Mycophenolate Mofetil Dose Reduction and the Risk of Acute Rejection after Renal Transplantation

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Abstract. Mycophenolate mofetil (MMF) significantly decreases acute rejection rates after renal transplantation, but intolerance often occurs, leading to dose reduction. The clinical effect of MMF dose reduction has not been clearly established. This study determined whether MMF dose reduction after renal transplantation was associated with subsequent risk of acute rejection. This retrospective cohort study assessed 213 renal transplant recipients. Cox regression was used to model MMF dose as a time-dependent variable, with time to first acute rejection as the primary outcome. One hundred twenty-six patients (59%) had a total of 176 MMF dose reductions during the study. MMF dose was reduced because of leukopenia (55.1%), gastrointestinal symptoms (22.2%), infection (7.4%), malignancy (1.1%), and unknown reasons (14.2%). The cumulative number of days with the MMF dose reduced below full dose was an independent predictor of acute rejection. The relative risk of rejection increased by 4% for every week that the MMF dose was reduced below full dose. No significant association was observed between the number of days with MMF dropped below full dose and allograft failure. The cumulative number of days with the MMF dose dropped below full dose is a significant predictor of acute rejection after renal transplantation. Clinicians need to be aware of the rejection risk when the MMF dose is reduced and maintain close surveillance on such patients.

Mycophenolate mofetil (MMF) significantly decreases acute rejection rates after renal transplantation (1). However, hematologic abnormalities and gastrointestinal intolerance occur commonly when recommended doses of MMF are used (2–4). In phase III studies involving MMF, between 12.7% and 37.3% of treated patients experienced diarrhea (2–4). Similarly, leukopenia was significantly more common in the MMF group, occurring in 10.9% to 35% of patients (2,3). These side effects often require MMF dose reduction or even discontinuation. Squifflet *et al.* (5) reported that 53% of patients receiving MMF and tacrolimus required a MMF dose reduction because of side effects. Roth *et al.* (6) reported that 29.2% of patients discontinued MMF altogether because of leukopenia or gastrointestinal intolerance.

The clinical effect of MMF dose reduction in renal transplantation has not been clearly established. Mourad *et al.* (7) reported that three patients developed acute rejection when their MMF dose was reduced for leukopenia. However, no statistical comparison was made to a control group (7). In a preliminary report, 50.3% of renal transplant recipients required a dose reduction of MMF because of side effects (8). The rate of acute rejection was significantly higher in those patients who had a MMF dose reduction compared with those who had no dose change (8). However, it is unclear from the abstract whether the rejection episodes occurred before or after the dose reduction and whether the dose reduction was properly analyzed by use of time-dependent methodology (8).

The objective of this study was to determine whether MMF dose reduction was associated with acute rejection after renal transplantation. We included all patients who received MMF along with a calcineurin inhibitor and documented all MMF dose changes. We used Cox regression methodology to model MMF dose as a time-dependent variable (9) and to determine whether it was independently associated with the risk of acute rejection.

Materials and Methods

Study Subjects and Design

This retrospective cohort study involved patients who underwent renal transplantation at the Ottawa Hospital from January 1, 1998, to June 30, 2002. Consecutive patients who were discharged home on a calcineurin inhibitor (tacrolimus or cyclosporine) and MMF were included in the analysis. Primary or repeat transplant recipients who received either a cadaveric or living donor kidney were included. The study was approved by the Ottawa Hospital Research Ethics Board.

Immunosuppression

All patients received intravenous methylprednisolone (500 mg) preoperatively followed by 1 mg/kg/d on the first postoperative day. Patients were switched to oral prednisone when tolerated, and the dose was tapered to reach a target of 7.5 mg/d by the third month. A 7- to

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14-d course of antithymocyte antibody (Thymoglobulin; Sangstat) was used in patients with delayed graft function, previous transplantation, panel-reactive antibody above 20%, positive B cell crossmatch, or any combination of these factors. The initial dose was 1.5 mg/kg/d, with subsequent adjustment based on hematologic parameters.

