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ORIGINAL ARTICLE

Reasons for dose reduction of mycophenolate mofetil during the first year after renal transplantation and its impact on graft outcome

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Summary

Mycophenolate mofetil (MMF) decreases the risk of acute rejection and is associated with improved graft survival in renal transplant recipients. However, MMF-related side effects often necessitate dose reduction, which may expose patients to a higher risk of acute rejection and graft loss. This study's aim was to examine the reasons for MMF dose reduction during the first post-transplant year and its impact on acute rejection, overall and death-censored graft loss. Methods: Single-center retrospective analysis of 749 renal transplant recipients treated with MMF in their initial maintenance immunosuppressive protocol. Results: In 365 patients (48.7%) a total of 530 MMF dose reductions were done. Reasons for reduction were hematologic toxicity (46.5%), infection (16.1%), gastrointestinal side effects (12.3%), malignancy (2.1%), study protocol (14.6%), and unknown (13.5%). MMF dose reduction as such was not an independent predictor of acute rejection or graft survival, although reductions in ≥50% of initial dose were significantly associated with acute rejection. Conclusions: In this retrospective cohort, by far the most important reason for MMF dose reduction during the first post-transplantation year was hematologic. MMF dose reductions in ≥50% increased the risk of acute rejection but did not compromise graft survival.

The introduction of mycophenolate mofetil (MMF) has represented a major advance in transplant medicine. Randomized, double-blind trials involving renal transplant patients have demonstrated lower early acute rejection rates [1–4]. In two retrospective registry studies, MMF reduced the incidence of late acute rejection [5] and was associated with improved graft survival [6]. As a result, MMF is now a standard component of most immunosuppressive regimens following renal transplantation.

Unfortunately, MMF use is associated with side effects that include gastrointestinal (GI) intolerance (particularly diarrhea), hematologic manifestations (leukopenia, thrombocytopenia, and anemia) and infections. Gastrointestinal intolerance is often considered to be the most frequent side effect, although reported incidences vary widely, reflecting a lack of standardized criteria for describing GI events. The incidence of diarrhea in the 3 pivotal randomized clinical trials ranged from 12.7 to 37.3% [1–3]. In a cohort of 6400 renal transplant recipients from the United States Renal Data System (USRDS), GI complications were diagnosed in 27.3% of patients at 1 year post-transplantation [7]. In contrast, randomized controlled trials comparing MMF and enteric-coated mycophenolate sodium (EC-MPS), have reported GI side effects in up to 80% of patients treated with MMF [8,9].

Mycophenolate mofetil side effects have been reported to necessitate dose reduction or discontinuation in 34.2–70.3% of patients [10–13]. This has been associated with increased risk of acute rejection and graft loss in several retrospective studies, although none of these adequately

corrected for confounding variables [10,11,14]. It is of note that in the clinical setting, the majority of MMF dose reductions happen during the first year post-transplantation [15].

This single-center retrospective cohort study of 749 kidney transplant recipients was intended to study the reasons for reduction of MMF dose during the first year post-transplantation and to investigate its impact on the incidence of acute rejections, overall graft survival, and death-censored graft survival correcting for well-known confounders.

Patients and methods

All patients who received a single renal transplant at the University Hospitals of Leuven between April 1996 (introduction of MMF in the Leuven renal transplant program) and February 2007 and were treated with MMF as part of their initial maintenance immunosuppressive regimen were included in this retrospective analysis. If a patient underwent more than one kidney transplantation in this period, only the last was considered. No other exclusion criteria were applied. Patient records were reviewed for baseline characteristics, donor source, initial maintenance immunosuppressive therapy as well as MMF dose changes, acute rejection episodes, graft, and patient survival. Reasons for MMF dose reduction were assessed by manual review of individual patient records and categorized as hematologic manifestations (anemia, thrombocytopenia, leukopenia, pancytopenia), gastrointestinal, infection, neoplasm, study protocol, unclear, or correction of erroneously high dose.

