OPEN

Mycophenolate Dose Reduction in Tacrolimus-based Regimens and Long-term Kidney Transplant Outcomes in Australia and New Zealand

Darren Lee, PhD,[1,2] Kevan R. Polkinghorne, PhD,[3,4,5,6] Helen Pilmore, PhD,[7] and William R. Mulley, PhD[3,6]

Background. Mycophenolate dose reduction (MDR) is associated with acute rejection and transplant failure in kidney transplant recipients (KTRs). The optimal dose to prevent rejection and reduce complications remains poorly defined in tacrolimus-based regimens. **Methods.** We assessed adult KTRs from 2005 to 2017 initiated on mycophenolate mofetil 2 g/d, tacrolimus, and prednisolone from the Australia and New Zealand Dialysis and Transplant Registry. KTRs with rejection within the first 30 d posttransplant were excluded. The primary outcome was time to first rejection between 30 d and 2 y posttransplant. Mycophenolate dose was modeled as a time-varying covariate using Cox proportional hazards regression. Secondary outcomes included assessment of early MDR to <1.5 g/d within the first 6 mo posttransplant and subsequent patient and death-censored graft survival. **Results.** In the primary analysis, 3590 KTRs were included. Compared with mycophenolate dose of ≥2 g/d, both 1.0–<1.5 and <1 g/d were associated with an increased risk of rejection during the 2 y posttransplant (hazard ratio [HR] 1.67; 95% confidence interval [CI], 1.29-2.16; $P < 0.001$ and HR 2.06; 95% CI, 1.36-3.13; $P = 0.001$, respectively) but not 1.5–<2 g/d (HR 1.20; 95% CI, 0.94-1.53; $P = 0.14$). Early MDR to <1.5 g/d occurred in 45.3% of KTRs and was an independent risk factor for death-censored graft failure (HR 1.32; 95% CI, 1.05-1.66; $P = 0.016$) but not death (HR 1.18; 95% CI, 0.97-1.44; $P = 0.10$), during a median follow-up of 5.0 (interquartile range, 2.6–8.5) y. **Conclusions.** Early MDR was a risk factor for subsequent rejection and graft failure in KTRs receiving contemporary tacrolimus-based regimens.

(*Transplantation Direct* 2024;10: e1659; doi: 10.1097/TXD.0000000000001659.)

Received 12 March 2024. Revision received 3 April 2024.
Accepted 3 April 2024.

[1] *Department of Renal Medicine, Eastern Health Clinic School, Monash University, Box Hill, VIC, Australia.*
[2] *Department of Nephrology, Austin Health, Heidelberg, VIC, Australia.*
[3] *Department of Nephrology, Monash Health, Clayton, VIC, Australia.*
[4] *Department of Medicine, Monash University, Clayton, VIC, Australia.*
[5] *Department Epidemiology and Preventative Medicine, Monash University, Clayton, VIC, Australia.*
[6] *Department of Medicine, Centre for Inflammatory Diseases, Monash University, Clayton, VIC, Australia.*
[7] *Department of Renal Medicine, Auckland City Hospital, Auckland, New Zealand.*

D.L., W.R.M., and K.R.P. participated in the research design and data analysis. D.L. participated in writing the article. D.L., W.R.M., K.R.P., and H.P. participated in revising the article.
The authors declare no funding or conflicts of interest.
Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).
Correspondence: Darren Lee, PhD, Department of Renal Medicine, Eastern Health Clinic School, Monash University, Level 2, 5 Arnold St, Box Hill, VIC 3128, Australia. (darren.lee@easternhealth.org.au).

ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000001659

After the publication of the ELITE-SYMPHONY study in 2007,[1] triple maintenance immunosuppression regimens comprising prednisolone, tacrolimus, and 2 g/d of mycophenolate mofetil (MMF) became the standard of care for kidney transplant recipients (KTRs) in most jurisdictions.[2,3] Although tacrolimus trough levels of <5 ng/mL are well established as a risk factor for developing de novo donor-specific antibodies (DSAs) and rejection,[4] contemporary data regarding the impact of mycophenolate dose reduction (MDR) in tacrolimus-based regimens on rejection and long-term patient and graft survival are conflicting.[5-13] Possible explanations for these results include the assessment of a heterogenous group of KTRs initiated on various immunosuppression regimens with <3 y of follow-up, including studies from earlier eras with cyclosporine-based regimens[5,6,14,15] or lower mycophenolate starting dose,[7,8,10,11,13] neither of which reflecting the current standard of care. Given the wide interindividual mycophenolic acid (MPA) pharmacokinetic variability, MPA exposure estimation might help determine the optimal mycophenolate dosing in KTRs.[16] However, the optimal target concentrations in the maintenance phase of immunosuppression to minimize complications remain unclear.[17,18] As a result, the minimum effective mycophenolate dose is not well defined.[5,6,19]

Reactive MDR is often necessary for the first year post-transplant primarily due to hematological and gastrointestinal toxicity as well as infective complications.[6,8,19,20] In the

ELITE-Symphony study, despite the trial protocol recommending the MMF dose to be maintained at 2 g/d throughout the study, the mean MMF dose at 12 and 36 mo were 1.531 and 1.353 g/d, respectively,[21] suggesting that maintaining a starting dose of 2 g/d may not be well tolerated. Alternatively, clinicians proactively reduced the MMF dose to avoid overimmunosuppression.

Using the binational, Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry to examine a contemporary cohort of KTRs on tacrolimus-based regimens and mycophenolate starting dose of 2 g/d, we aimed to (a) assess whether lower mycophenolate doses were associated with an increased risk of rejection in the first 2 y posttransplant, (b) identify the factors associated with early MDR within the first 6 mo posttransplant, and (c) compare the long-term patient and graft survival with or without early MDR. We hypothesized that early MDR was associated with an increased risk of subsequent rejection and graft failure in KTRs initiated on a contemporary tacrolimus-based regimen.

MATERIALS AND METHODS

Study Population

This is a retrospective observational cohort study. The ANZDATA registry collects data on consenting (>99%) patients receiving kidney replacement therapy in Australia and New Zealand (http://www.anzdata.org.au). Adult recipients of kidney-only transplants performed between January 1, 2005, and December 31, 2017, initiated on a daily MMF dose of 2 g/d (or an equivalent dose of mycophenolate sodium 1.44 g/d), tacrolimus, and prednisolone with at least a 12-mo follow-up, were eligible for inclusion. For the main cohort analysis, KTRs who experienced rejection, graft failure, or death within the first 30 d were excluded, as the first time point for reporting maintenance mycophenolate doses was 1 mo posttransplant (**Figure S1, SDC,** http://links.lww.com/TXD/A665). KTRs with missing data on any of the covariates included in the main model were also excluded. For the early MDR analysis cohort, KTRs with any unreported mycophenolate dose and no documented MDR (<1.5 g/d) within the first 6 mo were also excluded (**Figure S1, SDC,** http://links.lww.com/TXD/A665) because the possibility of early MDR could not be eliminated. The study was approved by the Eastern Health Office of Research and Ethics (LR20/046).

