Mycophenolic acid in kidney transplant patients with diabetes mellitus: does the formulation matter?

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Abstract

Diabetes mellitus is frequent in kidney transplant recipients and is commonly associated with gastrointestinal (GI) complications. Delayed gastric emptying affects 30% to 50% of patients with type 1 or 2 diabetes and can influence oral drug absorption. Time-to-peak concentration of mycophenolic acid (MPA) from mycophenolate mofetil (MMF) is longer in diabetic kidney transplant patients than patients without diabetes. By retaining gut contents in the stomach for longer, this could increase local GI toxicity in diabetic recipients due to an extended duration of exposure to MPA in the stomach. The enteric-coated mycophenolate sodium (EC-MPS) formulation delays the release of MPA until pH is higher than 5.5, such that absorption takes place more distally compared with MMF. Patient-reported outcomes data have been used to assess the effect of conversion to EC-MPS in maintenance kidney transplant patients with diabetes who were experiencing MMF-related GI symptoms. Results indicated that conversion leads to improved GI symptom burden despite higher MPA exposure under the EC-MPS regimen. Improved GI tolerance using EC-MPS has permitted maintenance of optimal MPA exposure in nondiabetic populations. Comparative trials to evaluate the GI symptom burden and maximum achieved MPA dosing using the EC-MPS and MMF formulations in de novo and maintenance diabetic kidney transplant recipients are merited.
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1. Diabetes mellitus in the kidney transplant population

Diabetes mellitus is now the most frequent indication for kidney transplantation, accounting for almost a third of transplants carried out in the United States [1]. The projected growth in the number of people with diabetes [2] indicates that transplantation for diabetic nephropathy is likely to continue to increase. In addition, approximately 20% of patients develop new-onset diabetes after transplantation under the influence of maintenance immunosuppression with steroids and calcineurin inhibitors (CNIs) [3-5]. A third of kidney transplant recipients show impaired fasting glucose [4,5].

Diabetic patients experience inferior outcomes posttransplant compared with nondiabetic individuals, with patient survival reported to be 5% to 20% lower in diabetic recipients during the first 3 to 5 years posttransplant [6-9] and an even greater disparity in subsequent years [6,10]. Preexisting diabetes does not appear to affect the risk of immunologic graft loss, because death-censored graft loss remains largely unaffected [8,10]. However, death with a functioning graft is nearly 10% more frequent in diabetic recipients than in patients without diabetes regardless of whether the diabetes was present pretransplant [11] or developed de novo after transplantation [8,12]. Major cardiac events are significantly more frequent in diabetic recipients vs nondiabetic recipients [7], as are infections and

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other complications such as neurologic disorders and peripheral circulatory disorders [13].

Diabetes mellitus is frequently associated with impaired gastrointestinal (GI) complications leading to upper and lower GI complications [14-17]. One report estimated that as many as 75% of patients visiting diabetes clinics experience significant GI symptoms [18]. Common symptoms include dysphagia, early satiety, anorexia, reflux, constipation, abdominal pain or bloating, nausea, vomiting, diarrhea, and dyspepsia [18]. In type 1 diabetes, GI disturbances appear to be focussed on the upper GI tract, where symptoms occur at a higher rate than in controls [14,15]. Gastrointestinal disorders appear to be particularly prevalent in type 2 diabetes, occurring in 60% to 70% of individuals [16,17] with events such as heartburn, dysphagia, and symptoms of upper dysmotility such as bloating, as well as lower GI tract disorders including diarrhea and constipation [19]. Studies in patients with either type 1 or 2 diabetes have shown that poor glycemic control may be associated with a higher prevalence of GI symptoms [18,19].

In the setting of kidney transplantation, the risk of diabetes-related GI symptoms is compounded by the GI complications associated with maintenance immunosuppression therapy with steroids [20], CNIs [21], azathioprine [20], and particularly, mycophenolic acid (MPA) [22]. Such complications typically include dyspepsia, abdominal pain, vomiting, and diarrhea [20-22]. Certain combinations of immunosuppressant agents place patients at a higher risk of GI symptoms. Notably, tacrolimus is known to be associated with higher rate of diarrhea than cyclosporine [21], and a large-scale analysis of United States Renal Data System data had indicated that kidney transplant recipients treated with a combination of tacrolimus and MMF experience a significantly increased risk of diarrhea [23]. Diabetic patients receiving tacrolimus-MPA may thus be especially vulnerable to GI complications.