For this analysis, data up till 400 days after transplantation were considered. Completeness of the electronic patient files was assured and there were no losses to follow-up. A 400-day follow-up period also allowed for registration of events potentially related to MMF dose changes in the first year but occurring some time after that. MMF dose reduction was defined as every reduction in the daily dose of MMF of at least 250 mg. Drug discontinuation in case of graft loss was not considered a dose reduction for this analysis (censoring for graft loss). Overall graft loss was defined as the definitive need for dialysis or patient death. In death-censored graft loss analysis, graft loss ascribable to patient death was considered a nonevent and censored. The definition of acute rejection was based on the combination of a deterioration of graft function, the histological finding of acute rejection according to the Banff criteria applicable at that particular time [16], and treatment with high doses of methylprednisolone in a tapering protocol.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median and interquartile range as appropriate.

The two primary outcome variables were acute rejection and graft loss. Variables that were considered as potential predictors included: recipient age, gender, and pretransplant comorbid conditions (diabetes mellitus, hypertension, BMI > 25 kg/m^2, total cholesterol level >190 mg/dl, low-density lipoprotein (LDL) cholesterol level >115 mg/dl, vascular disease), donor characteristics (age, living versus deceased), number of human leukocyte antigen (HLA) mismatches, panel reactive antibody level (PRA) ≥ 20%, delayed graft function, initial MMF dose, induction therapy, concomitant immunosuppressive therapy, MMF dose reduction, MMF dose reduction ≥50%, and MMF dose reduction >30 days. The univariate association between predictor variables and outcome variables was explored using Pearson chi-square test for categorical variables and Mann–Whitney *U* for continuous variables. The effect of dose reduction on rejection-free survival time and graft survival time was evaluated using Kaplan–Meier product-limit estimate with group comparisons performed via the log-rank test.

Multivariate Cox proportional hazards models were constructed to explore any independent association between MMF dose reduction and the two primary outcome variables, adjusting for other predictor variables. In the multivariate proportional hazards analysis, all covariates that were univariately associated with the outcome ($P < 0.2$) were included. This subset was devoid of multicollinearity (defined as a variance inflation factor greater than 4). Through backward elimination ($P < 0.05$) we identified the set of covariates that best predicts each of the outcome variables. In the same way, a multivariate model was used to identify baseline variables associated with the time to first hematologic toxicity-related dose reduction. A two-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using the PASW Statistics 18.0 software package.

Results

Patient population

The analysis included 749 patients, all of whom were treated with MMF in a b.i.d. regimen from the day of transplantation. The most frequently used immunosuppressive regimen in our institution is a combination of a calcineurin inhibitor (most frequently tacrolimus), MMF, and corticosteroids (methylprednisolone; 500 mg IV day 0, 40 mg IV day 1, followed by oral treatment). The initial maintenance total daily dose of MMF was 1000 mg in 420, 1500 mg in 20, 2000 mg in 302, and 3000 mg in seven transplant recipients. The standard starting dose of MMF in a tacrolimus regimen was 1 g daily, while in a cyclosporine regimen it was 2 g daily. Deviations from this standard dose were dictated by trial protocols only. Recipient-, donor- and

transplant-related baseline characteristics are presented in Table 1.

MMF dosing patterns

There were 777 MMF dose reductions during the first year after transplantation, including discontinuation of the drug. Consecutive dose reductions attributable to the same cause (e.g. an extended episode of leukopenia) were grouped into a single reduction event for the current analysis. After this correction, there were 530 events of dose reduction or discontinuation in 359 patients (47.9%). MMF was permanently discontinued in 79 (15.0%) and reduced in 451 (85.0%) of these events. Of the 451 dose reductions, 368 (69%) were ≥50% of the initial MMF dose. The median time to the first dose reduction or discontinuation was 82 days (26–143). The average duration of dose reduction was 107 ± 128 days with 48.3% of dose reductions lasting less than 31 days.

Reasons for MMF dose reductions

Overall, hematologic complications were the most frequent reason for MMF dose reduction: 245 (46.5%) of the reduction events, defined as leukopenia ($n = 178$), anemia ($n = 22$), thrombocytopenia ($n = 19$), and pancytopenia ($n = 40$). Infections (viral, fungal or bacterial) accounted for 85 dose reductions (16.1%); GI intolerance for 65 (12.3%). The nature of the GI problem was defined as anorexia ($n = 1$), vomiting ($n = 2$), and diarrhea ($n = 58$). In one patient MMF was stopped 4 days after transplantation because of a history of GI intolerance of MMF at a previous transplantation. In one patient, MMF was temporarily reduced during an episode of intestinal intussusception. In 2 cases, the GI intolerance was not further specified. Diagnosis of carcinoma or sarcoma (7 cases, 1.3%) and lymphoma (four cases, 0.8%) motivated MMF dose reduction in the remainder of the cases. In 71 (13.5%) dose reductions, the reason could not be determined from the medical record. Eight patients (1.5%) were started on a higher MMF dose than intended and the dose was corrected afterwards. Finally, in 77 cases (14.6%), MMF dose reduction was dictated by a clinical trial protocol. The frequency distribution of reasons for MMF dose reduction is shown in Figure 1. Note that the percentages sum up to more than 100 because some reasons for MMF dose reduction may have coincided, e.g. cytomegalovirus (CMV) infection and leukopenia.