Primary Exposure

The primary exposure was time-varying mycophenolate dose, categorized into 5 groups: 2 g/d or more, 1.5–<2 g/d, 1.0–<1.5 g/d, <1.0 g/d (but not 0 g/d), or discontinued (no mycophenolate, including those switched to an alternative agent). Total daily mycophenolate dose was collected at initiation, 1, 2, 3, 6, 12, and 24 mo posttransplant. For KTRs on mycophenolate sodium, the total daily dose was converted to the equivalent MMF dose (1.44 g/d equivalent to 2 g/d) for all analyses. Data were presented as "mycophenolate" dose for KTRs on either MMF or mycophenolate sodium.

Early MDR was defined as a mycophenolate dose either reduced to <1.5 g/d or discontinued (no mycophenolate, including those switching to an alternative agent) at any time point within the first 6 mo posttransplant.

Outcomes

The primary outcome of this study was time to first kidney allograft rejection between 30 d and 2 y posttransplant. Secondary outcomes included death, overall and death-censored graft failure, and kidney function. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2009 equation.[22]

Covariates

For all the analyses assessing time to first rejection, death-censored graft failure, all-cause death, and risk factors for early MDR, covariates included were recipient age, recipient sex, dialysis duration, donor age, donor type, HLA mismatches, peak panel-reactive antibody (PRA) ≥80%, and delayed graft function (DGF).

Statistical Analysis

For baseline characteristics, continuous variables were presented as median (interquartile range [IQR]) unless otherwise specified, and comparisons between groups were performed using the 2-tailed Mann-Whitney *U* test. Categorical variables were presented as numbers (percentage of group) and compared using Pearson chi-square tests.

To examine the effect of mycophenolate dose on the risk of subsequent rejection between 30 d and 2 y posttransplant, Cox proportional hazards regression analysis was used with the mycophenolate dose category considered as a time-varying covariate. Rejection episodes were attributed to the last reported mycophenolate dose before rejection. To assess the effect of early MDR on the risk of death-censored graft failure and death from 6 mo posttransplant, Cox regression analysis was used. For all Cox models, the proportional hazards assumption was assessed graphically and by Schoenfeld residuals and was not found to be violated. To examine for factors associated with early MDR, logistic regression was used. All models were adjusted for donor age, recipient age, and recipient sex because they were considered, a priori, as clinically relevant to rejection, early MDR, death-censored graft failure, and death. Dialysis duration, HLA mismatches, peak PRA, and DGF were covariates included in all multivariable models because they were associated with all outcomes assessed in the univariable analyses ($P < 0.2$). Other factors associated with the following individual outcomes in the univariable analyses were also included in the respective multivariable models: rejection (tacrolimus daily dose [per mg/kg increase]), early MDR (peripheral vascular disease, chronic lung disease, donor type, total ischemic time, T cell–depleting induction, cytomegalovirus donor positive recipient negative status, and transplant jurisdiction), death (coronary artery disease and cerebrovascular disease), and both death-censored graft failure and death (diabetes at transplant, peripheral vascular disease, chronic lung disease, smoking status, donor type, and rejection within 6 mo posttransplant).

The Kaplan-Meier method was used to estimate the unadjusted rejection-free survival in the first 2 y posttransplant associated with each mycophenolate dose category, and the patient survival, overall graft survival, and death-censored graft survival beyond 6 mo posttransplant stratified by early MDR status within the first 6 mo. The eGFR gradients from 6 mo to 10 y posttransplant were compared between KTRs with and without early MDR using a linear mixed model.

A *P* value of <0.05 was considered significant. Data analysis was conducted using Stata version 17 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics and Dynamics of MDR

A total of 5724 incident adult KTRs with ≥12 mo of posttransplant follow-up were identified in the ANZDATA registry. Of those, 1348 were excluded as the mycophenolate starting dose was not 2 g/d; 622 had rejection, graft failure, or death within the first 30 d; and 164 with missing data (**Figure S1, SDC,** http://links.lww.com/TXD/A665), leaving 3590 KTRs in the primary outcome analysis. Table 1 shows the baseline characteristics of the cohort. The median age was 52 (IQR, 41–60) y. A living donor kidney transplant was received by 30.9% of patients. A peak PRA of ≥80% was found in 5.4% of patients, and T cell–depleting agents for induction were received by 4.4% of patients.

Figure 1 illustrates the mycophenolate dose changes during the 2-y posttransplant period. The proportion of KTRs remaining on ≥2 g/d (which included 0.6%–1.6% on >2 g/d of the ≥2 g/d group and 0.1%–1.1% on >2 g/d of the entire cohort) decreased from 72% at 1 mo to 47% at 3 mo, 34% at 6 mo, and 17% at 2 y posttransplant. In contrast, the proportion of 1–<1.5 g/d increased from 4% at 1 mo to 36% at 2 y. Although the percentage of KTRs on 1.5–<2 g/d remained static during the 2-y period, there was a noticeable movement from ≥2 to 1.5–<2 g/d and from 1.5–<2 to 1–<1.5 g/d at each time point. In contrast, those reduced to 1–<1.5 g/d were unlikely to subsequently increase their dose. At 2 y, 13% of KTRs were no longer on mycophenolate. The majority of KTRs who discontinued mycophenolate remained off the medication (Figure 1). Figure S2 (**SDC,** http://links.lww.com/TXD/A665) shows that for those who discontinued mycophenolate within the first 6 mo, a switch to azathioprine was most common, with only a minority returning to the starting triple immunosuppression regimen of mycophenolate, tacrolimus, and prednisolone.

Mycophenolate Dose and Risk of Rejection

The risk of rejection increased in a dose-dependent manner as the total mycophenolate dose reduced such that those taking <1 g/d had double the risk of rejection compared with the ≥2 g/d group (hazard ratio [HR] 2.06; 95% confidence interval [CI], 1.36-3.13; *P* = 0.001; Table 2; Figure 2). There was no significant increase in the rejection risk for 1.5–<2 g/d (HR 1.20; 95% CI, 0.94-1.53; *P* = 0.14). Those who completely ceased mycophenolate also had a higher risk of rejection; however, this was not significantly different after multivariate adjustment (HR 1.45; 95% CI, 0.93-2.23; *P* = 0.10).

