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Impact of mycophenolate mofetil (MMF)-related gastrointestinal complications and MMF dose alterations on transplant outcomes and healthcare costs in renal transplant recipients

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Abstract: Mycophenolate mofetil (MMF), a mycophenolic acid prodrug, is a highly effective adjunct immunosuppressive agent in transplant therapy. Although MMF is generally well tolerated, optimal therapy may be limited by adverse effects, in particular gastrointestinal (GI) toxicity, which has been reported to occur in up to 45% of MMF-treated patients. MMF dose changes resulting from these adverse events may lead to sub-therapeutic dosing and impaired clinical outcomes. This retrospective study analyzed clinical records from 772 renal transplant patients from 10 US transplant centers who were initiated on MMF. The analysis revealed that 49.7% ($n = 382$) of patients experienced at least one GI complication within the first 6 months post-transplant, with 66.8% ($n = 255$) of these having multiple GI complications. Of the patients with GI complications, 39.0% experienced MMF dose adjustments or discontinuation of MMF therapy. Patients with GI complications who experienced MMF dose adjustments/discontinuation had a significantly increased incidence of acute rejections compared with patients without GI complications (30.2% vs. 19.4%; $p = 0.005$). Mean treatment costs were higher in patients with GI complications than in those with no GI complications, particularly in those who experienced MMF dose adjustments/discontinuation ($p = 0.0001$). The mean incremental cost for patients experiencing GI complications was US$3700 per patient during the 6 months post-transplant ($p < 0.001$), which was mainly attributable to hospitalization costs. In summary, GI complications and MMF dose adjustments/discontinuations are associated with a significant negative impact on transplant outcomes and markedly increase short-term treatment costs.

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The aim of immunosuppressant therapy after organ transplantation is to combine good efficacy (prevention of acute and chronic allograft dysfunction) with acceptable tolerability. Mycophenolate mofetil (MMF) – the morpholino-ester prodrug of mycophenolic acid (MPA) – is an effective adjunct immunosuppressive agent for the prevention of acute rejection in renal transplantation (1–3). Indeed, the combination of MMF with cyclosporine and corticosteroids has proven to be one of the most successful strategies used in transplantation, reducing episodes of acute rejection and allowing improved long-term patient and graft survival in renal transplant populations (4–7). It is now well

established that an acute rejection episode within the first 6 months after transplantation is an important risk factor for subsequent chronic renal-allograft dysfunction (8).

However, MMF therapy has been associated with gastrointestinal (GI) intolerance (9, 10), with GI complications being reported to occur in up to 45% of patients (1, 9). These complications range from relatively mild conditions, such as intermittent diarrhea or nausea, to life-threatening problems, such as colonic necrosis or perforation (9). The GI complications are related to the MMF dose, so dose reductions, treatment interruptions, discontinuations or withdrawals are often undertaken to ameliorate the symptoms (9, 11). Unfortunately, these dose adjustments can lead to sub-therapeutic dosing and impaired clinical outcomes (11–13). Indeed, MMF dosage adjustments or discontinuation due to, or in conjunction with, GI complications have been shown to significantly increase the risk of acute rejection and decrease long-term graft survival (11, 13). Evidence is now accumulating which shows that MMF dose reduction predicts acute rejection (14), with a recent study reporting that the relative risk of rejection increases by 4% for every week that the MMF dose is reduced below full dose of 2000 mg/d (12).

Attempts are now being made to quantify the financial burden that these MMF-related GI complications may place on healthcare systems. The data reported in the present study are from a retrospective economic analysis of patient records from 10 US transplant centers. The objectives of the study were to determine the incidence of GI complications associated with MMF therapy during the first 6 months after renal transplantation and to define the cost of treating them. The study was also designed to investigate the impact of GI complications on the incidence of acute rejection.

Patients and methods

The clinical records of 772 patients who received renal transplants between July 1995 and May 2000 and who were initiated on MMF therapy were retrieved from the databases of 10 US transplant centers. Patients were selected chronologically back in time from April 30, 2000 until 100 patients at each of the 10 US participating centers had been selected. Each center was to include a maximum 100 charts for final review.