Table 2 shows the distribution of reasons for dose reduction in the subgroups with <50% and ≥50% decrease in the initial MMF dose. Dose reductions of ≥50% were more often motivated by hematologic toxicity (52.7% vs. 29.6%, $P < 0.001$) and infection (12.5% vs. 4.9%, $P < 0.05$). Dose

Table 1. Baseline characteristics of the study population.

Total population (*n*)	749
Age (years), mean (SD)	52.3 (13.4)
Gender, *n* (%)	
Male	430 (57.4)
Female	319 (42.6)
Diabetes mellitus, *n* (%)	122 (16.3)
Hypertension, *n* (%)	454 (60.6)
BMI (kg/m²), mean (SD)*	24.6 (4.1)
Total cholesterol level > 190 mg/dl, *n* (%)†	314 (41.9)
LDL cholesterol level > 115 mg/dl, *n* (%)‡	229 (30.6)
Vascular disease, *n* (%)§	215 (28.7)
Donor source, *n* (%)	
Deceased	724 (96.7)
Living	25 (3.3)
Retransplantation, *n* (%)	116 (15.5)
Donor age (years), mean (SD)	43.3 (15.7)
Panel reactive antibody level, *n* (%)¶	605
≥ 20%	36 (6)
< 20%	569 (94)
HLA mismatches, total, *n* (%)	
0	74 (9.9)
1	79 (10.5)
2	195 (26)
3	250 (33.4)
4	100 (13.4)
5	33 (4.4)
6	9 (1.2)
Warm ischemia time (min), mean (SD)**	34 (7.1)
Cold ischemia time (h), mean (SD)††	16.2 (5.5)
Delayed graft function, *n* (%)‡‡	115 (15.4)
Patients receiving induction therapy, *n* (%)	273 (36.4)
Antithymocyte globulin	27 (3.6)
Daclizumab	79 (10.5)
Basiliximab	167 (22.3)
Patients receiving concomitant immunosuppressive therapy, n (%)§§	
Tacrolimus	620 (82.9)
Cyclosporine	104 (13.9)
Sirolimus	10 (1.3)
Belatacept	14 (1.9)
Patients receiving CMV prophylaxis, n (%)	520 (69.4)
Ganciclovir	407 (54.3)
Vanganciclovir	113 (15.1)
Patients participating in a clinical trial, n (%)	164 (21.9)

*70 patients with missing data.
†8 patients with missing data.
‡16 patients with missing data.
§Defined as a history of one or more of the following: myocardial infarction; percutaneous coronary intervention; angina pectoris; stroke; peripheral arterial disease; peripheral arterial stenting.
¶144 patients with missing data.
**9 patients with missing data.
††18 patients with missing data.
‡‡Defined as the need for dialysis in the first 7 days after transplantation.
§§1 patient with missing data.
BMI, body mass index; CMV, cytomegalovirus; HLA, human leukocyte antigen; LDL, low-density lipoprotein; SD, standard deviation.

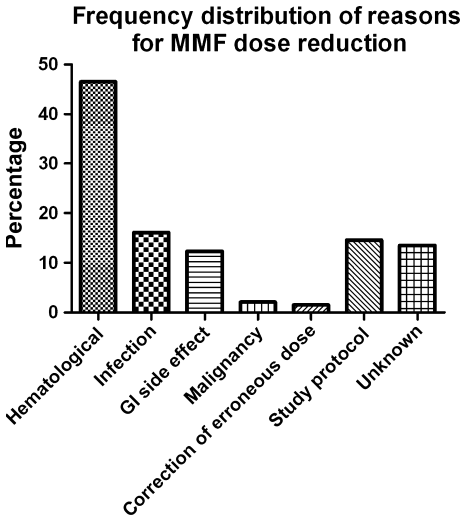

Figure 1 Frequency distribution of reasons for mycophenolate mofetil dose reduction in the first year after renal transplantation. Data are expressed as percentage of the 530 dose reduction events that occurred in the patient cohort. Percentages sum up to more than 100 as reasons may have coincided. GI, gastrointestinal.

