibitor; CsA, cyclosporine; FD, fixed-dose; FK, tacrolimus; GI, gastrointestinal; IL2-RA, interleukin-2 receptor antagonist; KTRs, kidney transplant recipients; MMF, mycophenolate mofetil; MPA, mycophenolic acid; Pred, prednisolone.

However, there was little change in acute rejection after sensitivity analyses performed with and without APOMYGRE.

Graft Function

The common measure of graft function was estimated creatinine clearance, as reported in APOMYGRE and OPERA (377 KTRs). No significant difference was observed between the CD and the FD groups (weighted mean difference [WMD], 2.46; 95% CI, −1.15 to 6.07; P=0.18; I^2=0%).

The serum creatinine level was also reported in APOMYGRE (130 KTRs), and again, no significant difference was observed between groups (WMD, −13.00; 95% CI, −30.46 to 4.46; P=0.14).

Gastrointestinal Adverse Events

The incidence of gastrointestinal adverse events (AEs) was reported in APOMYGRE (130 KTRs), with 24.6% (16 of 65) and 20.0% (13 of 65) in the CD and FD groups, respectively (RR, 1.23; 95% CI, 0.65–2.35; P=0.53).

FDCC, OPTICEPT, and OPERA (1624 KTRs) only recorded the incidence of diarrhea: CD versus FD, 28.9% (234 of 809) versus 27.0% (220 of 815; RR, 1.08; 95% CI, 0.92–1.25; P=0.35; I^2=0%).

Hematologic Adverse Events

One or more hematologic AEs, including anemia, leucopenia, and thrombocytopenia, were recorded in the four RCTs. The pooled estimate of APOMYGRE, FDCC, and OPERA (1283 KTRs) showed that the overall incidence of anemia was 29.8% (191 of 641) in the CD group and 26.2% (168 of 642) in the FD group, which were not significantly different (RR, 1.13; 95% CI, 0.97–1.32; P=0.12; I^2=0%).

The pooled estimate of the four RCTs (1754 KTRs) showed that the overall incidence of leukopenia was 20.4%

TABLE 2. Methodology of the pharmacokinetic measurement of MPA exposure

Trials	Method of MPA quantification	Time points of samplings (after MMF administration)	MPA AUC calculation	Schedule for TDM (posttransplantation)
APOMYGRE 2007	HPLC	20 min and 1 and 3 hr	Bayesian estimation	Days 7 and 14, months 1, 3, 6, and 12
FDCC 2008	EMIT (53%), HPLC (47%)	0, 30, and 120 min	Multiple regression	Days 3 and 10, week 4, months 3, 6, and 12
OPTICEPT 2009[a]	NR	0, 30, and 120 min	NR	Days 3, 10, and 30, months 3, 6, and 12
OPERA 2011	HPLC	20 min and 1 and 3 hr	Bayesian estimation	Weeks 2, 6, 12, 26, and 52

[a] MMF doses were adjusted based on trough levels, although abbreviated AUCs were also determined during the trial.

AUC, area under the curve; EMIT, enzyme multiplied immunoassay technique; HPLC, high-performance liquid chromatography; MMF, mycophenolate mofetil; MPA mycophenolic acid; NR, not reported; TDM, therapeutic drug monitoring.

