Transplant Research and Risk Management

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REVIEW

Mycophenolic acid agents: is enteric coating the answer?

This article was published in the following Dove Press journal:
Transplant Research and Risk Management
28 March 2011
Number of times this article has been viewed

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Abstract: Addition of mycophenolate mofetil (MMF) to calcineurin-based immunosuppressive therapy has led to a significant improvement in graft survival and reduction of acute rejection in renal transplant recipients. However, in clinical practice, MMF dose reduction, interruption, or discontinuation due to hematological and gastrointestinal (GI) side-effects occurred in up to 50% of the patients. Large retrospective analyses have demonstrated that patients requiring MMF dose manipulation due to adverse events experienced a higher rate of rejection and graft loss. Enteric-coated mycophenolate sodium (EC-MPS) was developed with the goal of improving upper GI side-effects. Here, we review the efficacy and safety of EC-MPS in de novo kidney transplant recipient, and in stable renal transplant patients who were converted from MMF. The changes in GI-related adverse events using patient-reported outcome instruments are also reviewed.

Keywords: enteric-coated mycophenolate sodium, mycophenolate mofetil, kidney transplant, efficacy, gastrointestinal tolerability

Introduction

Management of immunosuppression following transplantation is a complex interplay of balancing adequate level of immunosuppression to prevent allograft rejection, while minimizing the toxicity caused by these agents. Over the past several decades, the development of newer immunosuppressive agents with different mechanisms of action and side-effect profiles have led to a significant improvement in outcomes for organ transplantation. Introduction of calcineurin inhibitors (CNI) have resulted in improved short-term patient and allograft outcomes. Long-term allograft survival, however, remains an ongoing challenge and topic of ongoing research and development, since CNIs has been associated with nephrotoxicity and vasculopathy contributing to chronic allograft nephropathy (CAN).[1–3]

Mycophenolate mofetil (MMF; CellCept®, Roche, Nutley, NJ), a pro-drug of mycophenolic acid (MPA), was introduced to the market in 1995. Clinical studies have shown that the uses of MMF with CNI lead to improvement in graft survival and reduction in the incidence of early and late allograft rejection in kidney transplant recipients compared with azathioprine and CNI.[4–9] However, hematologic toxicity and gastrointestinal (GI) side-effects such as nausea, vomiting, diarrhea, gastritis, and ulcers, which generally lead to MMF dose reduction or interruption, could potentially limit or compromise its efficacy.

To address MPA-related upper GI side-effects, an enteric formulation of MPA (enteric-coated mycophenolate sodium [EC-MPS]; myfortic®, Novartis Pharma AT,

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Basel, Switzerland) has been developed. The expectation was that the addition of an enteric coating and the subsequent delayed release would result in fewer GI complications, improved patient tolerability, and increased drug exposure.

Clinical pharmacology

Mechanism of action

Once absorbed, both MMF and EC-MPS are converted to MPA, the active metabolite that exerts its activity through selective, reversible, and non-competitive inhibition of the inosine 5′-monophosphate dehydrogenase (IMPDH). IMPDH is the rate limiting enzyme in the de novo synthesis of purines necessary for DNA synthesis. IMPDH catalyzes the oxidation of inosine 5′-monophosphate to xanthosine 5′-monophosphate, an intermediate metabolite in guanosine monophosphate production. Interfering with IMPDH results in guanosine depletion and DNA synthesis inhibition. T- and B-lymphocytes are critically dependent on de novo synthesis of purines, whereas other cell lines are able to utilize recycled purines via the salvage pathway. MPA use, therefore, results in potent cytostatic effects on lymphocytes. In addition, MPA's activity is selective towards lymphocytes, as 2 distinct isoforms of IMPDH exist, type I and type II. Type I IMPDH is primarily found in resting, nonreplicating lymphocytes whereas type II exists predominantly in malignant and activated lymphocytes. Studies have demonstrated that MPA is nearly 5 times more active versus type II than type I IMPDH and therefore more selective in its activity towards activated lymphocytes. In addition, the synthesis of glycoproteins such as leukocyte surface adhesion molecules is also dependent on guanosine nucleotides. Therefore, MPA therapy also interferes with lymphocyte homing and decreases recruitment of host lymphocytes and monocytes to the allograft, thereby inhibiting rejection. MPA also suppresses the humoral immune response by B lymphocytes but does not inhibit cytokine production in humans.