Table 2. Reasons for MMF dose reduction in subgroups with <50% and ≥50% reduction in initial MMF dose.

Reason for dose reduction	Dose reduction <50% (%)	Dose reduction ≥50% (%)	*P*
Total	162	368	
Hematologic toxicity	48 (29.6)	194 (52.7)	<0.001
Anemia	2 (1.2)	18 (4.9)	<0.05
Leukopenia	36 (22.2)	137 (37.2)	<0.001
Thrombocytopenia	1 (0.6)	8 (2.2)	NS
Pancytopenia	9 (5.6)	31 (8.4)	NS
Gastrointestinal intolerance	26 (16)	38 (10.3)	NS
Infection	8 (4.9)	46 (12.5)	<0.05
Oncological	2 (1.2)	9 (2.5)	<0.01
Protocol	44 (27.2)	34 (9.2)	<0.001
Mistake	0 (0)	8 (2.2)	NS
Unclear	34 (21)	37 (10)	<0.01
Other	0 (0)	2 (0.5)	NS

NS, nonsignificant.

reductions of <50% were significantly more often driven by a clinical trial protocol (27.2% vs 9.2%, $P < 0.001$).

Variables associated with dose reductions for hematologic reasons

Variables independently associated with a higher risk of dose reduction for hematologic reasons in a multivariate analysis were: PRA ≥ 20% (HR 2.287 [1.330–3.932]; $P = 0.003$), delayed graft function (HR 1.790 [1.143–2.803]; $P = 0.011$), CMV prophylaxis with (val)ganciclovir (HR 2.040 [CI 1.335–3.117]; $P = 0.001$) and MMF dose on day 1 (HR 2.150 [1.553–2.976]; $P < 0.001$).

Acute rejection and graft outcome in relation to MMF dose reduction

At least one acute rejection episode occurred in 197 patients (26.3%). Acute rejections occurred after a median of 7 days (6–12); 91% of them occurred within the first 31 days after transplantation. Thirty-two patients suffered an acute rejection following dose reduction of MMF (8.8% of all patients who underwent dose reduction), after a median of 9 days (4–35). Patients who underwent at least one dose reduction/discontinuation had a significantly higher risk of acute rejection compared to patients without dose reduction (32.3% vs. 20.6%; $P < 0.001$). However, when correcting for confounding variables using a multivariate Cox proportional hazards model, there was only a trend toward a significant association (HR 1.354 [0.990–1.852]; $P = 0.058$). Covariates associated with an increased risk of acute rejection in the multivariate analysis were as follows: recipient and donor age, living donor, number of HLA mismatches, panel reactive antibody level ≥ 20%, and delayed graft function.

When the analysis was repeated comparing patients who lived at least one MMF dose reduction of ≥50% ($n = 274$) with the group of patients who lived only smaller dose reductions ($n = 85$) and the group in whom initial dose was not decreased ($n = 390$), only the first group had higher rejection incidence. This association remained significant, even after correction for relevant covariates (Table 3). Unadjusted Kaplan–Meier survival analysis of the time to first acute rejection is shown in figure 2.

Table 3. Results of multivariate Cox proportional hazards model for acute rejection.

Variable	Hazard ratio	95% Confidence interval		*P*
		Lower	Upper	
MMF dose reduction <50%	0.837	0.478	1.464	0.532
MMF dose reduction ≥50%	1.468	1.060	2.032	0.021
Recipient age at transplantation	0.984	0.972	0.996	0.007
Donor age	1.014	1.013	1.002	0.019
Living donor	2.207	1.175	4.146	0.014
HLA mismatch	1.162	1.027	1.314	0.017
Panel reactive antibody level ≥20%	2.664	1.615	4.397	<0.0001
Delayed graft function	2.130	1.473	3.081	<0.0001