Factors Associated With Early MDR (<1.5 g/d) Within 6 mo Posttransplant

After excluding 101 KTRs with any unreported data on mycophenolate dose at 1, 2, 3, or 6 mo and no documented MDR at any of these time points, 3489 KTRs were included in the early MDR analysis cohort (**Figure S1, SDC,** http://links.lww.com/TXD/A665). Overall, 45.3% of the cohort had an early MDR in the first 6 mo posttransplant. Table S1 (**SDC,** http://links.lww.com/TXD/A665) shows the baseline characteristics stratified by MDR status. Factors independently associated with an increased likelihood of an early MDR included increasing recipient age (OR 1.06 per 10 y increase; 95% CI, 1.00-1.13; *P* = 0.045), increasing donor age (OR 1.08 per 10 y increase; 95% CI, 1.03-1.13; *P* = 0.003), the use of T cell–depleting induction therapy (OR 1.74; 95% CI, 1.22-2.47; *P* = 0.002), and DGF (OR 1.69; 95% CI, 1.40-2.03; *P* < 0.001; Table 3). Compared with the overall early MDR rate in the cohort (45.3%), those

TABLE 1.

Baseline characteristics of kidney transplant recipients (N = 3590)

Characteristics	
Recipient characteristics at transplant	
Age, y	52 (41–60)
Female	1399 (39.0%)
BMI, kg/m^2	25.8 (22.5–29.7)
Diabetes	683 (19.0%)
Coronary artery disease	558 (15.5%)
Cerebrovascular disease	167 (4.7%)
Peripheral vascular disease	226 (6.3%)
Chronic lung disease	205 (5.7%)
Dialysis duration, y	2.4 (0.9–4.5)
Primary kidney disease	
Diabetic nephropathy	456 (12.7%)
Glomerulonephritis	1534 (42.7%)
Hypertension	224 (6.2%)
Polycystic kidney disease	516 (14.4%)
Reflux nephropathy	309 (8.6%)
Others or uncertain	551 (15.3%)
Transplant center jurisdiction	
New South Wales	1060 (29.5%)
Victoria and Tasmania	1352 (37.6%)
Queensland	231 (6.4%)
South Australia and the Northern Territory	420 (11.7%)
Western Australia	264 (7.4%)
New Zealand	263 (7.3%)
Donor characteristics	
Age, y	50 (39–60)
Female	1743 (48.6%)
Donor type	
Donation after circulatory death	572 (15.9%)
Donation after brain death	1910 (53.2%)
Living donor	1108 (30.9%)
HLA A-B-DR mismatches	
0	188 (5.2%)
1	279 (7.8%)
2	737 (20.5%)
3	620 (17.3%)
4	569 (15.8%)
5	771 (21.5%)
6	426 (11.9%)
Peak PRA, %, median (IQR)	0 (0–7)
PRA ≥80%,	194 (5.4%)
Repeat transplant	459 (12.8%)
Total ischemic time, h	9 (4-13)
Delayed graft function	768 (21.4%)
T cell–depleting induction	159 (4.4%)
CMV D$^+$R$^-$ status	409 (11.4%)

Continuous data are expressed as median (IQR); categorical data are expressed as n (%).
BMI, body mass index; CMV, cytomegalovirus; D$^+$R$^-$, donor positive recipient negative; IQR, interquartile range; PRA, panel-reactive antibody.

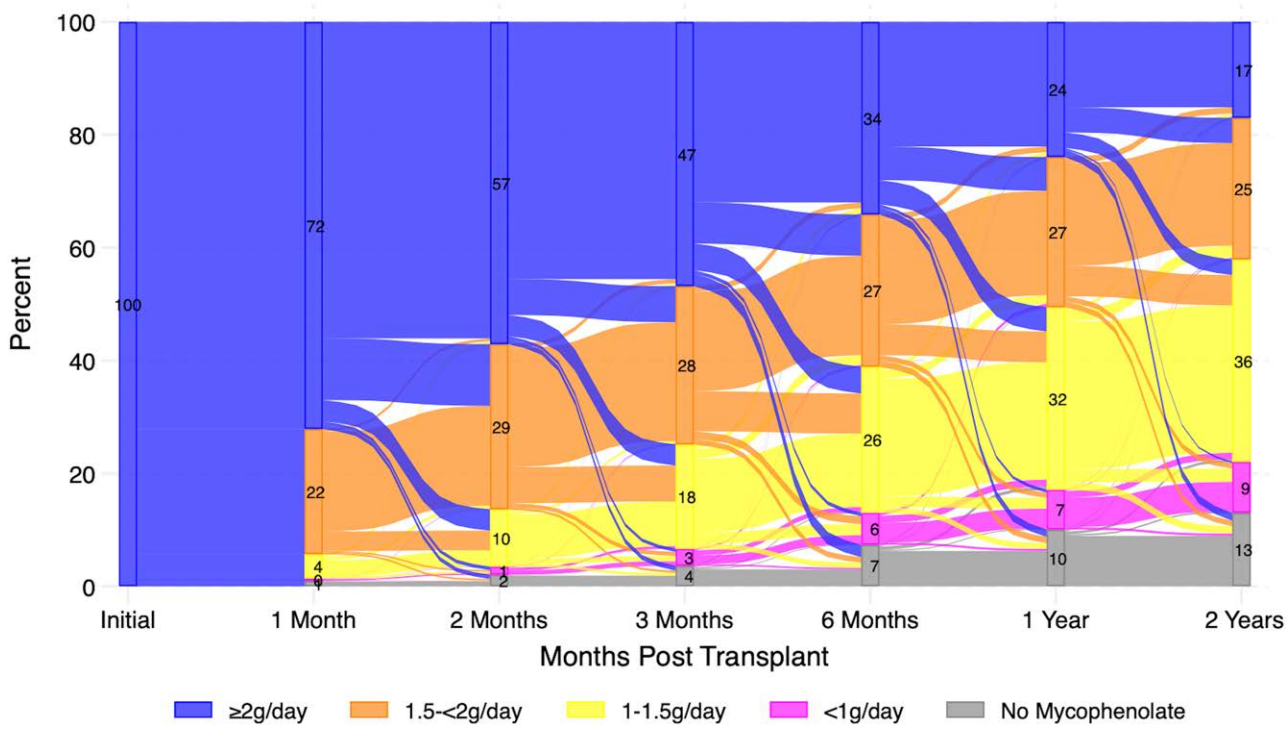


FIGURE 1. Mycophenolate dose changes during the first 2 y posttransplant. KTRs on >2 g/d dosing comprised ≤1.6% of the >2 g/d group and ≤1.1% of the entire cohort at any of the time points. KTR, kidney transplant recipient.

TABLE 2.

