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The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation

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Abstract: Background: Mycophenolate mofetil (MMF) has proven to be a very effective drug for the prevention of acute rejection following renal transplantation when dosed as prescribed at 2 or 3 g/d. However, circumstances arise in clinical transplantation where the dose must be lowered, either to avoid drug toxicity or because of concurrent infection. The impact on the incidence of acute rejection and graft survival when the MMF dose must be lowered has not previously been investigated.
Methods: In this study, a cohort of 721 kidney transplant recipients who received immunosuppression using MMF in conjunction with cyclosporine and prednisone and OKT3 (n = 425) or Simulect (n = 296) induction were evaluated. Clinical outcomes were compared and contrasted between patients with and without MMF dose changes within the first year post-transplantation.
Results: The majority of patients (70.3%, n = 507) had at least one dose change within the first post-transplant year. Compared with the 214 patients who did not have a dose change, these patients had a much higher incidence of acute rejection within the first post-transplant year (23.3% vs. 3.7%, $p < 0.001$). This resulted in a significantly decreased 3-yr death-censored graft survival (76.3% vs. 88.3%, $p = 0.003$). The incidence of acute rejection for patients who had a dose change was highest if the dose change occurred within the first post-transplant month (34.4%). The incidence of acute rejection for the dose change patients was influenced by recipient ethnicity (African-American vs. Caucasian) and the type of induction agent used (OKT3 vs. Simulect).
Conclusion: Altering the dose of MMF within the first post-transplant year correlated with a significantly worse clinical outcome in this cohort of renal transplant recipients. These data suggest that avoidance of MMF dose changes within the first year after renal transplantation would result in improved graft survival.

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Abbreviations: AUC, area under the time vs. creatinine curve; DCG, dose change group; MMF, mycophenolate mofetil; NDCG, no dose change group; OKT3, muromonab.

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Mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase, an important enzyme in the *de novo* pathway of purine synthesis. Lymphocytes are uniquely dependent on the *de novo* pathway of purine synthesis for cellular proliferation. Thus, MMF blocks alloantigen-driven lymphocyte proliferation that can occur following solid organ transplantation. Alloantigen stimulated lymphocyte proliferation is an important event in the successful development of acute rejection following organ engraftment. The clinical use of MMF following kidney transplantation has been extremely effective at minimizing the development of acute rejection (1–3).

Unfortunately, there are unwanted side-effects associated with MMF administration. MMF can cause bone marrow suppression resulting in leukopenia, anemia or thrombocytopenia, as well as

gastrointestinal side-effects such as emesis, diarrhea, esophagitis, gastritis, and gastrointestinal bleeding. These side-effects are dose-dependent, and thus can be ameliorated by reducing or stopping the MMF dose temporarily, or discontinuing the drug permanently. However, this may leave the transplant recipient at an increased risk of allograft acute rejection as a result of suboptimal immunosuppression.

Although immunosuppression is essential for allograft survival following transplantation, it also leaves the recipient more vulnerable to opportunistic infection. It has been our practice to lower the overall immunosuppression of transplant recipients if they develop a serious opportunistic infection. Generally, our first approach is to temporarily decrease or discontinue the dosing of MMF, depending on the severity of the infection.

The objective of this retrospective analysis was to describe our patterns of dosing of MMF in the first year post-transplant and to determine whether these changes in MMF dosing were associated with altered outcomes. Thus, the clinical outcomes were compared between patients who did, and those who did not, have MMF dose changes. The incidences of acute rejection, as well as patient and graft survival were analyzed.