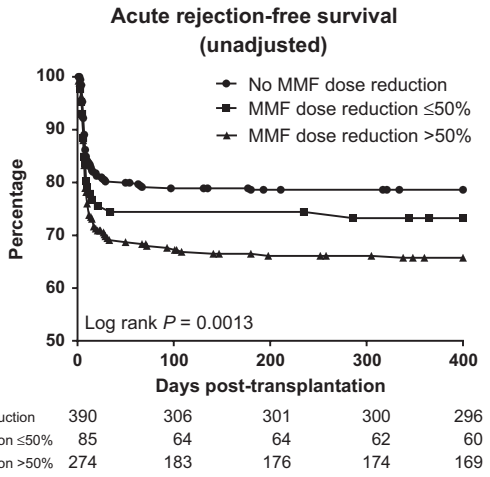

Figure 2 Unadjusted Kaplan–Meier estimate of acute rejection-free survival in patients who lived at least one mycophenolate mofetil (MMF) dose reduction in ≥50% of the initial dose, <50% of the initial dose or no MMF dose reduction during the first year after renal transplantation. Number of patients at risk at 0, 100, 200, 300, and 400 days post-transplantation are indicated below the figure.

Forty-nine of the 749 patients (6.5%) resumed dialysis or died before the 400th day after transplantation (overall graft loss). Twenty-three of these (3.1%) resumed dialysis (death-censored graft loss). Causes of graft loss censored for death are listed in Table 4. Graft loss occurred at a median of 78 days (23–193) after transplantation. Thirty-one graft losses (63.2%) occurred after reduction of MMF, with a median of 37 days (11–100) between dose reduction and graft loss. Dose reduction significantly increased the overall risk of graft loss (7.7% vs. 5.5%; $P = 0.016$), but not the risk of death-censored graft loss (3.6% vs. 2.6%; $P = 0.459$). This increased risk of graft loss did not persist when adjusting for confounding variables in a multivariate analysis (HR 1.170 [0.609–2.248]; $P = 0.636$; Table 5). Repeating the graft survival analyses adjusting for the magnitude of dose reduction did not reveal any relevant associations either.

Table 4. Causes of graft loss unrelated to patient death ($n = 23$).

Chronic allograft nephropathy	5 (21.7%)
Renal arterial/venous occlusion or thrombosis	4 (17.4%)
Acute rejection	3 (13%)
Primary nonfunction	3 (13%)
Graft infection	2 (8.7%)
Recurrence of renal disease	2 (8.7%)
Thrombotic microangiopathy	1 (4.3%)
BK nephropathy	1 (4.3%)
Cyclosporine nephrotoxicity	1 (4.3%)
Graft lymphoma	1 (4.3%)

Table 5. Results of multivariate Cox proportional hazards model for graft loss or death.

Variable	Hazard ratio	95% Confidence interval		*P*
		Lower	Upper	
Recipient age at transplantation	1.037	1.006	1.068	0.0180
Donor age	1.028	1.006	1.052	0.0146
Panel reactive antibody level ≥ 20%	3.486	1.417	8.576	0.0066
Delayed graft function	5.074	2.719	9.467	<0.0001

Discussion

In this single-center cohort of renal transplant recipients, the main reason for dose reduction of MMF in the first post-transplant year was hematologic (46.5%) toxicity. Infections and GI side effects motivated dose reduction in 16.1% and 12.3% of cases, respectively. Not surprisingly, MMF dose reductions of ≥50% of the initial dose were more often motivated by hematologic toxicity and infections than reductions of <50%. The latter were more often dictated by a clinical trial protocol. Several studies analyzing the indications for MMF dose reduction have reported a similar distribution [10,11,17]; others found GI side effects to be the most important reason, motivating 29.4–46.5% of dose reductions [12,18,19].

These studies only reflect events that were severe enough to warrant dose reduction. The overall incidence of MMF-related GI side effects, however, may be as high as 80%. The discrepancy between the high overall incidence of MMF-related GI side effects and their importance in motivating dose reductions reflects the fact that most MMF-related GI side effects are only mildly to moderately severe [20,21]. A substantial proportion of GI complaints may be self-limiting or can be managed adequately using conservative measures. Furthermore, many factors other than drug toxicity may cause GI events in renal transplant recipients. Of 108 renal transplant patients with severe diarrhea (89% of whom were treated with MMF), approximately 50% achieved resolution of diarrhea through measures other than reduction of immunosuppressive therapy [22]. Diarrhea only resolved in 29 of the 45 patients (64%) in whom MMF was reduced or discontinued. From these data, and supported by this study, it can be concluded that transplant clinicians tend to attribute more GI events to MMF than it is responsible for, potentially reducing MMF dose in an unnecessarily high proportion of patients.