Cox proportional hazards regression analysis of mycophenolate dose as a time-varying covariate on subsequent rejection risk at 2 y

	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Mycophenolate dose, g/d				
≥2 g/d		Reference	1	Reference
1.5–<2	1.21 (0.95-1.53)	0.12	1.20 (0.94-1.53)	0.14
1.0–<1.5	1.72 (1.34-2.20)	**<0.001**	1.67 (1.29-2.16)	**<0.001**
<1	2.14 (1.43-3.20)	**<0.001**	2.06 (1.36-3.13)	**0.001**
Discontinued	1.55 (1.02-2.34)	**0.039**	1.45 (0.93-2.23)	0.10

Other covariates included in the multivariate model are presented in Table S4 (**SDC,** http://links.lww.com/TXD/A665). Bold values display statistical significance ($P < 0.05$).
CI, confidence interval; HR, hazard ratio.

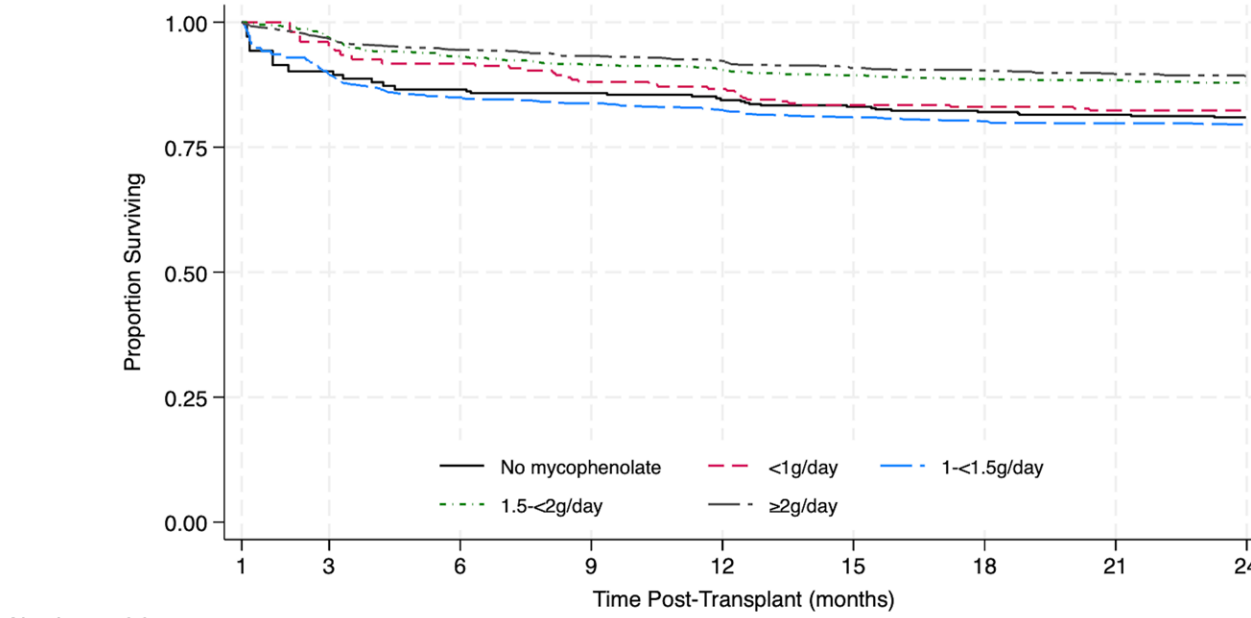
with transplants performed in Victoria/Tasmania and South Australia/the Northern Territory had higher adjusted odds of early MDR, whereas those performed in New South Wales and New Zealand were less likely to have a dose reduction (Table 3).

Long-term Patient and Graft Outcomes After Early MDR

Figure 3 compares the subsequent long-term outcomes of KTRs beyond 6 mo with or without early MDR within 6 mo posttransplant. Over a median follow-up of 5.0 (IQR, 2.6–8.5) y, patient survival (Figure 3A), overall graft survival (Figure 3B), and death-censored graft survival (Figure 3C) were all lower in the early MDR group (log-rank test $P = 0.001$, $P = 0.0007$, and $P = 0.03$, respectively). No significant difference was identified in the cause of death or death-censored graft failure with or without early MDR (**Table S2, SDC,** http://links.lww.com/TXD/A665). In the multivariable models (**Tables S3, S5, and S6, SDC,** http://links.lww.com/TXD/A665), MDR remained an independent risk factor for death-censored graft loss (HR 1.32; 95% CI, 1.05-1.66; $P = 0.016$) but not for death (HR 1.18; 95% CI, 0.97-1.44; $P = 0.10$). There was no difference in the eGFR gradients from 6 mo to 10 y posttransplant in KTRs with or without early MDR (linear mixed model: $P = 0.418$; Figure 3D). The mean eGFR was 54.4 ± 19.4 mL/min/1.73 m^2 at 6 mo to 53.0 ± 23.0 mL/min/1.73 m^2 at 10 y for KTRs with early MDR, compared with 58.2 ± 18.9 to 59.0 ± 21.6 mL/min/1.73 m^2 for those without early MDR.

DISCUSSION

This study examined the association of mycophenolate dosing with the subsequent risk of rejection and the long-term risk of death and graft failure. There were 2 key findings



Number at risk

No mycophenolate	35	124	245	243	317	312	308	306	0
<1g/day	14	109	200	192	241	232	231	229	0
1-<1.5g/day	156	691	875	863	1058	1039	1029	1024	0
1.5-<2g/day	859	989	918	902	856	846	839	837	0
≥2g/day	2670	1621	1089	1075	743	732	728	722	0

FIGURE 2. Rejection-free survival from 30 d to 2 y posttransplant stratified by mycophenolate dose group. Log-rank test $P < 0.001$.

in our study. First, compared with ≥2 g/d, mycophenolate doses of <1.5 g/d were associated with an increased risk of subsequent rejection in the first 2 y posttransplant in a dose-dependent manner. Second, early MDR to <1.5 g/d within the first 6 mo posttransplant was associated with an increased risk of subsequent death-censored graft failure.

Although previous retrospective cohort studies have similarly reported an association of early MDR with rejection, these included exclusively or primarily cyclosporine-based regimens, which are no longer the standard of care.[8,14,15] Cyclosporine inhibits the enterohepatic recirculation of, and hence the exposure to, MPA compared with tacrolimus cotreatment.[23] Even in studies that included KTRs initiated on tacrolimus-based regimens, the mycophenolate starting dose was not exclusively 2 g/d.[7,8,10,11,13] Given the superior outcomes from a mycophenolate starting dose of 2 g/d,[19,21] a lower starting dose can no longer be considered the standard of care. In contrast, our registry study included exclusively KTRs initiated on contemporary tacrolimus-based triple maintenance immunosuppression regimens with the mycophenolate starting dose of 2 g/d. We identified a possible minimum effective mycophenolate maintenance dose threshold of 1.5 g/d, below which there was an association with subsequent rejection. Therefore, this study is timely to add to the existing literature in this field. However, a significant association of mycophenolate discontinuation with rejection was not demonstrated. The most common immunosuppression regimen after mycophenolate discontinuation was triple immunosuppression with prednisolone, tacrolimus, and azathioprine. Given the observational nature of the registry data, it is not possible to exclude this group remaining on azathioprine to be at a lower immunological risk.