Cyclosporine was the predominant calcineurin inhibitor used from 1998 until mid-2001, after which tacrolimus was used. The starting dose of cyclosporine was 8 mg/kg/d with the dose adjusted to achieve a target trough level of 300 to 400 μg/L in the first 3 mo and 100 to 200 μg/L thereafter. Tacrolimus was initiated at 0.2 mg/kg/d, with the dose adjusted to achieve a target trough level of 10 to 15 μg/L in the first month, 8 to 12 μg/L in months 2 and 3, and 6 to 10 μg/L thereafter.

MMF was usually initiated at 1 g by mouth twice a day on postoperative day 1. Depending on physician preference, the introduction of MMF could be delayed or started at a reduced dose. The MMF dose was reduced for perceived side effects, and the dose was usually increased when the side effects resolved. If the side effects were initially severe, recurrent, or persistent the MMF was not increased back to full dose or it was permanently discontinued. Patients in our renal transplantation clinic were seen by either the transplantation surgeon or one of four different nephrologists. Mycophenolic acid levels were not measured.

The initial treatment for acute rejection was intravenous methylprednisolone (250 to 500 mg/d for 3 to 5 d). If vascular rejection was present or the episode was steroid resistant, antilymphocyte antibodies were added (Thymoglobulin or Orthoclone, muromonab-CD3; Janssen-Ortho).

Clinical Assessments

Episodes of unexplained renal dysfunction were evaluated with a renal biopsy unless contraindicated. Rejection episodes were classified according to the Banff 97 criteria (10). For this analysis, all patients with biopsy-proven grade I, II, or III acute rejection and those with features of antibody-mediated rejection (10) were considered to have a rejection episode. In addition, any patient with borderline changes and allograft dysfunction who received treatment for acute rejection was considered to have rejection (10). MMF dose was recorded daily during the initial hospitalization and at each clinic visit. Patients were followed until death, allograft failure, or December 31, 2002. All patients had a minimum follow-up of 6 mo.

Statistical Analyses

Cox proportional hazard regression was used to calculate unadjusted and adjusted hazard ratios and their 95% confidence interval (95% CI) for the association between MMF dose reduction and time to first acute rejection. The predictor variable of interest was the cumulative number of days with the MMF dropped below full dose. This was expressed as a time-dependent variable because its value can change on any day after transplantation. In these analyses, full dose was defined as 2000 mg/d because this was the standard dose at our center. If patients started at a dose below 2000 mg/d, their cumulative number of days at a dropped dose remained zero until they reached full dose. After they reached 2000 mg/d, this variable increased by one for every day patients received less than 2000 mg/d of MMF. Patients were followed from the date of transplantation until the first rejection episode, allograft failure, death, or December 31, 2002. We measured the association of the following variables with the outcome: cumulative number of days with the MMF dropped below full dose, age, race, gender, diabetes, donor source (cadaveric or living), delayed graft function (defined as the need for dialysis in the first week after transplantation), use of antibody induction, previous transplantation and calcineurin inhibitor (cyclosporine or tacrolimus). Only variables with a P value <0.2 were retained in the final model. A stratified analysis was performed to determine whether calcineurin inhibitor (cyclosporine or tacrolimus) modified the association of MMF dose reduction and rejection.

As a secondary analysis, Cox regression was used to determine the association between MMF dose reduction and the time to allograft failure (defined as the resumption of dialysis or death). In this analysis, acute rejection (expressed as a time-dependent variable) was included in the multivariable model along with the variables listed above.

Poisson regression was used to determine which variables were associated with cumulative number of days dropped below full-dose MMF. Because the follow-up time varied between individual patients, we modeled this variable as an incidence density (*i.e.*, number of days at reduced dose per observation time). The output from the Poisson regression is the incidence density ratio, which measures the ratio of incidence density for patients with and without the variable of interest. The same variables listed above for the Cox regression were examined in the multivariate Poisson regression model. All analyses were performed by SAS statistical software (version 8.1). P values are two-sided, and a value of less than 0.05 was considered statistically significant.