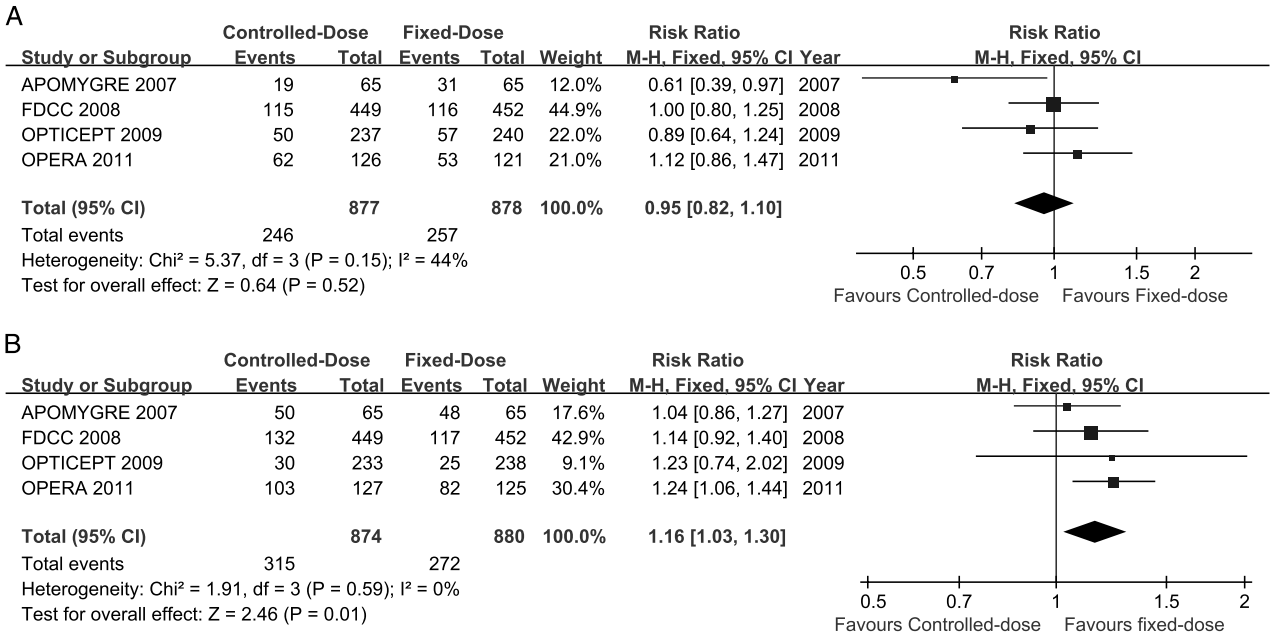

FIGURE 2. Forest plot showing the risk ratio of posttransplantation treatment failure (A) and infection (B). Fixed-effects model. Boxes represent risk ratio in individual trials, and diamonds represent summary effects. Relative ratio below 1 favors controlled-dose mycophenolate mofetil. Horizontal bars represent 95% CIs. CI, confidence interval.

(178 of 874) in the CD group and 18.3% (161 of 880) in the FD group, which were also not significantly different (RR, 1.12; 95% CI, 0.93–1.35; P=0.25; I^2=23%).

The incidence of thrombocytopenia was reported in FDCC (901 KTRs), with 5.1% (23 of 449) and 6.4% (29 of 452) in the CD and FD groups, respectively (RR, 0.80; 95% CI, 0.47–1.36; P=0.41).

Infections

Data regarding total infections were reported in all four RCTs (1754 KTRs). The application of CD MMF significantly increased the risk of total infections compared with FD MMF (36.0% vs. 30.9%; RR, 1.16; 95% CI, 1.03–1.30; P=0.01), with low heterogeneity (I^2=0%; Fig. 2B).

Bacterial infection, cytomegalovirus, herpes, and BK virus were the most commonly reported infections after kidney transplantation. Comparing CD with FD, bacterial infection (47.4% vs. 44.2%; RR, 1.07; 95% CI, 0.86–1.33; P=0.53; I^2=0%), cytomegalovirus (15.5% vs. 13.8%; RR, 1.12; 95% CI, 0.82–1.53; P=0.49; I^2=24%), and BK virus (3.0% vs. 3.4%; RR, 0.89; 95% CI, 0.33–2.43; P=0.83) were not significantly different, but herpes (9.4% vs. 3.7%; RR, 2.54; 95% CI, 1.09–5.95; P=0.03; I^2=49%) was significantly different.

Malignancy

FDCC and OPTICEPT reported the incidence of malignancy after kidney transplantation. The pooled incidence of malignancy was 1.3% (9 of 682) in the CD group and 2.2% (15 of 690) in the FD group. A meta-analysis showed that CD MMF did not decrease the probability of posttransplantation malignancy (RR, 0.61; 95% CI, 0.27–1.38; P=0.23; I^2=0%).