Materials and methods

Patients

Between July 1, 1995 and September 30, 2000, 721 patients who underwent renal transplantation at our institution were treated with MMF (Roche Laboratories Inc., Nutley, NJ, USA) as part of their maintenance immunosuppression regimen. This included 651 (90.3%) first transplants, 60 (8.3%) second transplants and 10 (1.4%) third transplants. Donor sources were 64.5% (465) cadaveric donor and 35.5% (256) living donor transplants. The majority of patients (76.7%, n = 553) were Caucasians, 20.7% (n = 149) were African-Americans, and 2.6% (n = 19) were Asian, Hispanic, or American-Indian. All patients had at least 1 yr of actual follow-up and all were begun on MMF on the day of transplantation using a bid-dosing schedule. Those patients entered into our various clinical trials were excluded from this analysis.

Immunosuppression

The standard immunosuppressive protocol included induction therapy in all patients with triple maintenance immunosuppression using Neoral (Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) prednisone and MMF. From July 1995 to October 1998, OKT3 (Ortho Biotech, Raritan, NJ, USA) induction was administered intravenously for 3–5 d (up to 10 d in cases of delayed graft function) using 5 mg/d. From October 1998 to September 2000, Simulect (Novartis, East Hanover, NJ, USA) was used for induction in place of OKT3 (20 mg intravenously on post-operative day no. 0 and 4). There were 425 (58.9%) patients who received OKT3 induction and 296 (41.1%) who received Simulect. A uniform oral prednisone taper was employed for all patients, starting at 2 mg/kg and decreasing to 0.25 mg/d on post-operative day 30 and 0.15 mg/kg at 1 yr. Initiation of Neoral was generally delayed until the second to fourth post-transplant day or until the serum creatinine fell below 3 mg/dL. Neoral was dosed on a bid schedule starting at 5–7 mg/kg/d and adjusted to target whole-blood cyclosporine trough levels. Cyclosporine trough levels were obtained weekly. Target cyclosporine trough levels were 250 ng/mL for the first 6 months, 200 ng/mL from 6 to 12 months, and 150 ng/mL beyond 12 months post-transplant. The MMF was administered as described below. Allograft function was monitored post-transplant with twice weekly serum creatinines.

Mycophenolate mofetil dosing patterns

All patients received MMF using a bid-dosing schedule. If the MMF dose was adjusted, for patient convenience it was almost always changed by 1 g/d or 500 mg/d. The initial dose of MMF was 2 g/d or more in 73.3% of patients. The remaining patients started on less than 2 g/d had neutropenia or thrombocytopenia necessitating a lower dose initially.

Acute rejection

The diagnosis of acute rejection was entertained in any patient with an increase in serum creatinine ≥25%. All acute rejection episodes were biopsy confirmed prior to treatment.

Statistics

Student's *t*-test and Pearson chi-square test were used for statistical comparison of mean values (± SEM) and proportions between groups, respectively. Kaplan–Meier product-limit estimate was used for the univariate analysis of death-censored graft survival time with group comparisons performed via the log-rank test.

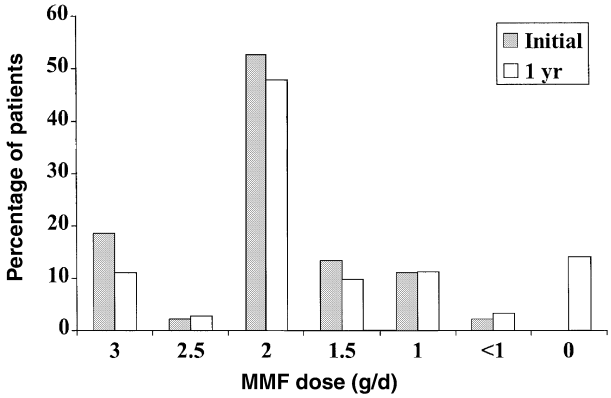

Fig. 1. The patient distribution of daily mycophenolate mofetil doses administered at the initiation of treatment (grey bars) and at the end of the first post-transplant year (white bars).