2. Effect of diabetes mellitus on drug absorption

One of the most frequent GI complications related to diabetes is delayed gastric emptying, which affects 30% to 50% of all diabetic individuals [24]. Once considered to be largely restricted to type 1 diabetes, recent studies have shown that patients with type 2 diabetes also have high rates of gastroparesis [25]: estimates in type 1 diabetes range from 27% to 58% compared with approximately 30% of type 2 diabetics [26]. The potential impact of gastroparesis on oral drug absorption in diabetic patients may have been underappreciated. Delayed gastric emptying may affect the pharmacokinetic profile of oral agents that are designed to be absorbed rapidly from the small intestine. In this case, some drug release in the stomach may occur, but absorption would occur more slowly than in the small intestine [24]. Concerns in the literature about the effect of gastroparesis on drug absorption in diabetic patients center on potential implications for blood glucose control [24,25]. However, for the transplant clinician, there is the added complication of how diabetes and related gastroparesis may influence absorption and blood concentrations of immunosuppressive agents. There is limited evidence to suggest that the time-to-peak concentration of cyclosporine [27] and tacrolimus [28] is delayed in kidney transplant patients with diabetes, regardless of whether or not symptoms of gastroparesis are present. The reasons for such altered pharmacokinetics in the absence of delayed gastric emptying are not clear [27]. A link between CNI pharmacokinetics and abnormal GI function has not been investigated other than the finding that diarrhea increases exposure to tacrolimus, but not cyclosporine [29].

Gastrointestinal complications in the diabetic kidney transplant patient may influence the pharmacokinetics of MPA. Mycophenolate mofetil (MMF), an immediate-release formulation, contains the mofetil ester of MPA, which is rapidly de-esterified in the stomach, releasing MPA [30,31]. Thus, absorption of MPA takes place partly in the stomach and the remainder in the proximal small intestine. The enteric-coated mycophenolate sodium (EC-MPS) is a delayed-release formulation in which the enteric coating dissolves at pH higher than 5.5 to 6.0, such that MPA delivery is delayed until the small intestine [32]. Crossover studies in kidney transplant patients have indicated that the peak concentration of MPA is achieved at 0.75 to 1.0 hours with MMF compared with 2.0 to 2.5 hours with EC-MPS [32,33], consistent with more distal absorption from the EC-MPS formulation. This would suggest that MPA delivery in the stomach from the MMF formulation may be increased in patients with gastroparesis, because the stomach contents are retained for longer, although this has not been investigated clinically.

This hypothesis is consistent with evidence from a meta-analysis of 6 trials [34] and prospective single-center studies [35-37] that has consistently shown that the time-to-peak concentration of MPA using the MMF formulation is longer in diabetic kidney transplant patients than in patients without diabetes (Table 1). Although total exposure, as defined by the area under the concentration-time curve (AUC), does not appear to be affected by concomitant diabetes, the extended t_{max} could be expected to translate to increased local exposure to MPA in the stomach. In nondiabetic transplant recipients, Naesens et al [39] have confirmed that the time-to-peak MPA concentration using MMF is significantly longer among patients with delayed gastric emptying (t_{max} 1.0 vs 0.5 hours without gastroparesis; $P = .029$), but as in diabetic recipients given MMF, total MPA exposure (AUC_{0-4}) was not affected. One single-center trial by Patel et al [38] has analyzed MPA pharmacokinetics using the EC-MPS formulation in diabetic vs nondiabetic kidney transplant patients. This study found no effect on time-to-peak concentration or any other pharmacokinetic parameter (Table 1), as would be anticipated in view of the delayed-release design, but confirmatory data are awaited. Only 2 of these studies, one using MMF [36] and one using EC-MPS [38], have specified the type of diabetes that was

Table 1
MPA pharmacokinetics in kidney transplant recipients with or without diabetes, receiving MMF or EC-MPS