The patient selection criteria included all patients who had received a kidney transplant on or before 30 April 2000, were started on MMF therapy and who had 6-month data available for consideration. If 6-month data were not available, the patient was excluded from review. Two major exclusions were documented as follows: any patient for whom MMF dosing or usage was dictated by a clinical trial protocol and any patient who had received a kidney-pancreas transplant.

The clinical records were reviewed for clinical outcomes and resource use during the first 6 months after transplantation. A case report form was utilized for data collection for each patient. The number of acute rejection episodes per patient (suspected or biopsy-confirmed) was noted. GI complications were classified as diarrhea, constipation, nausea, vomiting, dyspepsia, abdominal pain, bloating/fullness, gastritis, anorexia, ulceration, hemorrhage or others. Dose adjustments were classified as MMF dose reduction, dose interruption, dosing interval changes or discontinuation of MMF.

Patient records were also reviewed for resource use during the first 6 months post-transplant. Costs (in US$) were based on US Centers for Medicare and Medicaid Services reimbursement rates. Direct medical costs included hospitalization, medical consultations (clinic visits, telephone, and specialty consultations), emergency room visits and medications. Drug costs were taken to be 95% of published average wholesale prices and included both prescribed and over-the-counter medications.

The analyses employed standard cross-tabulation methods, stratifying the specified acute rejection and treatment cost measures (frequencies and percentages) by whether patients experienced GI complications. Tests of statistical significance of difference between GI complication groups were performed and were considered statistically significant at the $p < 0.05$ level. Logistic regression analysis was performed to determine if any patient characteristics were predictors of acute rejection episodes. Linear regression analysis was used to evaluate the impact of having a GI complication on treatment costs. All statistical procedures were performed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Initially, 772 patient transplant records were identified. Of these, 768 patient records were complete in terms of information regarding GI complications, incidence of acute rejections and costs, and were included in the review (four patient records were excluded as the patients had received i.v. corticosteroid treatment). The demographic characteristics of the study population are given in Table 1, where data were available.

Table 1. Demographic characteristics of the study population

Mean age (n = 765)	50.2 yr
Gender (n = 767)	
Male	452 (58.9)
Female	315 (41.1)
Race (n = 753)	
Caucasian	464 (61.6)
African American	193 (25.6)
Hispanic	76 (10.1)
Asian	17 (2.3)
Other	3 (0.4)
Donor source (n = 765)	
Cadaveric	464 (60.7)
Living	301 (39.3)
Mean number of days hospitalization for transplantation (n = 768)	8.3 d
Number of HLA matches (n = 755)	
0	127 (16.8)
1	156 (20.7)
2	136 (18.0)
3	159 (21.1)
4	56 (7.4)
5	51 (6.8)
6	70 (9.3)
Number of prior transplants (n = 768)	
0	666 (86.7)
≥1	102 (13.3)

Values in parentheses are in percentage.

Gastrointestinal complications affected 382 of the patients in the study (49.7%) within the first 6 months post-transplant. Of these 382 patients, 33.2% had a single episode whereas the remaining 66.8% (n = 255) had multiple records of GI complications (Table 2). Indeed, multiple GI complications in individual patients were common (ranging from 0 to 9 episodes), with 21.2% (81/382) experiencing four or more episodes of GI intolerability. In total, 944 episodes of GI complications were reported, giving an overall incidence across the entire study population of 1.23 ± 1.67 GI complications per patient (n = 768). At the point of observation of the first GI adverse event, the median dose of MMF was noted to be 2000 mg/d.

Table 2. Number of patients experiencing gastrointestinal (GI) complications and the frequency of such episodes

Patient group	Number of patients (%)
No GI complications	386 (50.3)
GI complications	382 (49.7)
1	127 (33.2)
2	107 (28.0)
3	67 (17.5)
4	40 (10.5)
5	23 (6.0)
6	7 (1.8)
7	6 (1.6)
8	2 (0.5)
9	3 (0.8)

Of the 382 patients who experienced GI complications within the first 6 months of post-transplant, 149 (39.0%) underwent MMF dose adjustments – dose reductions or interruptions, or changes to the frequency of dosing intervals – or MMF discontinuation (Fig. 1). The remaining 233 patients (61.0%) who experienced GI complications did not undergo MMF dose adjustments/discontinuation.