Results

Two hundred thirteen patients were treated with a calcineurin inhibitor and MMF and were included in this study. The baseline characteristics of the cohort are presented in Table 1. Cyclosporine was used by 64.3% of patients; the remainder used tacrolimus. The starting dose of MMF was 2000 mg/d in 175 patients, 1500 mg/d in five patients, and less than 1500 mg/d in 33 patients. The initial dose of MMF was below 2000 mg/d for the following reasons: concurrent antibody induction therapy ($n = 33$), thrombocytopenia ($n = 2$), and low recipient weight ($n = 3$).

Table 1. Baseline characteristics of the cohort

Characteristic	Value ($n = 213$)
Mean age (yr)	46.3 ± 13.5
Female gender (%)	42.3
Race (%)	
white	90.6
black	3.8
other	5.6
Diabetes (%)	23.5
Previous transplant (%)	13.6
Cadaveric donor (%)	67.6
Induction therapy (%)	48.4
Delayed graft function (%)	33.3
Calcineurin inhibitor (%)	
cyclosporine	64.3
tacrolimus	35.7
Duration of follow-up (days)	
mean	780 ± 428
median	807

Fifty-nine percent (126 of 213) of the patients had at least one MMF dose reduction. There were a total of 176 MMF dose reductions during the course of the study. The median initial MMF dose reduction was 1000 mg (interquartile range, 500 to 1500 mg). The most frequent reason for a dose reduction was leukopenia (55.1%). Nine of the patients who had a dose reduction because of leukopenia eventually developed cytomegalovirus infection. The MMF dose was reduced because of gastrointestinal symptoms such as nausea, vomiting, or diarrhea (22.2%), infection (7.4%), malignancy (1.1%), and unknown reasons (14.2%) in the remainder of cases. MMF was permanently discontinued in 16 patients.

In univariate Poisson regression, previous transplantation (unadjusted incidence density ratio, 2.27; 95% CI, 1.45 to 3.56) and antibody induction therapy (unadjusted incidence density ratio 1.72; 95% CI, 1.12 to 2.63) were the only factors associated with the cumulative number of days with a dose reduction under 2000 mg/d. In multivariate analysis, only previous transplantation remained statistically significant. Compared with primary transplant recipients, the cumulative number of days with a dose reduction under 2000 mg/d was 2.35 times higher (95% CI, 1.50 to 3.68) for patients with a previous transplant. The calcineurin inhibitor used (cyclosporine or tacrolimus) was not associated with the cumulative number of days with a dose reduction under 2000 mg/d.

Fifty-three patients (24.9%) had a rejection episode. In these patients, the median time to rejection was 22 d, with the majority occurring within the first 90 d after transplantation (Table 2). The histologic classification of the rejection episodes is summarized in Table 2. Figure 1 shows the number of patients undergoing MMF dose reduction, the proportion of patients on 2000 mg/d of MMF and the proportion of patients who had an acute rejection. The majority (58%) of MMF dose reductions occurred in the first 3 mo after transplantation. Thirty percent of the MMF dose reductions occurred between 3 and 12 mo after transplantation, and 12% occurred after the first year (Figure 1). The time to rejection mirrored the MMF dose reductions. The greatest number of rejection episodes occurred early after transplantation, when most of the MMF dose reductions took place.

Table 2. Summary of acute rejection episodes

Number of patients with acute rejection	53
Time to diagnosis after transplantation	
median (days)	22
0 to 90 days (%)	77.4
90 to 180 days (%)	9.4
beyond 180 days (%)	13.2
Histological classification (%)	
borderline changes	11.3
grade IA	28.3
grade IB	34.0
grade IIA	9.4
grade IIB	9.4
grade III	0
antibody mediated	7.5

We found a significant association between the cumulative number of days with MMF dropped below full dose and acute rejection (Table 3). The relative risk of rejection increased by 4% for every week that the MMF dose was reduced below full dose (unadjusted hazard ratio, 1.04; 95% CI, 1.01 to 1.08; $P = 0.02$) (Table 3). After controlling for age, gender, diabetes, donor source, race, delayed graft function, induction therapy, previous transplantation, and calcineurin inhibitor the cumulative number of days with the MMF dose dropped below full dose remained an independent predictor of acute rejection (adjusted hazard ratio, 1.04; 95% CI, 1.00 to 1.08; $P = 0.03$) (Table 3). Twelve patients either had rejection before reaching full-dose MMF or never reached full-dose MMF during the study period. The analysis was repeated with these 12 patients excluded, and the association of cumulative days at reduced dose and risk of rejection did not change. A stratified analysis showed a similar effect of MMF dose reduction on rejection, regardless of whether the patient received tacrolimus or cyclosporine.