Reference	Study design	n/N (diabetic patients/total) (%)	MPA formulation	Diabetes status	MPA t_{max} (h)	MPA C_{max} (μg/mL)	MPA AUC (μg·h/mL)
Van Hest et al [34]	Meta-analysis	49/468 (10.5)	MMF	Diabetes	Median: 1.1	–	–
				No diabetes	Median: 0.8*	–	–
Pescovitz et al [35] (African American patients)	Prospective, multicenter	15/39 (38.5)	MMF	Diabetes	–	Mean ± SD: 18.3 ± 6.8	Mean ± SD: 55.7 ± 15.5
				No diabetes	–	Mean ± SD: 18.5 ± 8.0	Mean ± SD: 52.0 ± 12.6
Pescovitz et al [35] (white patients)	Prospective, multicenter	12/43 (27.9)	MMF	Diabetes	–	Mean ± SD: 24.0 ± 14.2	Mean ± SD: 56.9 ± 17.7
				No diabetes	–	Mean ± SD: 18.8 ± 9.2	Mean ± SD: 50.0 ± 21.2
Akhlaghi et al [36]	Prospective, single-center	13[†]/24 (54.2)	MMF	Diabetes	Mean ± SD: 1.44 ± 0.69	Mean ± SD: 11.7 ± 10.3	Mean ± SD: 46.7 ± 45.5
				No diabetes	Mean ± SD: 0.88 ± 0.53[‡]	Mean ± SD: 11.1 ± 8.6	Mean ± SD: 35.2 ± 17.9
Van Hest et al [37]	Prospective, single-center	7/136 (5.1)	MMF	Diabetes	Mean ± SD: 1.48 ± 0.60	Mean ± SD: 10.6 ± 6.1	Mean ± SD: 27 ± 12
				No diabetes	Mean ± SD: 0.94 ± 0.67[‡]	Mean ± SD: 13.0 ± 11.0	Mean ± SD: 30 ± 16
Patel et al [38]	Prospective, single-center	18/9[§] (50%)	EC-MPS	Diabetes	Median, range:1.8, 1.5−7.1	Median, range:18.1, 5.7−38.7	Median, range:73.5, 32.9−11.4
				No diabetes	Median, range: 2.1, 1.0−7.0	Median, range:22.2, 5.5−45.5	Median, range:69.8, 48.3−92.5

Values shown are mean ± SD, unless otherwise indicated.
* $P = .045$.
† Six Type 1, 5 type 2, and 2 posttransplant diabetes.
‡ $P = .04$.
§ Five Type 1 and 4 type 2 diabetes.

present (approximately equal numbers of types 1 and 2), but no trial has specifically considered MPA pharmacokinetics in either category of diabetes. Interestingly, the study by Patel and colleagues [38] using the EC-MPS formulation suggested that inosine-5′-phosphate dehydrogenase activity was significantly lower in patients with diabetes, independent of the unbound or total concentration of MPA. This, theoretically, could suggest that high levels of MPA exposure may be unnecessary in diabetic recipients (ie, lower levels of MPA than in nondiabetic individuals may achieve adequate inosine-5′-phosphate dehydrogenase inhibition), but to date, this issue has not been explored and remains speculative.

There are no data concerning the relationship between MPA concentration and noninfectious diarrhea or other common GI adverse events observed in diabetic patients.

3. MPA-mediated GI toxicity

The GI toxicity of MPA may be largely mediated through a local action, rather than systemic exposure, with disturbances to GI function arising from direct contact between MPA and the luminal wall [30]. Other possible etiologies that have been proposed include opportunistic infectious gastroenteritis, modulation of the local immune response, local toxicity of the MPA metabolite acyl-MPA glucuronide, and combination toxicity with CNIs [30]. In a concentration-controlled trial of MMF in 154 kidney transplant patients, there was no relationship between MPA pharmacokinetic parameters (AUC, C_{max}, or trough level) and diarrhea, nausea, or abdominal pain [40,41]. Instead, the oral MMF dose showed a better correlation with risk of diarrhea and risk of discontinuation due to adverse events [40,41]. Early studies of MMF also showed that events such as gastritis and diarrhea were dose dependent [42]. If the MPA dose is associated with GI intolerance rather than MPA blood concentration—that is, with local exposure in gut following ingestion instead of systemic exposure—then gastroparesis would be expected to increase GI intolerance to MMF due to increased t_{max} resulting in prolonged enterocyte exposure to the active moiety in the stomach. An alternative hypothesis could be that the stasis in the stomach in patients with delayed gastric emptying might affect the total MPA release from MMF. An effect of increased stomach pH leading to decreased MPA exposure (C_{max} and AUC) has been shown in kidney transplant patients receiving concomitant treatment with a proton pump inhibitor and MMF [43,44] but not EC-MPS [44].