There were a total of 232 episodes of suspected or biopsy-proven acute rejection in the study population during the first 6 months after transplantation (range 0–5 episodes per patient). The incidence of acute rejections was significantly higher in patients with GI complications and MMF dose adjustments/discontinuation compared with patients without GI complications (30.2% vs. 19.4%; p = 0.007) (Fig. 2). Similarly, patients with GI complications who experienced MMF dose adjustments/discontinuation had a significantly increased (approximately 1.5-fold) rate of acute rejection episodes compared with patients without GI complications (p = 0.005) or with patients with GI complications but no MMF dose adjustments/discontinuation (p = 0.041) (Table 3).

Examination of healthcare costs within the first 6 months post-transplant revealed that the mean treatment costs were statistically significantly higher in patients experiencing GI complications compared with those with no GI complications (Table 4). The incremental cost for all patients with GI complications was US$3700 per patient (p < 0.001 vs. patients with no GI complications).

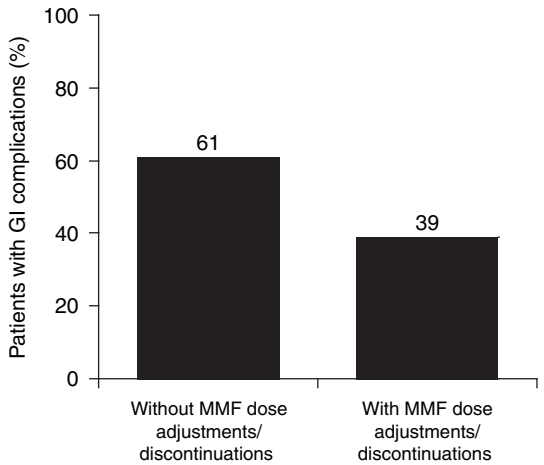

Fig. 1. Percentage of patients experiencing gastrointestinal complications (n = 382) who had mycophenolate mofetil dose adjustments/discontinuation.

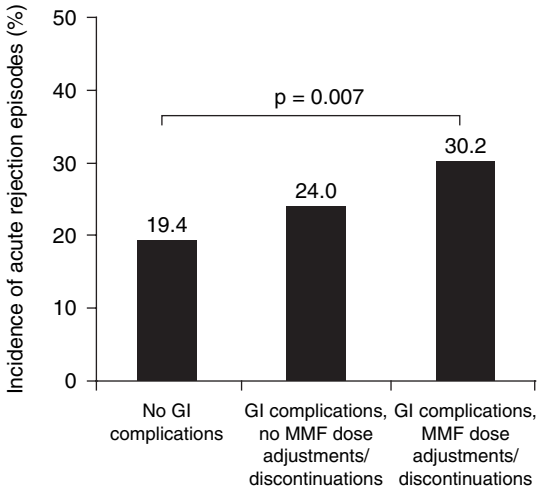

Fig. 2. Incidence of acute rejection episodes within 6 months post-transplant.

Table 3. Number of acute rejection episodes in patients with and without gastrointestinal (GI) complications

Patient subgroup	Total number of acute rejection episodes	Mean number of acute rejection episodes
Total (n = 768)	232	0.30
No GI complications (n = 386)	99	0.26
GI complications (n = 382)		
No MMF dose adjustments/ discontinuation (n = 233)	68	0.29
MMF dose adjustments/ discontinuation (n = 149)	65	0.44*,**

MMF, mycophenolate mofetil.
*p = 0.005 compared with patients with no GI complications.
**p = 0.041 compared with patients with GI complications but no MMF dose adjustments/discontinuation.

Table 4. Mean treatment costs associated with gastrointestinal (GI) complications per patient (including immunosuppressant drug therapy costs)

Patient subgroup	Mean cost ± SD (US$)	Incremental cost (US$)
No GI complications (n = 386)	13 112 ± 10 982	0
GI complications (n = 382)	16 812 ± 17 480	3700*
No MMF dose adjustments/ discontinuation (n = 233)	16 082 ± 18 370	2970**
MMF dose adjustments/ discontinuation (n = 149)	17 953 ± 15 985	4841***

Data have been corrected for dosing errors.
MMF, mycophenolate mofetil.
*p < 0.001, **p = 0.12, ***p = 0.0001, compared with patients with no GI complications.