Pharmacokinetics

A summary of the key pharmacokinetic differences of MMF and EC-MPS is shown in Table 1.

Absorption

Following oral administration, MMF is rapidly absorbed in the stomach and then extensively hydrolyzed to MPA via esterases found in the stomach, small intestine, blood, liver and tissues, releasing the active MPA component.[10] The absolute bioavailability after oral administration of MMF relative to intravenous administration was 94% in healthy volunteers.[11] Food had no effect on MPA area under the concentration time curve (AUC) but maximal concentration (C_{max}) decreased by 40% in the presence of food.[11]

Table 1 Comparative pharmacokinetics of mycophenolic acid after oral administration of mycophenolate mofetil and enteric-coated mycophenolate sodium

Pharmacokinetic parameter	MMF	EC-MPS
Oral bioavailability (%)	94	72
T_{max} (h)	0.9–1.3	2–2.5
C_{max} (ng/mL)	13–24	26–31
AUC (μg·h/mL)	38–65	52–72

Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum concentration; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; T_{max}, time to maximum exposure.

Whereas MMF is absorbed in the stomach, EC-MPS solubility is minimal in acidic media such as that of the stomach but increases with higher pH, which is analogous to the intestinal environment. In vitro studies demonstrated <40% MPA release from EC-MPS at a pH of 5.0 which then increases to 100% when pH is >6.0, with a slightly delayed release at pH 5.5.[12] MPA absorption following EC-MPS administration is approximately 93%.[13] In stable renal transplant recipients receiving maintenance immunosuppressive therapy, oral EC-MPS had a mean absolute bioavailability of 71%.[13] Food had no effect on MPA AUC but C_{max} decreased by 33% in the presence of food.[13]

Following oral administration of single doses of MMF and EC-MPS, equivalent MPA exposure was observed in stable renal transplant recipients receiving cyclosporine-based maintenance immunosuppression.[12] Two different EC-MPS doses were administered, 640 mg and 720 mg, and both delivered bioequivalent mean MPA exposure as 1000 mg MMF with similar AUC (Table 2). Differences were observed in mean MPA time to maximal exposure (t_{max}) between the different formulations, which was significantly delayed by approximately 90 minutes for the EC-MPS formulations as expected (Table 2). Another difference was mean MPA C_{max} which was attributed to formulation differences as well as inter-patient variability (Table 2).[12]

Studies on oral administration of maintenance MMF 1000 mg twice daily and EC-MPS 720 mg twice daily have shown bioequivalent MPA exposure in terms of steady state AUC in stable renal transplant recipients receiving cyclosporine-based maintenance immunosuppression (Table 3). Consistent with characteristics of the enteric-coated formulation, EC-MPS demonstrated delayed t_{max} compared with MMF.[14,15] And, as would be expected, the

Table 2 Plasma mycophenolic acid pharmacokinetic results

Dose	Median T_{max} (h)	Mean C_{max}		Mean $AUC_{0-\infty}$	
		(CV%)	90% CI	(CV%)	90% CI
MMF 1000 mg	0.75	30.2 (47%)		63.7 (24%)	
EC-MPS 640 mg	2*	30.1 (41%)	71%–140%	60.7 (25%)	87%–104%
EC-MPS 720 mg	2*	26.1 (47%)	57%–112%	66.5 (34%)	91%–109%

Note: *$P < 0.01$ compared with MMF.
Abbreviations: CV, coefficient of variation; CI, confidence interval; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.

enteric coating of EC-MPS causes a decrease in C_{max} that is not observed in the MMF formulation.[14]