Hematologic toxicity-related dose reductions of MMF were independently associated with PRA ≥ 20%, delayed graft function, CMV prophylaxis with (val)ganciclovir and

MMF dose on day 1. This underlines the significant and dose-dependent hematologic toxicity of MMF. Moreover, the mean time to any first dose reduction was 101.2 ± 92.5 days and to the first BM toxicity-related dose reduction 100.6 ± 84.8 days. This corresponds with a known pharmacokinetic property of MMF making systemic exposure to mycophenolic acid (MPA) peak around 2–3 months after transplantation. This so-called maturation is the result of a decrease in MPA clearance and metabolism, in part because of gradual tapering of corticosteroids that induce hepatic glucuronyl transferase activity [23,24].

The above-mentioned multivariate analysis also illustrates, however, that hematologic abnormalities in renal transplant recipients can be the result of a variety of factors other than MMF toxicity, as is the case for GI side effects. The complex etiology and treatment of anemia after renal transplantation have been discussed elsewhere [25]. Leukopenia has also been reported with the use of several medications routinely used after transplantation, including antithymocyte globulin [26], azathioprine [27], sirolimus [28], (val)ganciclovir [29], trimethoprim-sulfamethoxazole [30], and tacrolimus [31,32]. Tacrolimus interacts with MMF by inhibiting MPA glucuronidation, increasing systemic MPA exposure, which contributes to the higher rate of leukopenia and diarrhea observed with the combination of tacrolimus and MMF than with that of cyclosporine and MMF [32,33].

There are several ways to approach leukopenia after transplantation while minimizing reduction or discontinuation of immunosuppressive medication. For example, low dose valganciclovir (450 mg/d) appears to have a lower incidence of leukopenia than standard dose (900 mg/d), while remaining effective for CMV prophylaxis [34–36]. Granulocyte-colony stimulating factor can be used safely and effectively in patients with drug-induced leukopenia to reduce the extent and duration of dose reductions [37]. Leukopenia and anemia have also been shown to correlate well with MPA-AUC, whereas GI side effects and infections do not [38]. Therapeutic drug monitoring could be a viable option to guide dosing of MMF in patients with hematologic toxicity, although this has yet to be confirmed by prospective research.

The second main finding of this study is that MMF dose reductions ≥50% of the initial dose were independently associated with a 47% increase in the risk of acute graft rejection but did not compromise graft survival.

Previous studies have yielded conflicting evidence on whether or not MMF dose reduction increases the risk of acute rejection and graft loss. The THOMAS study demonstrated that MMF can be discontinued from a tacrolimus-based triple regimen 3 months after transplantation in low immunological risk patients without negative impact on acute rejection rate, graft and patient survival, and renal function at 6 months and 3 years [39, 40]. In another study of similar design, 152 patients treated with a tacrolimus/MMF/steroids triple regimen were randomized at 2 months post-transplantation to either continue MMF 1 g daily or taper to stop, with no difference in acute rejection rate or graft survival after 6 months [41]. A third prospective trial randomized patients on a tacrolimus-based regimen to taper MMF from 1.5 to 1 g daily at either 30 or 90 days, with no difference in overall graft and patient survival at a median of 5.6 years post-transplantation [42].

On the other hand, several retrospective studies have found MMF dose reductions to be associated with deleterious effects on graft and patient outcome. In a single-center analysis of 213 patients by Knoll *et al.* [10] acute rejection risk increased by 4% for every week that MMF dose was <2 g/d. Pelletier *et al.* [11], in a single-center study of 721 patients, found that patients with MMF dose change in the first post-transplant year had a significantly higher rate of acute rejection and a decreased 3-year death-censored graft survival compared with patients with no dose change (76.3% vs. 88.3%). Tierce *et al.* [14] specifically examined the effect of MMF dose reduction related to GI side effects. Patients with GI complications who underwent dose reduction had a higher incidence of acute rejection compared to patients with GI complications who remained on full-dose MMF (30.4% vs. 19.4%). Four large retrospective USRDS cohort studies showed that both MMF discontinuation and GI side effects were associated with decreased graft survival [7] and that for patients with a GI diagnosis, MMF dose reduction ≥50% and MMF discontinuation increased the risk of graft loss compared to no MMF dose reduction [43–45]. Ascribable to the nature of the registry data, these studies could not directly demonstrate causality between GI diagnosis and MMF dose reduction.