4. Efficacy in diabetic kidney transplant patients

The 2 available MPA formulations, MMF and EC-MPS, have shown equivalent efficacy outcomes following kidney transplantation in both de novo [45,46] and maintenance patients [47-50]. No study has been undertaken specifically to

Table 2
Efficacy outcomes at 1 year in kidney transplant patients with diabetes

Study	Study design	n (total)	n (diabetes)	Treatment failure (%)		Biopsy-proven acute rejection (%)	
				Diabetes	No diabetes	Diabetes	No diabetes
Comparison: diabetes vs no diabetes							
myPROMS (de novo patients) [50]	Single-arm, open-label, multicenter	456	79	19.0* (15/79)	24.9* (94/377)	17.7 (14/79)	23.1 (87/377)
myPROMS (maintenance patients) [50]	Single-arm, open-label, multicenter	588	92	3.3* (3/92)	1.6* (8/496)	2.2 (2/92)	1.6 (8/496)
Comparison: EC-MPS vs MMF				EC-MPS	MMF	EC-MPS	MMF
B301 [45,50]	Randomized, double-blind, multicenter	423	76	$17.6^\dagger$ (6/34)	$26.2^\dagger$ (11/42)	14.7 (5/34)	19.0 (8/42)
B302 [47,50]	Randomized, double-blind, multicenter	322	89	$7.3^\dagger$ (3/41)	$4.2^\dagger$ (2/48)	4.9 (2/41)	2.1 (1/48)

* Biopsy-proven acute rejection, acute rejection, graft loss, or death.
† Biopsy-proven acute rejection, acute rejection, graft loss, death, or loss to follow-up.

examine outcomes within the diabetic population, although subpopulation analyses of larger trials have been performed (Table 2). In an open-label, single-arm study of 456 kidney transplant patients receiving EC-MPS, cyclosporine, and steroids, the rate of biopsy-proven acute rejection was similar in the subpopulation of 79 de novo patients with pretransplant diabetes mellitus (17.7% at month 12) and the nondiabetic cohort (23.1%, not significant) [50]. No significant differences were observed between maintenance patients with or without diabetes (Table 2). Although it is important to note that this trial was not powered to detect efficacy differences between the diabetic and nondiabetic subgroups, these findings are consistent with the finding that total MPA exposure is not altered with either formulation in diabetic vs nondiabetic patients, because AUC appears to be the main determinant for rejection prophylaxis using MPA immunosuppression [49]. Regarding comparisons between MPA formulations, a subpopulation analysis of diabetic recipients in the pivotal, randomized trials of EC-MPS vs MMF in de novo [45] or maintenance [47] kidney transplant patients, found no difference in efficacy end points between formulations [50] (Table 2). Again, the studies were not designed or powered to compare efficacy between MMF and EC-MPS within the subpopulation of patients with diabetes, and more robust data are awaited.

5. Tolerability in diabetic kidney transplant patients

Open-label, multicenter studies using patient-reported outcomes have concluded that converting kidney transplant recipients with GI complications from MMF to EC-MPS is associated with a benefit in terms of GI symptom burden compared with MMF [51-54]. Moreover, several studies have indicated that improved GI symptoms appear to permit a significant increase in MPA dose following conversion to EC-MPS in GI-intolerant patients for whom MMF dose had previously been reduced [53,55-57]. The ability to increase the MPA dose following switch to EC-MPS would appear to be the consequence of improved GI tolerability using the enteric-coated formulation. Large-scale registry analyses [58,59] and retrospective clinical data [60] suggest that maintaining the recommended MPA dose—as a marker of total MPA exposure—is associated with higher kidney allograft survival [58]. Diabetic transplant recipients who are already exposed to diabetes-related GI complications may be more sensitive to MPA-related GI toxicity and could potentially benefit disproportionately from a GI standpoint with EC-MPS vs MMF. This may be particularly true in diabetic transplant recipients experiencing gastroparesis.