We found no significant association between the number of days with MMF dropped below full dose and allograft failure (unadjusted hazard ratio, 1.00; 95% CI, 0.99 to 1.01; $P = 0.54$) (Table 4). This association did not change after adjustment for important confounding variables (adjusted hazard ratio, 1.00; 95% CI, 0.99 to 1.02; $P = 0.44$) (Table 4).

Discussion

To our knowledge, this is the most detailed examination of the association of reduced MMF dose and the risk of acute rejection in renal transplant recipients. After adjusting for important factors, we found that the cumulative number of days of MMF dose reduction (after being reduced from full-dose MMF) significantly increased the risk of acute rejection.

This finding is clinically relevant. We found that rejection risk increased with more time at a reduced MMF dose. Accordingly, clinicians should consider minimizing the time that patients stay at a reduced dose of MMF. This is particularly important because side effects requiring MMF dose reduction occur frequently after transplantation. In our study, 59% of patients had the MMF dose reduced at least once, and several patients had repeated dose reductions. In other studies, the incidence of MMF dose reduction because of side effects ranged from 42% to 53% (5,7,8). Thus, a significant proportion of patients treated with MMF are at increased risk for acute rejection because of dose reductions prompted by side effects. In addition, acute rejection remains an important predictor of long-term renal allograft survival (11). Hariharan *et al.* (11) showed that the renal allograft half-life was only 8.8 yr for those who had a rejection and 17.9 yr for those without an acute rejection episode. Thus, the avoidance of acute rejection still remains an important goal of renal transplantation.

Our results are consistent with a previous study examining different MMF doses. Miller *et al.* (12) showed that patients who received a higher dose of MMF had a lower risk of rejection. Patients who received MMF 2000 mg/d had an acute