Distribution

At steady state, the mean (±SD) volume of distribution of MPA is 4 (±1.2) L/kg and 54 (±25) L/kg following oral MMF and EC-MPS administration, respectively. MPA is highly protein bound to plasma albumin; 97% to 99% in patients with normal renal and liver function.[11,13] MPA binds to plasma albumin in a concentration-dependent manner, the plasma concentration of unbound MPA increasing as the dose increases.[16] The protein binding of MPA's main metabolite, mycophenolic acid glucuronide (MPAG), is 82%.[11,13]

Metabolism

Following oral administration, MMF and EC-MPS are extensively converted to its active metabolite, MPA. MPA is metabolized primarily in the liver by uridine diphosphate glycuronosyltransferase (UGT) via glucuronidation to pharmacologically inactive MPAG, the predominant metabolite. At least 2 other minor MPA metabolites have been identified: a phenolic glucoside and an acyl glucuronide. While the phenolic glucoside has no inhibitory effect on IMPDH, the acyl glucuronide has been found to inhibit IMPDH in vitro in a concentration-dependent manner but its activity is independent of guanosine depletion.[17–19]

Elimination

Both MMF and EC-MPS are eliminated primarily via the kidneys. Orally administered radiolabeled MMF is recovered 93% in the urine and 6% in the feces. Most of the administered MMF is excreted in the urine as MPAG (87%) and <1% as unchanged MPA.[11] Similarly, following administration of oral radiolabeled EC-MPS administration, >60% was recovered as MPAG and approximately 3% as MPA in the urine.[13]

MPAG also undergoes entero-hepatic recirculation via secretion into the bile, deconjugation back to MPA by glucuronidase shed from gut flora and then reabsorption into the systemic circulation as MPA, producing a second plasma peak in MPA concentration that occurs at approximately 6 to 12 hours after MMF dose and 6 to 8 hours following EC-MPS dose. Entero-hepatic recirculation is estimated to contribute to approximately 40% of MPA exposure.[20] The mean apparent half-life ($T^{1/2}$) of MPA is 17.9 hours following oral MMF administration. Similarly, the mean elimination half-life of MPA and MPAG are 8 to 16 hours and 13 to 17 hours, respectively, following oral EC-MPS administration.

Special population

Renal impairment

Transplant recipients, especially renal transplant patients, may experience renal impairment in the immediate post-transplant period and may even require dialysis. A single-dose pharmacokinetic study of MMF in patients with varying degrees of renal dysfunction did not find an association between glomerular filtration rate (GFR) and MPA clearance.[21] However, MPAG clearance decreases with increasing renal impairment. Hemodialysis did not affect MPA clearance but did remove MPAG. Similarly, a multidose pharmacokinetic study of MMF in 8 renal transplant recipients with delayed graft function demonstrated increased MPA free fraction and

Table 3 Steady-state pharmacokinetic parameters of mycophenolic acid in patients treated with MMF and EC-MPS

Pharmacokinetic parameters	MMF	EC-MPS	Geometric mean of EC-MPS ratio (90% CI)
AUC (μg·h/mL)	58.39 ± 14.08 (24)	57.43 ± 15.03 (24)	0.98 (0.87–1.11)
C_{max} (μg/mL)	21.30 ± 9.13 (43)	18.93 ± 7.86 (42)	0.89 (0.70–1.13)
T_{max} (h)	0.8 (0.5–2.0)	1.5 (0–6.0)	0.5 (–1.5 to 5.5)*

Notes: mean ± SD (CV%), except T_{max} presented as median (range); *$P < 0.05$.
Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum concentration; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; T_{max}, time to maximum exposure.

free MPA AUC. These findings were attributed to altered MPA protein binding abilities due to the uremic state of the recipients as well as increased MPAG from accumulation, ultimately resulting in competition between MPAG and MPA in protein binding.[22]

Interaction with immunosuppressive drugs

Cyclosporine has been shown to reduce the AUC of MPA by inhibiting MPAG excretion into the bile via the bile-mediated multidrug resistance protein 2 (MRP-2) transporter. This reduces systemic MPA availability by decreasing the enterohepatic recirculation, leading to an elimination of the second MPA plasma concentration peak.[23–29]

Limited data have been reported on MMF and tacrolimus drug interaction. In vitro data showed that tacrolimus may increase MPA plasma concentration due to inhibition of UGT.[30] However, MPA AUC and MPAG levels were not statistically affected in rats treated with tacrolimus, compared with the control group treated with MMF alone.[24] Kagaya et al reported that, in 71 Japanese renal transplant patients, pharmacokinetics of MPA and MPAG were unaffected by higher tacrolimus blood concentration.[31] Thus, fixed-dose MPA therapy in combination with different CNI regimens may lead to different MPA exposure.