The practical implication of the 3 prospective trials seems to be that in low immunologic-risk patients on a tacrolimus-based regimen MMF can safely be reduced or discontinued after 3 months, when the highest risk of acute rejection has subsided. This clinical setting is clearly distinct from dose reductions directly related to side effects. There is only relatively weak evidence from retrospective studies that MMF dose reductions related to side effects increase the risk of acute rejection and graft loss, and the association appears to be stronger in cyclosporine-based than in tacrolimus-based regimens [46]. This study is the first retrospective analysis to thoroughly adjust for confounding variables. It reinforces previous concerns over the safety of MMF dose reductions and the fact that the magnitude of the dose reduction is an important factor. Patients that suffer from serious side effects and require dose reductions of ≥50% should continue to be monitored closely for graft function. The fact that we observed no effect on graft survival is reassuring. We performed subgroup analyses of the

effect of MMF dose reduction on acute rejection depending on whether the initial dose of MMF was 2 g or 1 g. MMF dose reductions ≥50% increased the risk of acute rejection in a very similar way in both subgroups, but these associations were not significant in a multivariate analysis (data not shown).

The main strengths of this study are the large number of patients from a single center included, the uniform follow-up of 400 days and the fact that the analysis was adjusted for established predictors of graft and patient outcome. Furthermore, every single renal transplant recipient treated with MMF in the initial immunosuppressive protocol in our center during an 11-year period was included in this analysis. The study population, clinical course after transplantation and general therapeutic modalities can therefore be regarded as representative of standard clinical practice.

This study has several limitations. First, because of the retrospective nature of this analysis, its results are only exploratory. Definitive conclusions regarding the impact of side effect-related dose reductions of MMF on graft and patient outcome would require prospective studies that employ predefined criteria for side effects and treat them according to standardized protocols.

Second, as another unfortunate consequence of the retrospective character of this study, PRA status prior to transplantation could only be retrieved for 605 patients (80.8%). In light of the well-established importance of PRA status as a predictor of acute rejection and graft outcome, we chose, however, to perform the multivariate outcome analyses using only data from the 605 patients with known PRA status. We performed a comparison of all baseline characteristics between patients with and without known PRA status. Patients without known PRA status were less likely to have total cholesterol level >190 mg/dl (31.3% vs. 44.5%; $P = 0.004$), less likely to have LDL cholesterol level >115 mg/dl (18.8% vs. 33.4%; $P = 0.001$) and had a higher initial daily dose of MMF (mean difference 0.123 g, CI 0.03–0.216; $P = 0.01$). However, as none of these variables were predictive of outcome in multivariate regression analysis, it seems unlikely that this hiatus has compromised the study's main conclusions. Third, it is possible that the follow-up period was not sufficiently long to detect differences in graft survival. Finally, MPA levels were not routinely measured. Systemic MPA exposure (as measured by trough level or AUC) is known to correlate with the incidence of acute rejection and multiple predictors of systemic MPA exposure have been identified. These include renal function, albumin level, hemoglobin, and the use of cyclosporine compared to tacrolimus [47,48]. We were unable to determine the relationship among these predictors, MPA levels, side effects, and graft outcome. We did, however, show that the type of calcineurin inhibitor was not predictive of acute rejection and that the effect of dose reductions on the incidence of acute rejection was not modulated by the type of calcineurin inhibitor in our cohort. Information on pre-transplant inosine monophosphate deydrogenase (IMPDH) activity would also have been interesting, as high IMPDH activity is an independent predictor of acute rejection [49]. Interindividual variability in IMPDH activity is substantial [50] and patients with an intrinsically high IMPDH activity might be more susceptible to the deleterious effects of MMF dose reduction.

In conclusion, in our transplant program, by far the most important reason for MMF dose reduction was hematologic toxicity. MMF dose reductions of ≥50% independently increased the risk of acute rejection but did not compromise graft survival.

Authorship

BB and YV: participated in study design. BB, TV and TC: participated in data retrieval and verification from the electronic patient file system. BB and TV: participated in analysis of the data and writing of the manuscript. BB, DK, KC, PE, MN, BM and YV: were involved in clinical follow-up of the described patient population, interpretation of the data, and in the revision of the manuscript.

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