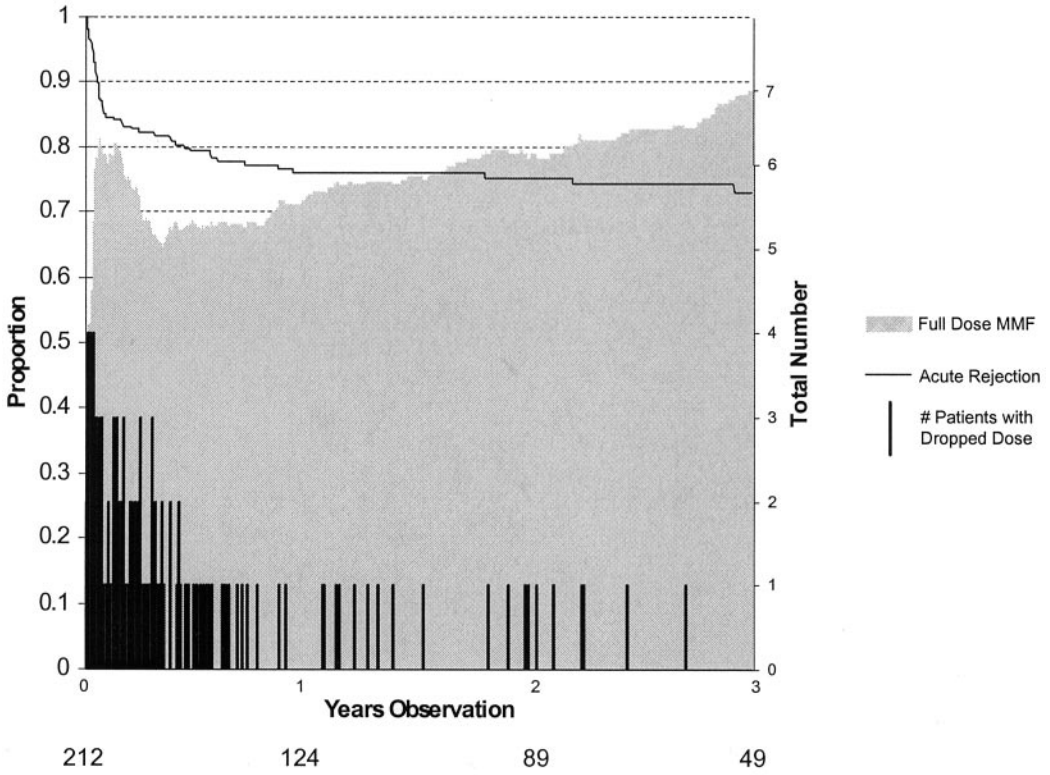

Figure 1. Mycophenolate mofetil (MMF) dosage and time to acute rejection. The figure presents three items for each day of observation (time is on the horizontal axis). The shaded area represents the proportion of patients on full-dose MMF (left vertical axis). The black lines show how many patients had their MMF dose dropped below full dose on the day of observation (right vertical axis). The line gives the proportion of patients who were rejection-free (left vertical axis). The total number of observed patients is presented at the bottom.

Table 3. Univariate and multivariate analysis for time to rejection[a]

Variable	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Cumulative number of days with MMF dropped below full dose (per 7 days)	1.04 (1.01 to 1.08)	0.02	1.04 (1.00 to 1.08)	0.03
Age (per decade)	0.79 (0.65 to 0.97)	0.03	0.81 (0.66 to 0.99)	0.04
Male gender (*versus* female)	0.61 (0.36 to 1.05)	0.08	0.63 (0.36 to 1.08)	0.09
Diabetes (*versus* no diabetes)	0.55 (0.26 to 1.17)	0.12	0.59 (0.28 to 1.28)	0.18
Cadaveric donor (*versus* living)	1.57 (0.84 to 2.93)	0.16	1.80 (0.95 to 3.43)	0.07
Race (*versus* Other)				
white	0.55 (0.20 to 1.53)	0.25	—	—
black	0.99 (0.22 to 4.47)	0.99	—	—
Delayed graft function (*versus* early function)	1.25 (0.72 to 2.18)	0.43	—	—
Induction therapy (*versus* no induction)	1.17 (0.68 to 1.99)	0.58	—	—
Previous transplant (*versus* primary transplant)	0.87 (0.39 to 1.93)	0.73	—	—
Cyclosporine (*versus* tacrolimus)	1.02 (0.57 to 1.82)	0.95	—	—

[a] Final multivariate model contains only variables with $P < 0.2$.

rejection rate of 8.6% compared with 32.2% for those who received MMF 1000 mg/d (12). In addition, a multivariate analysis showed that patients randomized to MMF 2000 mg/d had a 78% reduction in the risk of acute rejection that was independent of other important variables (12). The results of Miller *et al.* (12) suggest that patients who initially receive

Table 4. Univariate and multivariate analysis for time to renal allograft failure[a]

Variable	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Cumulative number of days with MMF dropped below full dose (per 7 days)	1.00 (0.99 to 1.01)	0.54	1.00 (0.99 to 1.02)	0.44
Age (per decade)	0.82 (0.57 to 1.18)	0.27	—	—
Male gender (*versus* female)	0.77 (0.31 to 1.91)	0.58	—	—
Diabetes (*versus* no diabetes)	0.98 (0.32 to 2.96)	0.97	—	—
Cadaveric donor (*versus* living)	1.43 (0.51 to 3.97)	0.49	—	—
Delayed graft function (*versus* early function)	5.46 (2.07 to 14.42)	0.0006	5.36 (2.03 to 14.18)	0.0007
Induction therapy (*versus* no induction)	1.24 (0.50 to 3.06)	0.64	—	—
Previous transplant (*versus* primary transplant)	1.80 (0.65 to 5.02)	0.26	—	—
Cyclosporine (*versus* tacrolimus)	0.84 (0.23 to 3.10)	0.79	—	—
Acute rejection (*versus* no acute rejection)[b]	6.92 (2.71 to 17.64)	0.0001	7.40 (2.83 to 19.38)	0.0001

[a] Final multivariate model contains only variables with $P < 0.2$.
[b] Expressed as a time-dependent variable.

low-dose MMF and never receive full-dose MMF are at increased risk of rejection. This is similar to our finding that patients who initially receive full-dose MMF but subsequently undergo dose reduction below 2000 mg/d are also at increased risk of rejection. This suggests that a critical amount of MMF is required to effectively prevent rejection.