Another important finding in our study was the association of early MDR to <1.5 g/d within the first 6 mo with inferior unadjusted patient and graft survival. After adjusting for other factors, early MDR remained an independent risk factor for death-censored graft loss but not for death. As KTRs requiring MDR were an older and more vulnerable group at increased risk of death posttransplant, this could explain why MDR was not associated with death after adjusting for recipient age and comorbidities. Given our finding of increased rejection risks with lower mycophenolate doses, we postulate that early MDR would be associated with an increased incidence of chronic alloimmune injury and premature allograft failure from chronic rejection. This is supported by a recent study showing that MDR to <1 g/d was associated with the development of de novo DSAs.[24] However, we were unable to identify any significant differences in the causes of death-censored graft failure between groups. Given the observational nature of the registry data, it is difficult to ascertain from our study that MDR led to alloimmune injury and subsequent death-censored graft loss. Previous studies have reported conflicting findings, with some showing a similar association of early MDR with graft failure[5-7] but not in others.[8,15] Most of these studies included primarily KTRs initiated on cyclosporine-based regimens.[5,6,15] Unlike our study, these studies did not examine the effect of early MDR on patient survival.

Consistent with previous studies, recipient age[6,20,25] and donor age[6] (which could reflect older KTRs accepting kidneys from older donors despite adjustment in the logistic regression) were associated with early MDR. Although deceased donor transplantation was not a risk factor for MDR in our study,[25] an association with DGF was identified. It is unclear why T cell–depleting induction therapy was a factor for early

TABLE 3.

Multivariable logistic regression analysis of factors associated with early mycophenolate dose reduction

	OR (95% CI)	*P*
Recipient characteristics		
Age (per 10 y increase)	1.06 (1.00-1.13)	**0.045**
Sex (male vs female)	0.88 (0.76-1.01)	0.08
Peripheral vascular disease (yes vs no)	1.08 (0.84-1.37)	0.55
Chronic lung disease (yes vs no)	1.08 (0.83-1.40)	0.57
Dialysis duration (per year increase)	1.01 (0.98-1.03)	0.68
Transplant center jurisdiction[a]		
New Zealand	0.59 (0.46-0.75)	**<0.001**
Australian States		
New South Wales	0.77 (0.66-0.88)	**<0.001**
Victoria and Tasmania	1.45 (1.27-1.65)	**<0.001**
Queensland	0.94 (0.74-1.19)	0.59
South Australia and the Northern Territory	1.59 (1.32-1.92)	**<0.001**
Western Australia	1.03 (0.82-1.30)	0.82
Donor characteristics		
Age (per 10 y increase)	1.08 (1.03-1.13)	**0.003**
Donor type: living donor (yes vs no)	1.08 (0.85-1.36)	0.55
HLA A-B-DR mismatches		
0	1	Reference
1	0.71 (0.48-1.06)	0.10
2	0.86 (0.61-1.21)	0.38
3	0.82 (0.58-1.17)	0.27
4	0.95 (0.67-1.36)	0.78
5	0.95 (0.67-1.35)	0.79
6	0.93 (0.64-1.34)	0.69
Peak PRA ≥80% (yes vs no)	0.92 (0.66-1.29)	0.63
Total ischemic time (per hour increase)	1.01 (0.99-1.03)	0.21
Delayed graft function (yes vs no)	1.69 (1.40-2.03)	**<0.001**
T cell–depleting induction (yes vs no)	1.74 (1.22-2.47)	**0.002**

[a]Relative to the combined average.
Bold values display statistical significance ($P < 0.05$).
CI, confidence interval; OR, odds ratio; PRA, panel-reactive antibody.

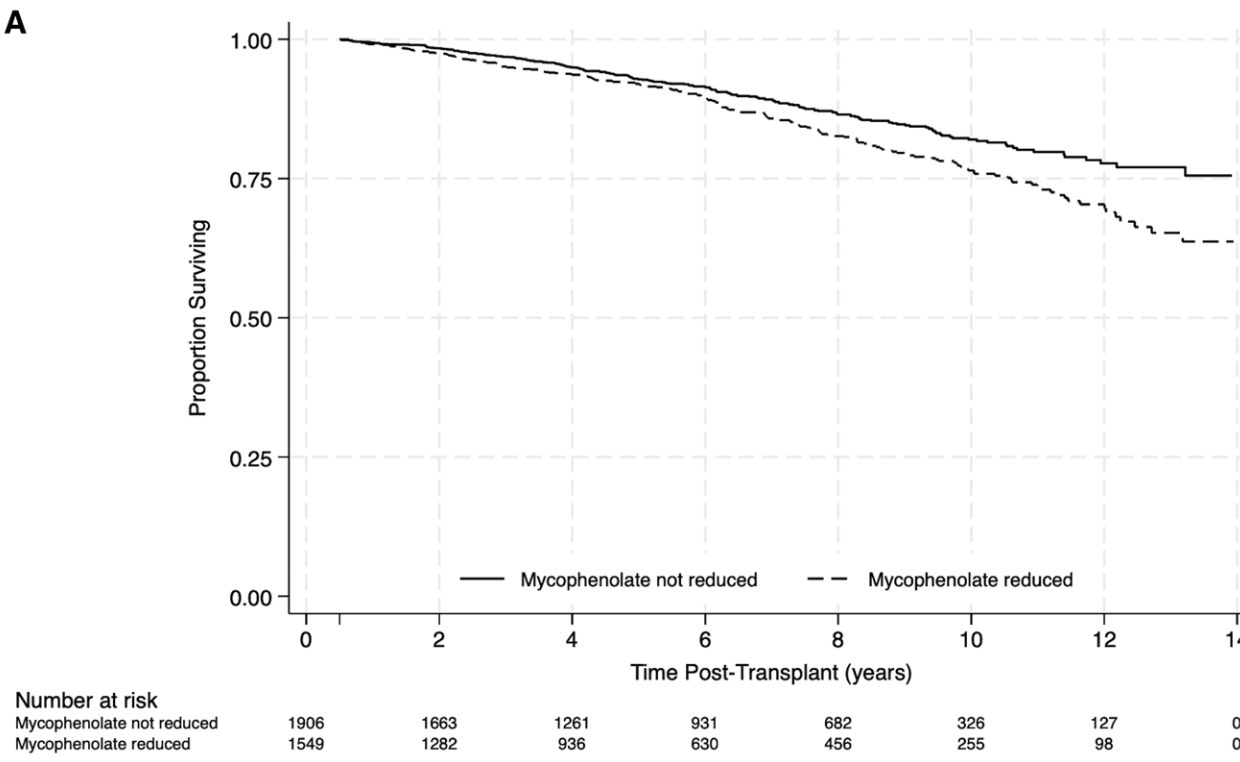
MDR. Basixilimab was the most common induction therapy used in Australia and New Zealand, unlike the United States and some parts of the world. Those treated with T cell–depleting induction likely represented a group with substantially higher immunological risk who received additional immunosuppression, which predisposed them to infective complications or cytopenia and necessitated early MDR.