Cost-Effectiveness Analysis

The cost-effectiveness of CD versus FD MMF was reported in the post hoc analysis of APOMYGRE (*18*). The mean total yearly cost per KTR was €47,477 in the CD

TABLE 3. Meta-analysis results of CD versus FD MMF for each component of treatment failure

Outcome	RCTs (n)	Incidence (CD vs. FD)	Relative risk (95% CI)	Heterogeneity	
				P	I^2
Acute rejection[a]	4	18.9% (166/877) vs. 18.6% (163/878)	0.97 (0.66–1.42)	0.04	65%
BPAR	4	14.4% (126/877) vs. 14.5% (127/878)	0.95 (0.59–1.52)	0.02	68%
SCAR	1	9.3% (8/86) vs. 10.0% (8/80)	0.93 (0.37–2.36)	—	—
Graft loss	4	3.4% (30/877) vs. 4.6% (40/878)	0.75 (0.47–1.19)	0.70	0
Death	4	2.3% (20/877) vs. 2.8% (25/878)	0.80 (0.45–1.43)	0.44	0
MMF discontinuation	4	8.2% (72/877) vs. 8.8% (77/878)	0.93 (0.69–1.27)	0.95	0

[a] Acute rejection includes BPAR, SCAR at protocol biopsy, and presumptive acute rejection without biopsy performed.

BPAR, biopsy-proven acute rejection; CD, controlled-dose; CI, confidence interval; FD, fixed-dose; MMF, mycophenolate mofetil; RCT, randomized controlled trials; SCAR, subclinical acute rejection.

group and €46,783 in the FD group (P=0.7). The three largest expenditure categories (in decreasing order) were hospitalization, outpatient medications (including CNIs and MMF), and transportation. The observed incremental cost-effectiveness ratio was €3757 per treatment failure. The cost for MMF TDM was €452 per KTR, which is less than 1% of the total cost.

DISCUSSION

Summary of Key Findings

Combined data from the four eligible RCTs involving 1755 KTRs showed that, compared with FD MMF, CD MMF increased the risk of opportunistic infection by approximately 16% without overall benefit to prevent treatment failure (acute rejection, graft loss, death, and MMF discontinuation), reduced the incidence of gastrointestinal AEs, hematologic AEs, or malignancy, or protected graft function. Our findings suggest that TDM for MMF cannot be recommended as routine practice for KTRs. This finding is contrary to transplant clinicians' anticipation that CD MMF would result in a lower proportion of KTRs achieving treatment failure and MPA-associated AEs.

Previous Reviews

Only one previous systematic review (*19*) has addressed this topic, and it reported that the role of MMF TDM was uncertain. The majority of eligible studies were retrospective in nature, and only one RCT (APOMYGRE) was included. Such retrospective studies are unable to justify the adoption of a costly TDM regimen in everyday clinical practice. Identified studies involved adult or pediatric solid organ transplant recipients; thus, the patient population was much more heterogeneous, and an accurate comparison is difficult because the data on KTRs were analyzed together with those of liver and heart recipients. Clearly, the conclusions that can be drawn from these retrospective studies are limited.

Current Methodology of the Pharmacokinetic Measurement of Mycophenolic Acid Exposure

Due to its higher sensitivity and specificity, high-performance liquid chromatography, rather than enzyme multiplied immunoassay technique, is regarded as the gold standard technique for MPA concentration measurement (*6*). A full $AUC_{0-12\ hr}$ measurement is the most accurate predictor of MPA exposure; however, it is laborious, costly, and clinically impractical (*10*). Conversely, single-point measurement is at the other extreme (*4*). A practical alternative is the use of limited samplings coupled with multiple regression or Bayesian estimation (*11, 12*). Barraclough et al. (*20*) compared the ability of different MPA AUC estimations to predict MPA exposure for KTRs and demonstrated that Bayesian estimation is slightly superior to trough and multiple regression predictions in correlation and accuracy and may be the preferable methodology.

Regarding limited sampling methods, no consensus sampling time points are regarded as optimal (*21*). In the four eligible RCTs, three sampling time points were used: 20 min and 1 and 3 hr in APOMYGRE and OPERA and 0, 30, and 120 min in FDCC and OPTICEPT. Optimizing TDM does not necessarily require a high frequency of AUC measurements. Monitoring is recommended every week during the first month after transplantation and every 1 to 3 months thereafter for up to 1 year; after 1 year, if graft function has stabilized, MPA exposure can be assessed each time the immunosuppressive regimen is changed or a potentially interacting medication is introduced or withdrawn (*6, 21, 22*).