Of the patients with GI complications, mean treatment costs were higher for those who underwent MMF dose adjustments/discontinuation (US$17 953 per patient; p = 0.0001 vs. patients with no GI complications) compared with those with GI complications that did not require MMF dose adjustments/discontinuations (US$16 082 per patient; p = 0.12 vs. patients with no GI complications) (Table 4). For the entire study population, the mean total cost of GI complications per patient was US$983 ± US$4000 (n = 768).

Table 5. Details of mean treatment costs associated with GI complications per patient (n = 768)

Category	Number of patients	Mean cost ± SD (US$)
Non-drug therapy costs		
Procedures/laboratory tests	382	71 ± 183
Clinic visits	381	36 ± 55
Emergency room visits	86	47 ± 63
Specialty consultations	146	51 ± 75
Hospitalizations	76	9598 ± 8766
Immunosuppressant therapy costs		
No GI complications	386	8080 ± 4960
GI complications	382	8691 ± 13 197
No MMF dose adjustments/ discontinuation	233	9364 ± 14 544
MMF dose adjustments/ discontinuation	149	7639 ± 10 718

The main costs associated with the GI complications were because of hospitalization. In total, 76 of the 382 patients with GI complications (19.9%) were hospitalized within the first 6 months post-transplant as a result of their GI complications (Table 5). The difference between mean costs for patients with and without GI complications was not significant, similarly costs within the GI complication group for those undergoing dose reduction or dose adjustment was also not significant. Linear regression analysis confirmed that having a GI complication had a direct effect on specialty consultation costs (p = 0.04), and the mean costs were US$84.92 for patients with GI complications compared with US$47.36 for those without, independent of acute rejection. Furthermore, the cost of immunosuppressant therapy was higher in patients with GI complications than in those without GI complications (US$8691 vs. US$8080, respectively) (Table 5). This was because of more outlying patients with immunosuppressive therapy costs in excess of US$100 000 in the GI complication group than in the non-complication group. Median costs were lower in those patients with GI complications compared with those without (US$7254 vs. US$7785, respectively). With the outliers removed from both groups, both the mean and the median immunosuppressive therapy costs were lower in the GI complication group. This may be attributable to the reduction or discontinuation of MMF therapy.

Discussion

GI complications are a common consequence of MMF therapy, and the incidence reported in this retrospective analysis (49.7%) is consistent with findings from other studies (1, 11, 13). As the dose of MMF is significantly associated with the occurrence of GI complications (15), MMF dose adjustment/discontinuation is frequently associated with GI complications (10–12). In view of the fact that many patients experience more than one GI complication, some patients may have their MMF dose altered several times.

It is widely recognized that acute rejection is an important risk factor for chronic rejection (1, 2, 8, 16, 17). As there is a strong correlation between MPA area under the curve and acute allograft rejection (15), dose reductions to improve the side effect profile can result in poorer transplant outcomes.

The present study revealed that the occurrence of GI complications was associated with a significant increase in the rate of acute rejections, particularly when accompanied by MMF dose adjustments or discontinuation. These results support the recent findings of Knoll et al. (12) and Pelletier et al. (11) which showed that MMF dose reductions significantly increased the incidence of episodes of acute rejection. For example, in the latter study of 721 renal transplant recipients, 507 patients (70.3%) had at least one MMF dose change within the first post-transplant year and patients who underwent dose changes were found to have a significantly higher incidence of acute rejection compared with those who did not (23.3% vs. 3.7%; $p < 0.0001$) (11). In our study, the incidence of acute rejection increased significantly from 19.4% in patients without GI complications to 30.2% in patients who required MMF dose adjustments/discontinuation because of GI complications.

In a study of long-term transplant outcomes in renal allograft recipients, Hardinger et al. (13) observed a significantly lower 4-yr graft survival in patients who experienced GI complications. In this study, patients without GI complications who continued on MMF therapy had the highest 4-yr graft survival rate (87.1%). In patients who experienced GI complications and discontinued MMF, a significantly lower 4-yr graft survival was observed (87.1% vs. 70.2%; $p < 0.0001$) or who experienced GI complications but continued on MMF therapy (87.1% vs. 83.0%; $p = 0.001$). A recent communication also found that, in a cohort of 3675 MMF patients with GI events, episodes of MMF dose reduction or discontinuation increased the relative hazard of graft loss compared with patients not undergoing MMF modification. In this study, a multivariate analysis showed that the increase in hazard ratio for graft loss followed a positive gradient: 1.87 for episodes dose reduction up to 50% of the original MMF dose, 2.47 during episodes of more than 50% reduction of the original dose and 3.69 during episodes of discontinuation (18).