It is possible that KTRs requiring early MDR simply reflected a cohort more susceptible to adverse events and inferior outcomes, with factors associated with MDR, such as frailty[25] not captured by the registry. Given the retrospective nature of a registry study, it is impossible to determine the causality between MDR and inferior outcomes. It is also difficult to ascertain the proportion of early MDR being a reactive response to adverse events or a proactive measure to minimize immunosuppression-related complications, either targeting at-risk KTRs or adhering to center-specific protocols, with or without MPA exposure measurements.[16] Given that KTRs from Victoria/Tasmania and South Australia/the Northern Territory were more likely to have early MDR, it would seem likely that at least some of the KTRs had early MDR based on a regional preemptive protocol-driven approach. Asian KTRs have been shown to have higher MPA exposure despite being maintained on lower mycophenolate doses when compared with Caucasians.[26] In addition, previous studies have identified that for KTRs 60 y or older, both reactive and preemptive MDR were associated with a reduced risk of serious infections and improved graft survival, respectively, without a significant increase in the rejection risk.[20,27] Regardless of whether MDR was proactive or reactive due to increased susceptibility to toxicity on standard dosing, early MDR might not increase the risk of rejection or graft failure in some ethnicities or susceptible KTRs, and this tailored response is justifiable. Given the wide interindividual pharmacokinetic variability, the use of MPA exposure measurements, either routinely early to avoid overimmunosuppression or after a proactive or reactive dose reduction to avoid underimmunosuppression, could be a useful tool to help define the tailored mycophenolate dose. However, the optimal target concentrations to minimize complications remain unclear in the maintenance phase with tacrolimus cotreatment, and this tool is yet to be accessible in all jurisdictions globally.[16,17]

Limitations

Our analysis is limited by the time points at which relevant data were reported to ANZDATA, meaning that the precise dates of mycophenolate dose changes were unavailable. Additionally, multiple-dose changes occurring between reporting time points would not be captured, because only the dose at the reporting time point would be entered. Nevertheless, we were able to demonstrate that those with a dose reduction were unlikely to subsequently increase the dose, and those with discontinuation were also unlikely to recommence mycophenolate. Uncaptured confounders, such as frailty and infection episodes, are inevitable in registry studies. Therefore, we cannot determine the causality of early MDR or whether this is simply a risk factor for inferior patient and graft survival in susceptible individuals. Data for pretransplant DSAs were not reported to the ANZDATA registry to stratify the baseline immunological risk. However, calculated PRA and HLA mismatches were included as covariates for the analyses. Our Australian and New Zealand cohort included mostly Caucasians treated with basiliximab induction, and therefore, our findings might not apply to some regions of the world. Finally, the study period predated the publication by Wiebe et al,[4] which showed tacrolimus trough levels of <5 ng/mL being a risk factor for developing de novo DSAs and rejection. As tacrolimus levels were not reported to ANZDATA, it is not possible to exclude the possibility of higher target tacrolimus levels in more recent years, and therefore, our findings are not applicable to the KTRs nowadays. However, multiple cohort studies from Australia, which included KTRs during our study period, achieved median/mean tacrolimus levels of 7.1–9.8 ng/mL in the first 6 mo posttransplant[19,28,29] and 7.5 ng/mL at 5.5 ± 6.1 y posttransplant.[30] Therefore, it is unlikely that tacrolimus exposure was significantly lower in our study compared with the current targets, especially in the first 6 mo posttransplant when the effect of early MDR was assessed in this study.

In conclusion, MDR to <1.5 g/d was associated with an increased risk of rejection and inferior long-term death-censored graft survival in this contemporary binational cohort of KTRs on tacrolimus-based regimens. Further studies should incorporate the use of MPA exposure and determine the optimal area under the curve range in the maintenance phase to target the subgroups of at-risk KTRs requiring early MDR for tailored alternative immunosuppressive regimens and strike