The differences of MPA exposure due to drug interaction with different CNIs could have significant clinical consequences. Clinical studies have reported a clear association between the risk of acute rejection and total MPA area under the curve (AUC_{0-12h});[32–36] the relationship between adverse effects of MPA, such as anemia, leukopenia, GO symptoms, and infection, and the AUC_{0-12h} is less well established.[32,34,37] Some studies have found better correlation between the incidence of infection or leukopenia with free rather than total MPA level.[38–40] Others have suggested that adverse events are better predicted by MMF dose, rather than blood concentration.[33,41]

Therapeutic drug monitoring

Different strategies, including single-point sampling strategies, particularly trough (C_0) concentration, full dose interval AUC monitoring (AUC_{0-12h}), and multiple-point limited sampling strategies (LSS), for therapeutic drug monitoring (TDM) in MMF-treated patients have been explored. Clinical studies have shown that AUC_{0-12h} provides the most reliable measurement of MPA exposure and correlates well with clinical outcomes.[42,43] Data on the relationship between C_0 and efficacy are conflicting, and correlation between C_0 and AUC_{0-12h} displays significant inter- and intra-patient variability.[34–57] Alternatively, limited sampling strategies, where MPA exposure is estimated from a few samples, have shown good correlation with AUC_{0-12h}.[44,45] Recently, prospective, randomized, multicenter studies validating the benefit of TDM using LSS have been published.[35,36] The APOMYGERE trial, applying the population-based pharmacokinetic model and maximum a posteriori probability Bayesian methodology, found that the incidence of treatment failure was significantly lower in the concentration-controlled group. The fixed dose versus concentration controlled (FDCC) study did not find any differences in the incidence of treatment failure between the concentration-controlled and fixed-dose groups. However, based on the lack of difference in MPA exposures between the groups, one possible reason for the discrepancy in efficacy outcome could be attributed to the investigators' unwillingness to increase doses to achieve target MPA concentration.

Data on LSS TDM in EC-MPS treated patients is quite limited. Two clinical studies evaluating the predictive value of LSS in EC-MPS–treated patients have been published. De Winter et al analyzed the value of using LSS for EC-MPS based on samples drawn within 2 or 3 hours post-dose for the estimation of MPA AUC_{0-12h} and found LLS to be imprecise and not to perform sufficiently well to be used in clinical setting.[58] The authors suggested that the poor predictive performance of LSS is due to the variable absorption of EC-MPS compared with MMF. Sommerer et al evaluated the value of LLS by using blood samples drawn within the first 4 hours after EC-MPS administration and found that despite highly variable absorption, there was a significant correlation between estimated abbreviated MPA AUC_{0-3h} and AUC_{0-4h}, and measured AUC_{0-12h} ($r^2 = 0.702$ and $r^2 = 0.812$).[59] Of note, LSS of EC-MPS in this study was evaluated only in combination with cyclosporin A (CsA). Additional randomized controlled studies are needed to validate the value of LSS for EC-MPS in combination with both FK-506 and CsA before this strategy can be used routinely in clinical practice.

Clinical efficacy

De novo kidney transplant

EC-MPS is US Food and Drug Administration approved for prophylaxis of organ rejection in patients receiving renal transplantation. Therapeutic equivalence of MMF and EC-MPS was assessed in a phase III, multicenter, randomized, double-blind, parallel group study of 423 patient undergoing de novo renal transplantation.[60] Patients were randomized to receive either EC-MPS (n = 213) 720 mg