Results

Patterns of MMF dosing

The MMF dose adjustments were common in the first post-transplant year, with 70.3% (n = 507) of patients having at least one dose change (dose change group, DCG). The remaining patients (29.7%, n = 214) had no dose change (no dose change group, NDCG). Of the 507 dose-adjusted patients, 102 (20.1%) had their MMF discontinued within the first post-transplant year. The indications for discontinuing MMF were similar to those for dose reduction, namely hematologic abnormalities, gastrointestinal symptoms, or the presence of concurrent infection. There were a total of 1702 dose changes that occurred in 507 DCG patients in the first post-transplant year. Thus, on average there were 3.36 dose changes per patient (range 1–8). The initial change was a reduction in 74.6% of patients (n = 378). Most dose changes occurred within the first 120 d post-transplant (70.7% of all dose changes). Subsequent dose adjustments consisted of both increases and decreases. The distributions of patient daily MMF doses at the time of transplant and at 1 yr are shown in Fig. 1. A subanalysis of 508 MMF dose changes in 322 patients was performed to determine the reasons for the MMF dose change. The results are included in Table 1.

Mycophenolate mofetil dose adjustment correlates with an increased incidence of acute rejection

For the entire cohort of 721 patients, 150 (20.8%) of them experienced acute rejection post-transplant. Most patients developed acute rejection (126 of 150, or 84%) within the first post-transplant year. To analyze the relationship between MMF dose adjustment and acute rejection, the incidence of acute rejection in the DCG patients was compared with that for the NDCG patients (Table 2). The DCG patients experienced a much higher incidence of acute rejection within the first post-transplant year (23.3% vs. 3.7%). Additionally, all the acute rejections in the NDCG patients (n = 8) occurred within the first 60 d after transplant, whereas 43.4% (51/118) of acute rejections in the DCG patients occurred beyond 60 d. The incidence of acute rejection occurring after the first post-transplant year was low in both groups, 3.4% for the DCG and 4.3% for the NDCG. The increased incidence of acute rejection within the first year post-transplant was much greater for those DCG patients who had an initial dose reduction (29.9%) compared with those who had a dose increase (10.1%).

We performed a subanalysis of the 378 DCG patients who had an initial dose reduction to determine the relationship between the timing of their MMF dose reduction and the incidence of acute rejection. The results are shown in Table 3. Early MMF dose reduction was associated with the highest incidence of acute rejection (34.4%).

Correlation between MMF dose adjustment and acute rejection is similar in Caucasian and African-American ethnic groups

African-American recipients were evaluated independently to determine if the African-American NDCG patients had the same low incidence of acute rejection as the study patients as a whole (Table 4). Indeed, they were found to have an acute rejection incidence of 2.5% (1/33) in the first

Table 1. Indications for 508 MMF dose changes in 322 patients

37%	Hematologic (neutropenia and/or thrombocytopenia)
29%	Concurrent infection (CMV, HSV, fungal, UTI, other)
21%	GI side-effects (diarrhea, abdominal pain, intestinal bleeding)
11%	'Others'

CMV, cytomegalovirus; HSV, herpes simplex virus; UTI, urinary tract infection; GI, gastrointestinal.

Table 2. Relationship between MMF dose adjustment and incidence of acute rejection

	Acute rejection (n)	
	First year	Total
DCG (n = 507)	23.3% (118)	26.7% (135)
NDCG (n = 214)	3.7% (8)	7.0% (15)
Significance	p < 0.0001	p < 0.0001

DCG, dose change group; NDCG, no dose change group.

Table 3. Relationship between the timing of MMF dose reduction and the incidence of acute rejection for 378 patients who had an initial dose reduction

Time post-transplant	All patients (n)	Acute rejection patients (%)
0–30 d	157	34.4 (n = 54)
31–120 d	167	23.4 (n = 39)
121–365 d	54	22.2 (n = 12)
No dose change	214	3.7 (n = 8)

Table 4. Relationship between MMF dose adjustment in the first post-transplant year and the incidence of acute rejection for African-American and Caucasian recipients

			Acute rejection		
Recipient	Group	n	First year (%)	Total (%)	Significance (p)
African-American (n = 149)	NDCG	40	2.5 (1)	7.5 (3)	
	DCG	109	30.3 (33)	35.8 (39)	<0.001
Caucasian (n = 553)	NDCG	168	4.2 (7)	7.1 (12)	
	DCG	385	19.2 (74)	21.8 (84)	<0.001

DCG, dose change group; NDCG, no dose change group.

post-transplant year compared with 4.2% (7/168) for Caucasian recipients. However, the acute rejection incidence within the first post-transplant year for the African-American DCG patients was even higher than that noted for the Caucasian patients (30.3% vs. 19.2%).