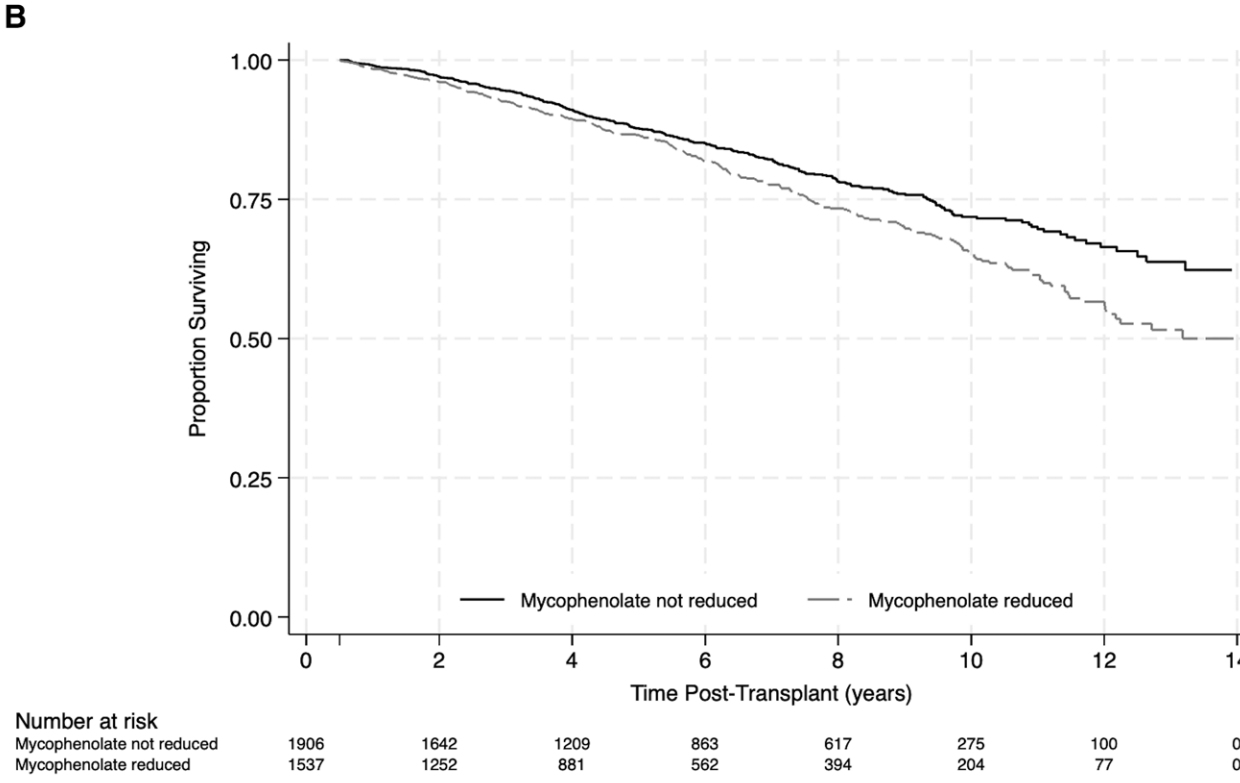
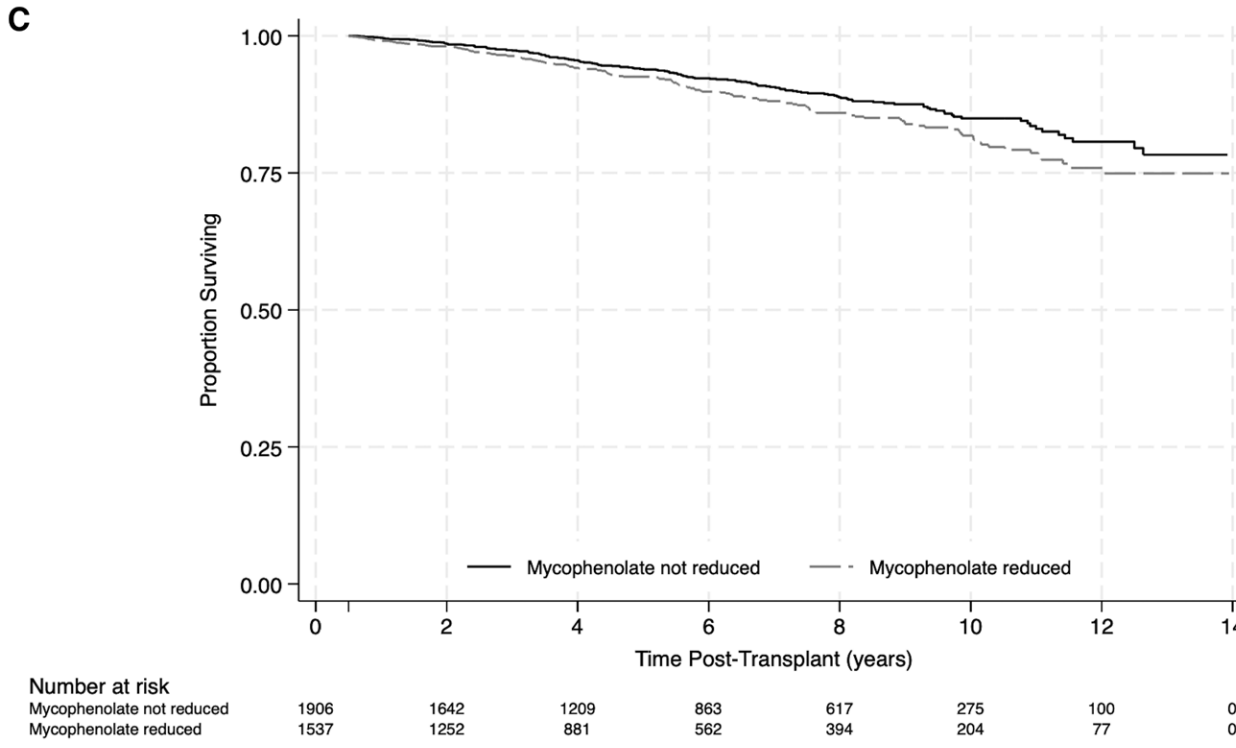


FIGURE 3. Long-term patient and graft outcomes after early mycophenolate dose reduction within the first 6 mo posttransplant: (A) Patient survival, (B) overall graft survival, (C) death-censored graft survival, and (D) eGFR. Log-rank test: (A) $P = 0.001$, (B) $P = 0.0007$, and (C) $P = 0.03$. Linear mixed model for eGFR gradients from 6 mo to 10 y posttransplant: $P = 0.418$. Mycophenolate dose reduction is defined as <1.5 g/d within the first 6 mo posttransplant. eGFR, estimated glomerular filtration rate.



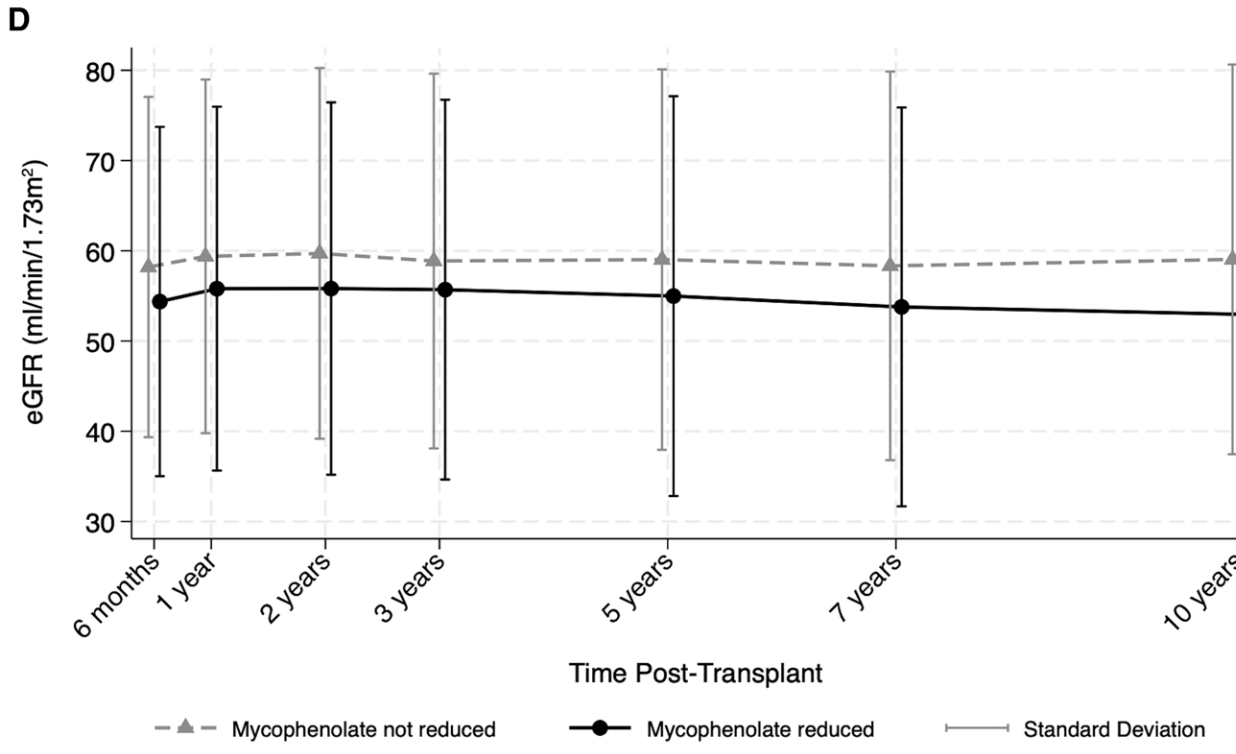


FIGURE 3. Continued

the balance of efficacy and minimizing complications from immunosuppression.