Strengths and Limitations

Our systematic review identified all available RCTs evaluating CD versus FD MMF for KTRs. Our methodology was robust, searching all possible studies, even in the abstract form and non-English-language sources, and used a strict assessment of trial quality. To avoid heterogeneity, our study did not include trials in which enteric-coated mycophenolate sodium (EC-MPS) was investigated, because EC-MPS has different pharmacokinetic properties from MMF, and strategies to estimate MPA exposure from EC-MPS have not yet been developed (*21*). Consequently, the current study provides critical information to guide clinical decisions on TDM for MMF.

Nevertheless, there are potential caveats affecting the validity of our findings. First, the proportion of KTRs achieving the target therapeutic window was similar between the two groups throughout the follow-up period (CD vs. FD, 68.6% vs. 63.6%) in FDCC (with the largest sample size among the four RCTs, 901 of 1755) because transplant clinicians were sometimes reluctant to make dosage changes according to the results of the MPA AUC. The failure to achieve the target therapeutic window may have contributed to the inability to detect significant differences between the CD and FD MMF arms in efficacy outcome measures. Second, the four RCTs differed in how they evaluated MPA exposure. APOMYGRE and OPERA used limited sampling methods combined with Bayesian estimation to make dosing adjustments, FDCC used limited sampling methods combined with multiple regression, and OPTICEPT used trough concentration measurements. Given the different predictive values for MPA exposure, uniformity in efficacy and safety across trials could not be expected and was not observed. Third, all KTRs included in our study were receiving CNI-based immunosuppression regimens. If there are differences in the efficacy and safety of MMF TDM between CNI-treated and non-CNI-treated KTRs, then our findings may not apply to non-CNI-treated KTRs.

Clinical Implications

The relationship between MPA exposure and the risk of acute rejection in KTRs treated with MMF has been confirmed by numerous pharmacokinetic studies (*8*). CD MMF may overcome the problems of interpatient variability and time-dependent variation of MPA pharmacokinetics. Based on the four RCTs, the mean MPA AUC was higher in the CD group in the early posttransplantation period (<1 month) but generally was not maintained thereafter; furthermore, a higher proportion of KTRs had an MPA AUC more than 60 mg hr/L in the CD group. Thus, CD MMF administration does not translate into overall benefit to prevent treatment failure but is prone to develop posttransplantation infections. In the current clinical practice, routine MMF TDM cannot be recommended for KTRs. Our meta-analysis highlights selectively performing TDM for MMF only for the high-risk KTRs (*22*). It may be a cost-effective strategy. Unfortunately, limited data are available on the assessment of high-risk factors for deciding MMF TDM. The

current consensus indications for MMF TDM in KTRs are delayed graft function, immunosuppressive protocols excluding induction therapy, steroids or CNIs, and CNI minimization (*9*). To better define subpopulations that might benefit, a post hoc exploratory analysis of FDCC and OPTICEPT was performed, revealing that other potential indications were body weight less than 50 or more than 100 kg, pediatric KTRs, second or third transplantation, panel-reactive antibodies more than 15%, four or more human leukocyte antigen mismatches, and black race (*7, 23–26*). The identification of risk factors eligible for MMF TDM poses a potentially useful field of research in clinical transplantation.

In summary, CD MMF based on TDM is, to some extent, prone to result in some AEs without overall benefit to prevent treatment failure. Therefore, TDM for MMF cannot be recommended as routine practice for KTRs, and it may be targeted toward high-risk KTRs, who must be defined in the future.

MATERIALS AND METHODS

Search Strategy

The electronic databases Medline, Embase, and the Cochrane Library were searched from the start date of each resource up to June 2012 (date of literature search) with logical combinations of the following terms: kidney, renal transplantation, allograft, MMF, CellCept (Roche, Basel, Switzerland), MPA, FD, CD, AUC, TDM, limited to humans, and RCTs. No restriction of report language, age of KTRs, or immunosuppressive protocols was applied to the search strategy. In addition, the results were supplemented by searching clinical trial registries (including but not limited to WHO International Trial Registry Network, ClinicalTrials.gov, and Australian & New Zealand Clinical Trials Registry), bibliographies of reviews and identified RCTs, transplant textbooks, abstracts of transplant conference proceedings, and directly contacting the manufacturers of MMF (CellCept).