The relationship between MMF dose adjustment and acute rejection is influenced by the induction agent received

We performed a comparison of the incidence of acute rejection within the first post-transplant year between the DCG and NDCG patients stratified for the type of induction agent they received at the time of transplantation (Table 5). Regardless of induction agent used, the NDCG patients had an incidence of acute rejection significantly below that of the DCG patients ($p < 0.01$ for both OKT3- and Simulect-treated patients). However, the Simulect-treated DCG patients had a significantly lower incidence of acute rejection within the first post-transplant year compared with the OKT3-treated DCG patients (14.8% vs. 24.6%, $p < 0.01$).

Effect of MMF dose adjustment, recipient ethnicity, and induction therapy on death-censored graft survival

The 3-yr death-censored graft survival was compared between the NDCG and DCG patients stratified for their ethnicity and the type ofinduction agent received at the time of transplantation (Table 6). For the entire patient cohort, the significantly increased incidence of acute rejection in the DCG patients resulted in a much worse death-censored graft survival 3 yr after transplantation (76.3% vs. 88.3%, $p = 0.003$). The worse graft survival for the DCG patients only occurred in those who received OKT3 induction (74.2% vs. 87.8% for Simulect-induced patients, $p = 0.002$). The DCG patients who received Simulect induction had a 3-yr graft survival equal to that seen in NDCG patients. African-American DCG patients had a 3-yr graft survival similar to that seen in Caucasian DCG patients. However, African-American NDCG patients did not have an improved 3-yr graft survival compared with their DCG counterparts as was noted for the Caucasian NDCG recipients.

Table 5. Comparison of the acute rejection incidence in the first post-transplant year between DCG and NDCG patients, stratified by the type of induction agent received

			Acute rejection		
Induction	Group	n	First year (%)	Total (%)	Significance (p)
OKT3 (n = 425)	NDCG	80	5.0 (4)	6.3 (5)	<0.01
	DCG	345	24.6 (85)	28.9 (100)	<0.01
Simulect (n = 296)	NDCG	134	5.9 (8)	7.4 (10)	<0.01
	DCG	162	14.8 (24)	16.0 (26)	<0.01

DCG, dose change group; NDCG, no dose change group.

Table 6. Comparison of 3-yr death-censored graft survival for DCG patients and NDCG patients stratified by ethnicity and type of induction therapy received

		3-yr Graft survival		
	n	NDCG (%)	DCG (%)	Significance (p)
Ethnicity				
African-American	149	75.2	71.1	ns
Caucasian	553	90.4	78.2	0.004
Induction agent				
OKT3	425	89.5	74.2	<0.01
Simulect	296	90.0	87.8	ns

DCG, dose change group; NDCG, no dose change group; OKT3, muromonab; ns, non-significant.

Discussion

This study was undertaken to determine whether, in our transplant program, kidney transplant recipients were likely to have their MMF dose altered during the first post-transplant year when the renal allograft was at greatest risk for immunologic injury. We were quite surprised to find that greater than two-third of patients had their dose

altered within the first post-transplant year. This incidence was even higher than the 57% reported in a study of renal transplant recipients who received 3 g/d of MMF for treatment of refractory acute rejection (4). However, the indications for dose changes were not unexpected. Hematologic and gastrointestinal side-effects, which in the sub-analysis reported in this study represented about half of the indications for dose adjustment, have been well described (1–3). Concurrent infection made up the bulk of remaining indications for dose adjustment, reflecting our programmatic approach to immunosuppression management when patients develop post-transplant infections.