twice daily or MMF 1000 mg twice daily within 48 hours post-transplant. The primary efficacy evaluation was treatment failure, defined as the first occurrence of biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up at 6 months. The incidence of treatment failure between the EC-MPS–treated and MMF-treated patient was similar at 6 months (25.8% vs 26.2%, respectively) and 12 months (28.6% vs 28.1%, respectively). The incidence of BPAR at 6 and 12 months was also similar between the two groups (21.6% vs 22.9%, and 22.5% vs 24.3%). The overall safety profile and GI adverse events were similar for both groups. Similarly, 15% of EC-MPS–treated patient and 19.5% of MMF-treated patients required dose adjustment due to GI adverse events. After completing 1-year follow up, patients were invited to participate in a 2-year open-label extension study. Patients who were initially randomized into the MMF group were converted to receive EC-MPS 720 mg twice daily (newly exposed). The overall incidence of graft loss and side-effects was comparable between the newly exposed and those who initially randomized to EC-MPS patients (EC-MPS long-term). Only 4.8% (n = 6) of the newly exposed patients and 3.1% (n = 4) of EC-MPS long-term experienced BPAR. Likewise, a pooled analysis of three 12-month substudies of the *myfortic* Prospective Multicenter (*my*PROMS) study (US01, DE01, FR01) evaluated the efficacy and tolerability of EC-MPS in 456 de novo renal transplant recipients.[61] All patients received CsA, EC-MPS, and corticosteroids with IL-2R antibody induction. Patients in US01 and DE01 were randomized to the higher or lower CsA C_2 target range, while patients in FR01 were randomized to early or delayed initiation of CsA. The primary efficacy endpoint was the incidence of treatment failure and graft function at 6 and 12 months. There were no significant differences in the incidence of BPAR, graft and patient survival, and graft function between CsA-treated groups at 6 and 12 months. At 12 months, 25.9% (n = 188) experienced treatment failure, with 22.1% incidence of BPAR, 3.1% graft loss, and 1.3% death. GI adverse events were reported in 77.6% (n = 354) and the proportion of patients requiring a reduction, interruption, or discontinuation of EC-MPS due to GI events was only 16.2%.

Recently, Sollinger et al retrospectively evaluated transplant outcomes in 1709 renal transplant patients who received either MMF (n = 1111) or EC-MPS (n = 598).[62] Graft survival and renal function were similar between the two groups during the study period. However, the incidence of BPAR was significantly higher in the MMF-treated cohort (MMF 30.2% vs EC-MPS 21.9%) at 2 years. Interestingly, significantly higher numbers of MMF-treated patients required dose reduction (MMF 74.4% vs EC-MPS 64%) and dose discontinuation (MMF 33.3% vs EC-MPS 27.9%) compared with EC-MPS. Of note, significantly more patients in the EC-MPS group received induction therapy with alemtuzumab, while significantly more patients in the MMF group received basiliximab or thymoglobulin. These differences could potentially affect the allograft outcomes. Similar to the results observed by Sollinger et al,[62] a pooled analysis of several prospective studies by Salvadori et al also found significantly lower incidences of BPAR in EC-MPA–treated patients compared with those that received MMF.[63] The rate of treatment failure (EC-MPS 23.9% vs MMF 28.9%), graft loss (EC-MPS 3.5% vs MMF 6.1%), and death (EC-MPS 1.2% vs MMF 2.3%) was also significantly lower in the EC-MPS group. In contrast to the study by Sollinger et al,[62] the mean MPA equimolar dose (±SD) during months 0 to 12 in this study was similar between both groups (EC-MPS 1820 ± 370 mg/day vs MMF 1860 ±290 mg/day), suggesting that EC-MPS provides a graft survival benefit compared with MMF. A retrospective analysis by Cooper et al in 379 renal transplant recipients who were initiated on EC-MPS or MMF also found similar results.[64] Compared with MMF, the incidence of BPAR was significantly lower in the EC-MPS group (14% vs 23.1%, respectively). However, the incidence of GI complications (EC-MPS 52.8% vs MMF 48.9%) and patients requiring dose manipulation due to GI complication (EC-MPS 19.7% vs MMF 25.3%) was similar between groups.