Selection Criteria

To be eligible, the following inclusion criteria had to be met: (a) the publication type was RCT, (b) participants were recipients of a single kidney allograft (first or repeat) from a living or deceased donor, (c) the immunosuppression regimen consisted of MMF, and (d) participants were randomly allocated to either the CD group or the FD group. To obtain a uniform study population and to minimize heterogeneity, participants who received another solid organ in addition to a kidney transplant were excluded. Participants who were randomized but subsequently did not receive a kidney transplant were considered justifiable exclusions from the ITT population (so-called "modified ITT", which was put forward by the Centre for Evidence in Transplantation; http://www.transplantevidence.com/library_rct.php). When results from the same participants in a clinical trial were published more than once, the first complete publication was identified (the index publication) and used as the primary data source. However, any other additional publications that included additional outcomes of interest also contributed to the meta-analysis.

Data Collection

All citations identified by the search strategy were independently evaluated by X.W. and X.Q. using titles, abstracts, and, where required, the full text to identify eligible trials. Data extraction was independently conducted by the same two reviewers using a predesigned data extraction form, including study design, participant demographics, interventions, and outcome measures. Trial authors or sponsors were contacted for missing data. X.W. and X.Q. then met to combine their findings, and the information was subsequently entered into Review Manager (RevMan version 5.1.6; The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen). The primary treatment endpoint was the proportion of KTRs experiencing treatment failure, which was defined as any one of the following events (whichever was reached first): acute rejection, graft loss, death, or MMF discontinuation. Acute rejection was measured in three ways: biopsy-proven acute rejection, subclinical acute rejection at the protocol biopsy, and acute rejection diagnosed clinically without biopsy. The secondary treatment outcomes were graft function, gastrointestinal AEs, hematologic AEs, infections, malignancies, and cost-effectiveness.

Methodological Quality of Trials

The quality of the trials was independently assessed by X.W. and Y.W. based on the Jadad score (0–5) across four items: randomization, blinding, withdrawals, and dropouts (*27, 28*). A score of three or more is considered good quality. Additionally, allocation concealment and ITT analysis were assessed. Disagreements on data collection and quality assessment were resolved by consensus or, when necessary, by consulting T.L.

Statistical Analysis

All statistical analyses were performed using RevMan version 5.1.6. $P<0.05$ was considered to be statistically significant. Dichotomous measures were expressed as RR, and continuous variables were expressed as WMD. All summary effects are presented with 95% CI. Meta-analysis was undertaken using the fixed- or random-effects models (depending on the absence or presence of heterogeneity) to estimate effect sizes for each outcome measure. Heterogeneity across RCTs was investigated via forest plots, Cochrane's Q ($P<0.1$), and I^2 statistics ($I^2>50\%$). If significant heterogeneity existed, a sensitivity analysis was additionally used to explore possible sources of heterogeneity. Publication bias was assessed by analyzing funnel plot asymmetry.

ACKNOWLEDGMENTS

The authors thank the editors and reviewers for the constructive comments and suggestions that were of great help in improving the quality of article.