In the subpopulation analysis of diabetic recipients taking part in the pivotal, randomized trials of EC-MPS vs MMF [45,47], there was no difference in the incidence of GI disorders between the EC-MPS- and MMF-treated patients in the de novo (n = 79) or maintenance cohorts (n = 86) [50]. These studies, however, were designed to establish
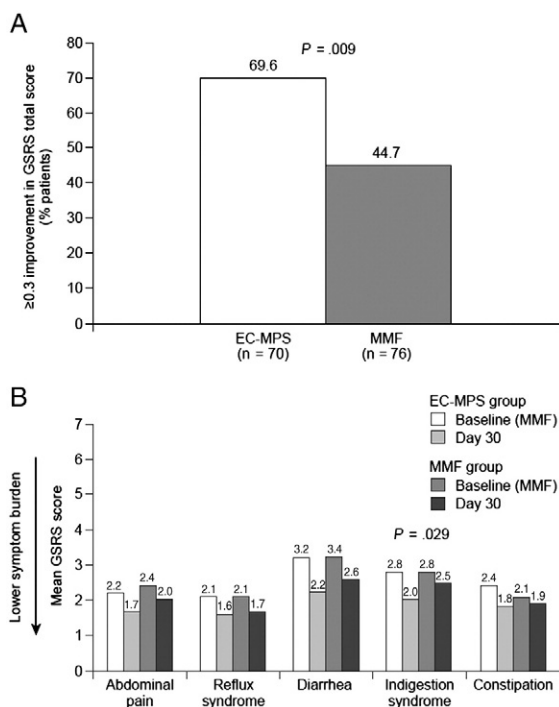
Fig. 1. Change in GSRS in patients with diabetes taking part in the myGAIN study [62] (A) proportion of patients with an improvement of 0.3 points or higher in total GSRS score (primary end point); (B) subscale values at baseline (ie, on MMF treatment) and at day 30 postrandomization.

therapeutic equivalence of the 2 formulations and used standard adverse event reporting procedures, which are not powered to evaluate the GI symptom burden.

More recently, the myGAIN study has been undertaken in which patient-reported outcomes instruments were used to evaluate the effect of conversion from MMF to EC-MPS on GI symptom burden [61]. myGAIN was a prospective, double-blind, multicenter study involving 396 maintenance kidney transplant patients who were experiencing GI symptoms attributed to MMF by the treating physician. Patients were randomized to remain on MMF with an EC-MPS placebo, or to convert to equimolar EC-MPS with an MMF placebo. The primary end point was an improvement of 0.3 points or more from baseline to week 4 in the total score on the Gastrointestinal Symptom Rating Scale (GSRS) [62]. The threshold of 0.3 points was established based on the minimum change that either patients or clinicians believed to be important [63]. Among the 146 patients with diabetes, a significantly greater proportion reached the primary end point after conversion to EC-MPS compared with those who remained on MMF (69.6% vs 44.7%, $P = .009$) (Fig. 1A). The improvement was numerically superior with EC-MPS vs MMF on all GSRS subscales, reaching significance on the indigestion syndrome subscale (Fig. 1B). Between-group differences could not be attributed to the time posttransplant, the mean bioequivalent dose, GI medication, or insulin use (as an indication of diabetes severity), all of which were similar between groups. Of note, the mean MPA trough level

at day 30 was highest among diabetic patients receiving EC-MPS (3.8 ± 4.7 ng/mL in diabetic patients vs 3.4 ± 3.6 ng/mL in patients without diabetes); in the MMF cohort, the MPA concentration was 2.9 ± 2.6 ng/mL in diabetic patients and 3.4 ± 3.0 ng/mL in patients without diabetes. Thus, the greater response to EC-MPS in diabetic patients was observed despite the highest systemic MPA exposure, consistent with the proposal that GI toxicity is related to local activity as determined by MPA formulation and dose [30]. It therefore appears possible that EC-MPS may permit improved MPA exposure in parallel with superior GI tolerance in diabetic kidney transplant recipients.

6. Conclusions

Patients with diabetes mellitus—either preexisting, occurring de novo, or progressing to clinical disease from pretransplant abnormalities of glucose metabolism—represent an important subgroup within the kidney transplant population. Any action that can be taken to improve outcomes in this disadvantaged cohort should be pursued. One largely unexplored area is whether strategies to maintain adequate MPA exposure should be tailored for kidney transplant patients with diabetes. In addition to the important benefit of minimizing GI symptoms in these patients who are already highly prone to diabetes-related GI complications, superior MPA tolerability would be expected to permit higher MPA exposure. Subpopulation analyses of diabetic patients taking part in equivalence trials of EC-MPS vs MMF have shown similar efficacy and tolerability with either formulation, but the most sensitive use of patient-reported outcomes in the myGAIN trial indicated that significantly more patients experienced an improvement in overall GI symptom burden with EC-MPS. Comparative trials undertaken specifically to evaluate relative outcomes using the EC-MPS and MMF formulations in de novo and maintenance diabetic kidney transplant recipients, incorporating use of validated patient-reported outcome instruments, are merited.

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