There are few published data documenting the monetary cost of GI complications in renal transplant recipients. The recent United States Renal Data System (USRDS) database analysis by Hardinger et al. (13) included estimates of the cost of MMF-related GI complications. They reported that GI complications in conjunction with discontinuation of MMF therapy added US$7895 to second year post-transplant treatment costs ($p = 0.0042$), whereas managing the GI complications while continuing MMF treatment added US$4600 ($p < 0.0001$) (13). Similarly, in the present study, occurrence of GI complications was associated with a marked increase in short-term treatment costs. Indeed, the incremental costs were US$2970 (patients with GI complications but no MMF dose adjustments) and US$4841 (patients who had MMF adjustments/discontinuation because of GI complications) for the first 6 months post-transplantation.

There are potential limitations to the present study, which was based on a retrospective analysis of registry data. Such registry analyses are highly dependent on the quality of data recorded and may be susceptible to bias in data selection and analysis. On the contrary, registry data are likely to be more reflective of clinical practice and exclude any potential investigator bias that may occur in randomized clinical trials.

We conclude that GI complications are a common complication of immunosuppressive regimens involving MMF. The ensuing MMF dose adjustments or discontinuation of MMF therapy appear to be associated with a significant negative impact on clinical outcomes and on healthcare costs. Thus, there is a clear clinical requirement to ensure that transplant physicians are aware of the impact of GI complications – particularly in combination with MMF dose adjustments or discontinuation – on transplant outcomes, and therefore act to maximize MMF efficacy while minimizing GI complications.

References

1. European Mycophenolate Mofetil Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. Lancet 1995: 345: 1321.

2. 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 1996: 61: 1029.
3. Sollinger HW for the US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995: 60: 225.
4. Ojo AO, Meier-Kriesche HU, Hanson JA et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. Transplantation 2000: 69: 2405.
5. Offermann G. Five-year results of renal transplantation on immunosuppressive triple therapy with mycophenolate mofetil. Clin Transplant 2003: 17: 43.
6. Meier-Kriesche HU, Steffen BJ, Hochberg AM et al. Long-term use of mycophenolate mofetil is associated with a reduction in the incidence and risk of late rejection. Am J Transplant 2003: 3: 68.
7. Meier-Kriesche HU, Steffen BJ, Hochberg AM et al. Mycophenolate mofetil versus azathioprine therapy is associated with a significant protection against long-term renal allograft function deterioration. Transplantation 2003: 75: 1341.
8. Meier-Kriesche HU, Ojo AO, Hanson JA et al. Increased impact of acute rejection on chronic allograft failure in recent era. Transplantation 2000: 70: 1098.
9. Behrend M. Adverse GI effects of mycophenolate mofetil: aetiology, incidence and management. Drug Saf 2001: 24: 645.
10. Bennett WM. Immunosuppression with mycophenolic acid: one size does not fit all. J Am Soc Nephrol 2003: 14: 2414.
11. Pelletier RP, Akin B, Henry ML et al. The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. Clin Transpl 2003: 17: 200.
12. 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.
13. Hardinger KL, Brennan DC, Lowell J, Schnitzler MA. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. Transpl Int 2004: 17: 609.
14. Hale MD, Nicholls AJ, Bullingham RE et al. The pharmacokinetic–pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther 1998: 64: 672.
15. van Gelder T, Hilbrands LB, Vanrenterghem Y et al. 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 1999: 68: 261.
16. Almond PS, Matas A, Gillingham K et al. Risk factors for chronic rejection in renal allograft recipients. Transplantation 1993: 55: 752.
17. Sijpkens YW, Doxiadis II, Mallat MJ et al. Early versus late acute rejection episodes in renal transplantation. Transplantation 2003: 75: 204.
18. Schnitzler MA, Hardinger KA, Brennan DC. MMF Dose Modification Following GI Complications in Renal Transplantation. Poster presentation. Boston, MA: ATC, 2004.