REFERENCES

1. Guerra G, Ciancio G, Gaynor JJ, et al. Randomized trial of immunosuppressive regimens in renal transplantation. *J Am Soc Nephrol* 2011; 22: 1758.
2. Sunder-Plassmann G, Reinke P, Rath T, et al. Comparative pharmacokinetic study of two mycophenolate mofetil formulations in stable kidney transplant recipients. *Transpl Int* 2012; 25: 680.
3. Gourishankar S, Houde I, Keown PA, et al. The CLEAR study: a 5-day, 3-g loading dose of mycophenolate mofetil versus standard 2-g dosing in renal transplantation. *Clin J Am Soc Nephrol* 2010; 5: 1282.
4. Miura M, Niioka T, Kato S, et al. Monitoring of mycophenolic acid predose concentrations in the maintenance phase more than one year after renal transplantation. *Ther Drug Monit* 2011; 33: 295.
5. van Gelder T. Mycophenolate blood level monitoring: recent progress. *Am J Transplant* 2009; 9: 1495.
6. Saint-Marcoux F, Vandierdonck S, Premaud A, et al. Large scale analysis of routine dose adjustments of mycophenolate mofetil based on global exposure in renal transplant patients. *Ther Drug Monit* 2011; 33: 285.
7. van Gelder T, Silva HT, de Fijter H, et al. How delayed graft function impacts exposure to mycophenolic acid in patients after renal transplantation. *Ther Drug Monit* 2011; 33: 155.
8. Glander P, Sommerer C, Arns W, et al. Pharmacokinetics and pharmacodynamics of intensified versus standard dosing of mycophenolate sodium in renal transplant patients. *Clin J Am Soc Nephrol* 2010; 5: 503.
9. Le Meur Y, Borrows R, Pescovitz MD, et al. Therapeutic drug monitoring of mycophenolates in kidney transplantation: report of The Transplantation Society consensus meeting. *Transplant Rev (Orlando)* 2011; 25: 58.
10. Staatz CE, Tett SE. Maximum a posteriori Bayesian estimation of mycophenolic acid area under the concentration-time curve: is this clinically useful for dosage prediction yet? *Clin Pharmacokinet* 2011; 50: 759.
11. Musuamba FT, Rousseau A, Bosmans JL, et al. Limited sampling models and Bayesian estimation for mycophenolic acid area under the curve prediction in stable renal transplant patients co-medicated with ciclosporin or sirolimus. *Clin Pharmacokinet* 2009; 48: 745.
12. Zhao W, Fakhoury M, Baudouin V, et al. Limited sampling strategy for estimating individual exposure of tacrolimus in pediatric kidney transplant patients. *Ther Drug Monit* 2011; 33: 681.

13. Kuypers DR, Le Meur Y, Cantarovich M, et al. Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. *Clin J Am Soc Nephrol* 2010; 5: 341.
14. van Gelder T, Silva HT, de Fijter JW, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation* 2008; 86: 1043.
15. Le Meur Y, Buchler M, Thierry A, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transplant* 2007; 7: 2496.
16. Gaston RS, Kaplan B, Shah T, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. *Am J Transplant* 2009; 9: 1607.
17. Le Meur Y, Thierry A, Glowacki F, et al. Early steroid withdrawal and optimization of mycophenolic acid exposure in kidney transplant recipients receiving mycophenolate mofetil. *Transplantation* 2011; 92:1244.
18. Rousseau A, Laroche ML, Venisse N, et al. Cost-effectiveness analysis of individualized mycophenolate mofetil dosing in kidney transplant patients in the APOMYGRE trial. *Transplantation* 2010; 89: 1255.
19. Knight SR, Morris PJ. Does the evidence support the use of mycophenolate mofetil therapeutic drug monitoring in clinical practice? A systematic review. *Transplantation* 2008; 85: 1675.
20. Barraclough KA, Isbel NM, Staatz CE. Evaluation of the mycophenolic acid exposure estimation methods used in the APOMYGERE, FDCC, and Opticept trials. *Transplantation* 2010; 90: 44.
21. Tett SE, Saint-Marcoux F, Staatz CE, et al. Mycophenolate, clinical pharmacokinetics, formulations, and methods for assessing drug exposure. *Transplant Rev (Orlando)* 2011; 25: 47.
22. van Gelder T, Le Meur Y, Shaw LM, et al. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* 2006; 28: 145.
23. Kaplan B, Gaston RS, Meier-Kriesche HU, et al. Mycophenolic acid exposure in high- and low-weight renal transplant patients after dosing with mycophenolate mofetil in the Opticept trial. *Ther Drug Monit* 2010; 32: 224.
24. Hocker B, van Gelder T, Martin-Govantes J, et al. Comparison of MMF efficacy and safety in paediatric vs. adult renal transplantation: subgroup analysis of the randomised, multicentre FDCC trial. *Nephrol Dial Transplant* 2011; 26: 1073.
25. van Gelder T, Tedesco Silva H, de Fijter JW, et al. Renal transplant patients at high risk of acute rejection benefit from adequate exposure to mycophenolic acid. *Transplantation* 2010; 89: 595.
26. van Agteren M, Armstrong VW, van Schaik RH, et al. AcylMPAG plasma concentrations and mycophenolic acid-related side effects in patients undergoing renal transplantation are not related to the UGT2B7-840G>A gene polymorphism. *Ther Drug Monit* 2008; 30: 439.
27. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1.
28. Pengel L, Morris P. The transplant library of randomized controlled trials and systematic reviews. *Transplantation* 2011; 92: 613.