ACKNOWLEDGMENTS

The authors acknowledge the ANZDATA registry. The analysis and interpretation are those of the authors, not ANZDATA.

REFERENCES

1. Ekberg H, Tedesco-Silva H, Demirbas A, et al; ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357:2562–2575.
2. ANZDATA Registry. 44th Report, Chapter 7: Kidney Transplantation. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. Available at https://anzdata.org.au. Accessed January 31, 2024.

3. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). *OPTN/SRTR 2020 Annual Data Report*. U.S. Department of Health and Human Services, Health Resources and Services Administration. 2022. Available at http://srtr.transplant.hrsa.gov/annual_reports/Default.aspx. Accessed January 31, 2024.
4. Wiebe C, Rush DN, Nevins TE, et al. Class II Eplet mismatch modulates tacrolimus trough levels required to prevent donor-specific antibody development. *J Am Soc Nephrol*. 2017;28:3353–3362.
5. Opelz G, Dohler B. Effect on kidney graft survival of reducing or discontinuing maintenance immunosuppression after the first year post-transplant. *Transplantation*. 2008;86:371–376.
6. Bunnapradist S, Lentine KL, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. *Transplantation*. 2006;82:102–107.
7. Langone A, Doria C, Greenstein S, et al. Does reduction in mycophenolic acid dose compromise efficacy regardless of tacrolimus exposure level? An analysis of prospective data from the Mycophenolic Renal Transplant (MORE) Registry. *Clin Transplant*. 2013;27:15–24.
8. Vanhove T, Kuypers D, Claes KJ, et al. Reasons for dose reduction of mycophenolate mofetil during the first year after renal transplantation and its impact on graft outcome. *Transpl Int*. 2013;26:813–821.
9. Su V, Greanya ED, Ensom MH. Impact of mycophenolate mofetil dose reduction on allograft outcomes in kidney transplant recipients on tacrolimus-based regimens: a systematic review. *Ann Pharmacother*. 2011;45:248–257.
10. Pascual J, van Hooff JP, Salmela K, et al. Three-year observational follow-up of a multicenter, randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplant. *Transplantation*. 2006;82:55–61.
11. Sulowicz W, Bachleda P, Rydzewski A, et al. Discontinuation of mycophenolate mofetil from a tacrolimus-based triple regimen 2 months after renal transplantation: a comparative randomized, multicentre study. *Transpl Int*. 2007;20:230–237.
12. Vanrenterghem Y, van Hooff JP, Squifflet JP, et al; European Tacrolimus/MMF Renal Transplantation Study Group. Minimization of immunosuppressive therapy after renal transplantation: results of a randomized controlled trial. *Am J Transplant*. 2005;5:87–95.
13. Walker R, Thomas M, Goodman D, et al. Combination therapy with tacrolimus and mycophenolate mofetil: effects of early and late minimization of mycophenolate mofetil after renal transplant. *Clin Transplant*. 2008;22:594–602.
14. Knoll GA, MacDonald I, Khan A, et al. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. *J Am Soc Nephrol*. 2003;14:2381–2386.
15. Pelletier RP, Akin B, Henry ML, et al. The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. *Clin Transplant*. 2003;17:200–205.
16. Metz DK, Holford N, Kausman JY, et al. Optimizing mycophenolic acid exposure in kidney transplant recipients: time for target concentration intervention. *Transplantation*. 2019;103:2012–2030.
17. Kuypers DR, de Jonge H, Naesens M, et al. Current target ranges of mycophenolic acid exposure and drug-related adverse events: a 5-year, open-label, prospective, clinical follow-up study in renal allograft recipients. *Clin Ther*. 2008;30:673–683.
18. Daher Abdi Z, Premaud A, Essig M, et al. Exposure to mycophenolic acid better predicts immunosuppressive efficacy than exposure to calcineurin inhibitors in renal transplant patients. *Clin Pharmacol Ther*. 2014;96:508–515.
19. Dave V, Polkinghorne KR, Leong KG, et al. Initial mycophenolate dose in tacrolimus treated renal transplant recipients, a cohort study comparing leukopaenia, rejection and long-term graft function. *Sci Rep*. 2020;10:19379.
20. Rennie TJW, Petrie M, Metcalfe W, et al. The impact of age on patient tolerance of mycophenolate following kidney transplantation. *Nephrology (Carlton)*. 2020;25:566–574.
21. Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the symphony study: observational results 3 years after transplantation. *Am J Transplant*. 2009;9:1876–1885.
22. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
23. van Gelder T, Hesselink DA. Mycophenolate revisited. *Transpl Int*. 2015;28:508–515.
24. Wiebe C, Balshaw R, Gibson IW, et al. A rational approach to guide cost-effective de novo donor-specific antibody surveillance with tacrolimus immunosuppression. *Am J Transplant*. 2023;23:1882–1892.
25. McAdams-DeMarco MA, Law A, Tan J, et al. Frailty, mycophenolate reduction, and graft loss in kidney transplant recipients. *Transplantation*. 2015;99:805–810.
26. Li P, Shuker N, Hesselink DA, et al. Do Asian renal transplant patients need another mycophenolate mofetil dose compared with Caucasian or African American patients? *Transpl Int*. 2014;27:994–1004.
27. Badowski M, Gurk-Turner C, Cangro C, et al. The impact of reduced immunosuppression on graft outcomes in elderly renal transplant recipients. *Clin Transplant*. 2009;23:930–937.
28. Chua JCM, Mount PF, Lee D. Lower versus higher starting tacrolimus dosing in kidney transplant recipients. *Clin Transplant*. 2022;36:e14606.
29. Flint SM, Walker RG, Hogan C, et al. Successful ABO-incompatible kidney transplantation with antibody removal and standard immunosuppression. *Am J Transplant*. 2011;11:1016–1024.
30. Phipps LM, Chen SC, Kable K, et al. Nosocomial pneumocystis jirovecii pneumonia: lessons from a cluster in kidney transplant recipients. *Transplantation*. 2011;92:1327–1334.