Conversion from MMF to EC-MPS

In a phase III, randomized double-blind, multicenter, parallel group study, Budde and colleagues evaluated whether renal transplant recipients maintained on MMF could be safely converted to EC-MPS therapy.[65] The study included 322 renal transplant recipients. All patients received MMF 1000 mg twice daily in combination with cyclosporine, with or without corticosteroid for 14 days during the run-in period. Patients were then randomized to receive either EC-MPS (n = 159) 720 mg twice daily or MMF (n = 163) 1000 mg twice daily for 12 months. Primary safety endpoints included incidence and severity of GI adverse events (AEs) at 3 months, and neutropenia within the first 3 months. Secondary safety endpoints included incidence and severity of GI AEs, neutropenia, infections, discontinuation due to AEs, and serious AEs for the duration of the study. The incidences of GI AEs were similar between the EC-MPS and the MMF-treated patients at 3 months (26.4% vs 20.9%) and 12 months (29.6% vs 24.5%, respectively). There were no statistically significant

differences in the incidence of neutropenia within 3 months (0.6% vs 3.1%), which remained unchanged through the remainder of the study. The overall incidence of infection was similar between the two groups (EC-MPS 58.5% and MMF 58.9%). Incidence of efficacy failure, defined as first occurrence of BPAR, graft loss, or death, at 12 months was also similar between MMF- and EC-MPS–treated patients (2.5% vs 6.1%, respectively). At 12 months, in an open-label extension, 130 patients who were initially randomized to MMF were converted to EC-MPS (newly exposed) and 130 patients initially randomized to EC-MPS continued on EC-MPS (EC-MPS long-term).[66] Serum creatinine level, incidence of adverse events, including GI side-effects, and malignancy were similar in both groups.

Similarly, a pooled analysis from 3 subprotocols of the *my*PROMS study (Asia, Europe, and Latin America) evaluated efficacy and safety of converting stable renal transplant recipients from MMF to bioequivalent doses of EC-MPS.[67] All study participants received EC-MPS in combination with CsA, with or without corticosteroid. A total of 588 patients was included in the analysis. The rate of treatment failure within 6 months of EC-MPS conversion was 1.9% (n = 11), with 1.7% incidence of BPAR, no incidence of graft loss, and 1 death due to traffic accident. Renal allograft function remained stable throughout the study period, with baseline creatinine clearance of 65.3 ± 20.4 mL/minute and 66.9 ± 21.4 mL/minute at 6 months. EC-MPS was well tolerated, with a majority of adverse events reported as mild to moderate in severity.

The results of these studies suggest that EC-MPS has an efficacy and safety profile similar to that of MMF in de novo renal transplant recipients, and that stable renal transplant patients can be safely converted from MMF to EC-MPS without compromising outcomes.

Patient-focused perspective

In clinical practice, MMF dose reduction, interruption, or discontinuation due to GI side-effects has been reported to occur in up to 50% of the patients.[68,69] Retrospective analyses have shown that patients who required MMF dose manipulation experienced higher rates of rejection and graft loss.[68–71] Although EC-MPS was developed with the intent of reducing GI-related toxicity, data on benefit are conflicting. Early studies comparing therapeutic equivalence of EC-MPS with MMF in de novo renal transplant patients, and a conversion study from MMF to EC-MPS, did not show any significant differences in GI toxicity.[60,65] However, 3 clinical studies that used a validated patient-reported outcome (PRO) instrument demonstrated improvement in GI adverse events following conversion from MMF to EC-MPA.[72–74]