In our analysis, the cumulative number of days with the MMF dose reduced below full dose was not predictive of allograft failure. This finding may be because of the study's sample size. The original MMF trials failed to show any improvement in graft survival despite a significant reduction in acute rejection episodes (2–4). A large study of 66,774 renal transplant patients was required to demonstrate that MMF significantly improved renal allograft survival (13). It is possible that a study involving a larger number of patients could show a significant effect of MMF dose reduction on renal allograft survival. However, given the strong association between acute rejection and graft survival (11), the results of the study presented here suggest that caution should be exercised when the MMF dose is reduced.

In univariate analysis, previous transplantation and antibody induction therapy were associated with the cumulative number of days with a MMF dose reduction. Only previous transplantation remained significant on multivariable analysis. Most of the patients who underwent repeat transplantation had received azathioprine with their first transplant. Azathioprine has well known hematologic toxicity (14) that may be severe (15). It is possible that these patients had underlying bone marrow damage from prior azathioprine exposure. The introduction of MMF during repeat transplantation could exaggerate the known myelosuppressive effects of MMF (14), leading to a greater number of days with a MMF dose reduction.

Monitoring of mycophenolic acid (MPA) levels has not become routine because the relationship between MPA levels, toxicity, and efficacy remains controversial. In a concentration controlled study of MMF, the trough or area under the curve (AUC) concentration of MPA was not associated with the occurrence of adverse events whereas the MMF dose was significantly related to side effects (16). In another study, Mourad *et al.* (7) showed that the AUC and the early MPA level (30 min after the dose) were significantly higher in patients with MMF side effects. In that study, three patients developed acute rejection after the MMF dose was reduced for side effects (7). At the time of the three rejection episodes, the trough and AUC concentration of MPA were lower than in the patients without side effects, but no statistical comparison was performed (7). Although no drug levels were performed in our study, it is plausible that patients with side effects had high MPA concentrations and that MMF dose reduction over a number of days reduced the MPA level below a critical threshold leading to acute rejection.

The strengths of this study included a high degree of follow-up, complete ascertainment of the acute rejection episodes, and the correct use of a time-dependent variable for the MMF dose reductions. Drug dosage changes and rejection episodes were not missed because all patients were followed closely at one institution rather than being sent back to a referring center.

This analysis has several limitations. First, MPA levels were not measured in this study because this was not routine practice at our center. Thus, we were unable to determine whether the patients requiring a MMF dose reduction had higher MPA exposure or whether the patients who experienced rejection episodes had lower MPA levels. Second, black patients made up only 3.8% of the entire cohort. Although we did not show that race was an important predictor of acute rejection, this was likely due to the small number of nonwhite patients. Studies from the United States have consistently shown that African American patients are at increased risk for acute rejection (17) and may require larger doses of MMF to achieve the same efficacy as white patients (18). Had our study involved more black patients, we might have shown an even greater association between the cumulative days with MMF reduced below full dose and acute rejection. Finally, the standard dose of MMF was 2000 mg/d, and no patient received 3000 mg/d. Thus, we could not evaluate whether MMF dose reduction below 3000 mg/d was associated with acute rejection.

In conclusion, this analysis has shown that the cumulative number of days with the MMF dose dropped below 2000 mg/d is a significant predictor of acute rejection after renal transplantation. Prospective studies are needed to determine whether MPA monitoring in the setting of MMF toxicity would lead to more rational drug dose changes and diminish the risk of acute rejection. Until such trials have been completed, clinicians should be aware of the risk involved when the MMF dose is reduced and maintain close surveillance of these patients.