This study found a remarkable correlation between a history of mycophenolate dose adjustment within the first post-transplant year and the incidence of acute rejection after kidney transplantation. The 3.7% acute rejection incidence in the first post-transplant year for the NDCG patients is far below that reported in the previous multicenter trials (1–3). In contrast, the 23.3% incidence observed in the DCG patients is very similar to that reported in these same studies. We conclude that suboptimal MMF exposure in the early post-transplant period leaves a patient at higher risk of acute rejection. This is not a novel observation. Previous pharmacokinetic studies in renal and cardiac transplant recipients have reported a higher incidence of acute rejection with lower mycophenolic acid plasma concentrations or area under the concentration–time curve (*AUC*) (5–11).

It is interesting to note that all first year acute rejections in the NDCG patients occurred within the first 60 d post-transplant. In contrast, 43.4% (51 of 118) of all first year acute rejections in the DCG occurred beyond 60 d post-transplant. This suggests that while first year acute rejection in the NDCG probably occurred as a result of 'breakthrough' rejection, much of the first year acute rejection in the DCG may have occurred as a result of suboptimal immunosuppression. Not surprisingly, the earlier the dose reduction occurred in the DCG, the higher the incidence of acute rejection (Table 3).

Comparison of the relationship between MMF dose changes and acute rejection between Caucasian and African-American recipients revealed a greater risk of acute rejection in African-American recipients when the dose is adjusted in the first year post-transplant. The higher risk of acute rejection in African-American recipients agrees with previous reports (12). However, it is notable that the African-American NDCG recipients in this study had a similarly low incidence of acute rejection in the first post-transplant year as the Caucasian NDCG recipients. This suggests that our current immunosuppressive regimen, when administered as intended without dose adjustments, provides very effective prophylaxis against acute rejection, even in the high-risk African-American recipient.

The low incidence of acute rejection in the NDCG patients resulted in a significantly improved death-censored 3-yr graft survival compared with the DCG patients. However, this was only true for the non-African-American recipients. The 3-yr death-censored graft survival for non-African-American recipients was 90.4% in the NDCG patients vs. 78.2 in the DCG patients ($p = 0.004$), whereas for African-American patients the 3-yr death-censored graft survival was 75.2 and 71.1%, respectively ($p = 0.98$). The relatively poor 3-yr graft survival in the African-American NDCG patients was unexpected given their low incidence of acute rejection. Currently we do not have an explanation for this finding, although we have previously noted that African-American ethnicity is a risk factor for graft loss beyond 6 months post-transplant independent of acute rejection (13).

The increased incidence of acute rejection seen in the DCG patients was more pronounced in those recipients who received induction with OKT3 vs. induction with Simulect ($p < 0.01$). We initially hypothesized that this was due to Simulect saturation of IL-2 receptors resulting in early protection from acute rejection when the MMF dose was modified. However, there was no significant difference in the incidence of early acute rejection (< 60 d post-transplant) between patients induced with OKT3 vs. Simulect [62% vs. 57% of all first year acute rejection episodes, respectively ($p = 0.31$)]. Also the percentage of African-American recipients, who had a higher incidence of acute rejection, was similar in both groups (about 22%). Thus, we have no explanation for the difference in acute rejection incidence between the OKT3 and Simulect-induced patients at this time.

In summary, in our transplant program, adjustment of the MMF dose occurs frequently in the first year post-transplant, most commonly because of side-effects of the drug. This dose adjustment appears to carry a significant risk to the patient of developing acute rejection, and this translates into a poorer graft survival at 3 yr post-transplant. Therefore, dose adjustment should be employed only when absolutely necessary. Avoidance of infection and especially drug toxicity after renal transplantation would significantly reduce the need for MMF dose adjustment. Such a reduction should translate into a decrease in the incidence of acute rejection resulting in improved graft survival.

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