In a prospective, open-label, multicenter study, Chan and colleagues evaluated the benefit of converting renal transplant patients who experienced GI-related symptoms from MMF to EC-MPS utilizing the same patient-reported outcome measures.[72] Patients were divided into 2 cohorts: those with a GI complaint qualified for MMF to EC-MPS conversion (Cohort A, n = 177) and those without GI complication who remained on MMF (Cohort B, n = 101). Patients were evaluated at baseline (Visit 1) and at a second study visit (Visit 2) at Day 30 following conversion. PROs consisted of 3 self-administered questionnaires, including the Gastrointestinal Symptom rating Scale (GSRS), the Gastrointestinal Quality of Life Index (GIQLI), and the Psychological General Well-being Index (PGWBI). In addition, the Overall Treatment Effect (OTE) scale was used to evaluate the health-related quality of life (HRQoL) at Visit 2. At baseline, Cohort A reported a significantly worse symptom burden, more impaired GI-specific HRQoL, and lower general HRQoL, indicated by significantly higher scores on all GSRS subscales, and lower scores on GIQLI and PGWBI compared with Cohort B. Significant improvement in GSRS, GIQLI, and PGWBI subscales of patients in Cohort A were observed after conversion to EC-MPS at Visit 2. Overall, 66% of the patients in Cohort A reported an overall improvement in GI symptoms at Visit 2, compared with only 8% in Cohort B. The results of the study showed that in patients who experienced mild to moderate GI-related side-effects, switching from MMF to EC-MPS improves patient function and well-being within 4 to 6 weeks.

In addition, in a 3-month, longitudinal, prospective, multicenter, open-label study, Bolin et al evaluated the improvement in GI symptom burden in MMF-treated patients who were converted to EC-MPS.[73] The ITT population included 720 patients. The GSRS was used to evaluate the change in GI symptom burden at each study visit. In addition, patients also completed the OTE scale for GI symptoms and OTE for HRQoL at a visit 3 months after conversion, to provide an overall evaluation of treatment effect. The primary endpoint of the study included the change in overall GSRS score from baseline to 3 months. On conversion to EC-MPS, a significant improvement in GSRS score from baseline (2.63 ± 0.03) was observed at month 1 (1.87 ± 0.03), and was sustained to month 3, suggesting a lack of placebo response alone. At baseline, the GSRS subscale scores were similar among patients receiving CsA or tacrolimus. In addition, regardless of the type of CNI regimen, a significant improvement

in GSRS subscale scores was observed. Three months after converting to EC-MPS, patient rating of OTE for GI symptoms indicated that 66% of the patients considered their symptoms had improved compared with baseline. The results of the study demonstrated a significant improvement in GI symptoms after the conversion to EC-MPS.

In a prospective, randomized, multicenter, open-label trial of 135 renal transplant recipients, Shehata and colleagues evaluated whether the conversion from MMF to EC-MPS can reduce GI side-effects thus permitting MPA dose to be increased.[74] After screening (Visit 1), patients who experienced GI side-effects while on MMF therapy were randomized to either remaining on MMF or converting to equimolar doses of EC-MPS (Visit 2). MMF or EC-MPS dose was then increased at the investigator's discretion to maximum tolerated doses at Visit 3. The final visit (Visit 4) occurred 12 weeks after randomization. Five self-administered patient questionnaires were used, including GSRS, Gastrointestinal Quality of Life Index (GIQLI), SF-36 health survey, OTE scale, and Bristol Stool Chart. Compared with the MMF group, the number of patients in the EC-MPS group receiving a higher MPA dose at 12 weeks compared with randomization was significantly greater (EC-MPS 47.1% vs MMF 16.4%). At the final visit, only 26.2% of the MMF-treated patients were receiving the maximum recommended dose, compared with 50% of EC-MPS–treated patients. Conversion to EC-MPS was also associated with a significant improvement in GI symptoms, reflected in the improvement in GSRS score, GIQLI score, and SF-36 score at Visit 3.

Conclusion

Comparable safety and therapeutic equivalency of EC-MPS and MMF have been demonstrated in both registered studies and post-marketing reports.[60–67] Though designed specifically to improve GI adverse events, prospective randomized controlled studies did not find significant differences between the EC-MPS and MMF formulations.[60,65] However, MMF to EC-MPS conversion studies that implemented PRO measures consistently reported a significant improvement in patient-reported GI symptoms,[72–74] and in one study, increased numbers of patients were maintained on the maximum recommended EC-MPS dose.[74] These results could potentially translate into improved long-term patient and allograft outcomes, as MPA dose reduction has consistently demonstrated higher rates of rejection and graft loss.[68–70] More studies are necessary to clearly establish a place for EC-MPS in an ever-changing and complex immunosuppressive landscape.

Disclosure

None of the authors declare conflicts of interest.

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