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References

1. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C: Mycophenolate mofetil in renal allograft recipients: A pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 63: 39–47, 1997
2. European Mycophenolate Mofetil Cooperative Study Group: Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 345: 1321–1325, 1995
3. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group: A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 61: 1029–1037, 1996
4. Sollinger HW: Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 60: 225–232, 1995
5. Squifflet JP, Backman L, Claesson K, Dietl KH, Ekberg H, Forsythe JL, Kunzendorf U, Heemann U, Land W, Morales JM, Muhlbacher F, Talbot D, Taube D, Tyden G, van Hooff J, Schleibner S, Vanrenterghem Y: Dose optimization of mycophenolate mofetil when administered with a low dose of tacrolimus in cadaveric renal transplant recipients. *Transplantation* 72: 63–69, 2001
6. Roth D, Colona J, Burke GW, Ciancio G, Esquenazi V, Miller J: Primary immunosuppression with tacrolimus and mycophenolate mofetil for renal allograft recipients. *Transplantation* 65: 248–252, 1998
7. Mourad M, Malaise J, Chaib ED, De Meyer M, Konig J, Schepers R, Squifflet JP, Wallemacq P: Correlation of mycophenolic acid pharmacokinetic parameters with side effects in kidney transplant patients treated with mycophenolate mofetil. *Clin Chem* 47: 88–94, 2001
8. Pelletier RP, Akin EB, Bumgardner GL, Rajab A, Elkhammas EA, Henry ML, Ferguson RM: Mycophenolate mofetil dose reduction influences clinical outcome following kidney transplantation [Abstract]. *Am J Transplant* 2[Suppl 3]: 467, 2003
9. Wolfe RA, Strawderman RL: Logical and statistical fallacies in the use of Cox regression models. *Am J Kidney Dis* 27: 124–129, 1996
10. Racusen LC, Solez K, Colvin RB, Bonsib SM, Castro MC, Cavallo T, Croker BP, Demetris AJ, Drachenberg CB, Fogo AB, Furness P, Gaber LW, Gibson IW, Glotz D, Goldberg JC, Grande J, Halloran PF, Hansen HE, Hartley B, Hayry PJ, Hill CM, Hoffman EO, Hunsicker LG, Lindblad AS, Yamaguchi Y: The Banff 97 working classification of renal allograft pathology. *Kidney Int* 55: 713–723, 1999
11. Hariharan S, Johnson C, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D: Improved graft survival after renal transplantation in the united states, 1988 to 1996. *N Engl J Med* 342: 605–612, 2000
12. Miller J, Mendez R, Pirsch JD, Jensik SC: Safety and efficacy of tacrolimus in combination with mycophenolate mofetil (MMF) in cadaveric renal transplant recipients. *Transplantation* 69: 875–880, 2000
13. Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman AB, Cibrik D, Magee JC, Wolfe RA, Agodoa LY, Kaplan B: Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation* 69: 2405–2409, 2000
14. EBPG Expert Group on Renal Transplantation: European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.9.2. Haematological complications: Leukopenia. *Nephrol Dial Transplant* 17[Suppl]: 49, 2002
15. Huebner G, Karthaus M, Pethig K, Freund M, Ganser A: Myelodysplastic syndrome and acute myelogenous leukemia secondary to heart transplantation. *Transplantation* 70: 688–690, 2000
16. Van Gelder T, Hilbrands LB, Vanrenterghem Y, Weimar W, de Fijter JW, Squifflet JP, Hene RJ, Verpooten GA, Navarro MT, Hale MD, Nicholls AJ: A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 68: 261–266, 1999
17. Meier-Kriesche HU, Ojo A, Magee JC, Cibrik DM, Hanson JA, Leichtman AB, Kaplan B: African-American renal transplant recipients experience decreased risk of death due to infection: Possible implications for immunosuppressive strategies. *Transplantation* 70: 375–379, 2000
18. Neylan JF: Immunosuppressive therapy in high-risk transplant patients: Dose-dependent efficacy of mycophenolate mofetil in African-American renal allograft recipients. *Transplantation* 64: 1277–1282, 1997

See related editorial, “Immunosuppression with Mycophenolic Acid: One Size Does Not Fit All,” on pages 2414–2416.