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Research Article

Enteric-Coated Mycophenolate Sodium and Gastrointestinal Prophylaxis in Renal Transplant Patients

Karen Parker[1], Winifred Bryant[2], Connie Garris-Sutton[2], Fatima Rana[2], and Paul Bolin[2]

[1] *Vidant Medical Center, Greenville, NC, USA*
[2] *Department of Internal Medicine, Division of Nephrology and Hypertension, Brody School of Medicine at ECU, Greenville, NC, USA*

Corresponding Author: Karen Parker; email: nephrologyresearch@ecu.edu

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Abstract. *Background*: The purpose of this study was to evaluate the discontinuation or reduction of gastrointestinal (GI) co-medication use and subjects' subsequent GI symptoms and psychological well-being after conversion from mycophenolate sodium (MMF) to enteric-coated mycophenolate sodium (EC-MPS). *Study Design*: Prospective, single-center, open label, longitudinal study. *Settings and Participants*: 54 renal transplant subjects who were successfully converted from MMF to EC-MPS previously due to GI symptoms. *Intervention*: Subjects were asked to reduce or discontinue their GI co-medication in a programmed fashion over a three month period. Subjects were subsequently followed for one year. *Outcomes*: Patient reported use of GI medications, symptoms, complaints, and overall quality of life. *Measurements*: Assessments were performed using validated patient-reported outcome instruments. Cost savings was also measured. *Results*: Successful discontinuation or reduction of GI co-medication was achieved in 78% patients after 30 days and maintained through day 90. No significant changes in GI symptom assessments were observed from baseline to day 30 or 90 despite discontinuation or reduction in GI co-medication. Twelve month follow up demonstrated sustained improvement in 91% of these patients. Annual cost savings per patient after reduction or discontinuation of GI medication were estimated to be \$925-\$1850 for H-2 blockers and \$1861-\$3722 for proton-pump inhibitors. *Limitations*: Results were based on a single center, open label experience and relied on patient reported data. *Conclusions*: This study supports successful long-term minimization of GI co-medications in maintenance renal transplant patients after conversion to EC-MPS. Data suggest that after conversion to EC-MPS renal transplant patients can successfully reduce or discontinue GI co-medication while maintaining their health-related quality of life and overall well-being.

Keywords: transplant; immunosuppression; gastrointestinal complications

1. Introduction

Recent significant improvements in acute rejection rates coupled with the need to minimize long-term drug toxicity have led to a number of changes in immunosuppression regimens. Introduction of mycophenolate mofetil (MMF, CellCept, Genentech, San Francisco, CA) has been associated with improved outcomes in both acute rejection rates and long term graft survival [1, 2]. These outcomes associated with MMF are dose dependent [3]. However, achieving optimal dosing of MMF has been limited by a number of side effects including gastrointestinal (Gl) intolerance [4].

Table 1: Validated gastrointestinal health-related quality-of-life scales.

Gastrointestinal Symptom Rating Scale (GSRS)	Gastrointestinal Quality of Life Index (GIQLI)	Psychological General Well-Being Index (PGWBI)
• Reflux, abdominal pain, constipation, diarrhea, and indigestion	• Reflux, abdominal pain, constipation, diarrhea, and indigestion	• Anxiety, depressed mood, positive well-being, self-control, general health, vitality
• 15 items	• 36 items	• 22 items
• GERD[a], dyspepsia, IBS	• Nonspecific, GERD, IBS	• GERD, dyspepsia
• Very good to good reliability, validity, and responsiveness	• Good reliability, validity, and responsiveness	• Very good reliability, validity, and responsiveness
• Lower numbers represent fewer or less severe symptoms	• Higher numbers respresent better QoL	• Higher numbers represent better QoL

Table 2: Patient calculated monthly and annual savings.

	Cost Savings/Month		**Annual Projected Savings**	
H2RA				
	Average	Range	Average	Range
qd[a]	$61.68	$5–$77	$740.16	$61–$925
bid[b]	$138.01	$75–$154	$1656.11	$894–$1850
PPI				
	Average	Range	Average	Range
qd	$106.15	$0–$155	$1273.76	$0–$1861
bid	$273.49	$220–$310	$3281.92	$2636–$3722

[a]qd = once a day

[b]bid = twice a day

Multiple studies have documented Gl toxicity in 20–50% of patients on MMF, including the study conducted by Tierce and colleagues which demonstrated over 49% of patients experienced at least one GI complication within their first 6 months post-transplant [5]. MMF reduction has been associated with improvement in Gl symptoms; however, MMF dose reduction to manage GI intolerance has been associated with lower graft survival [1, 2].

Enteric-coated mycophenolate sodium (EC-MPS, Myfortic, Novartis, East Hanover, NJ) was developed to limit Gl side effects. Earlier literature documented the need for MMF dose reductions due to GI side effects [5]. Other studies have shown improvement in severity of overall and specific GI symptoms and had less Gl-related adverse events after conversion to EC MPS from MMF [6–8]. The *my*TIME trial showed improvement in patient GI symptom burden after conversion and observed that 80% of the study population was taking one or more co-medications for GI complications prior to conversion and throughout the study [2]. This observation prompted us to further investigate the necessity for GI co-medications. The current study was conducted on a single center study population of the previously mentioned multi center randomized controlled *my*TIME trial. The aim of the study was to evaluate the potential reduction or discontinuation of GI co-medication use and its subsequent effect on patients' GI symptoms and psychological well-being after conversion to EC-MPS.

2. Methods

2.1. Study design and conduct. This was a 15-month, observational, prospective single center, open label study in adult renal transplant recipients who had successfully completed the *myTlME* trial. The *myTlME* trial required equimolar conversion from MMF to EC-MPS in transplant patients with GI complaints related to MMF therapy. Therefore, all of the current study subjects were receiving EC-MPS, a calcineurin inhibitor (CNI), and prednisone with at least one Gl co-medication. A sample of 61 subjects was recruited from 93 patients. The *myTIME* study required subjects to be 18 to 75 years old, had received a first or second renal transplant and be at least four weeks post transplant. Patients were excluded if they had a clinically significant infection requiring continued therapy, severe diarrhea, active peptic ulcer disease or any other Gl problem that would preclude them from discontinuing their Gl co-medication.

Patients were followed for 90 days in a programmed attempt to reduce or discontinue their Gl co-medication and were evaluated using patient reported outcome (PRO) measures at baseline, 1-month and 3-month with a 12-month follow up visit. A stepwise approach to reduce the dose of GI co-medication was used to determine the lowest possible dose necessary for each patient. The study was approved by the Institutional Review Board and informed consent was obtained from patients prior to the study. Each patient served

Table 3: Demographics and baseline characteristics.

	All ($n = 61$)[a]	TAC Only ($n = 41$)	CsA Only ($n = 20$)
Age (yrs)	52 (35–69)	51 (36–69)	52 (35–66)
Male	25 (41.0%)	10 (24.4%)	15 (75.0%)
Female	36 (59.0%)	31 (75.6%)	5 (25.0%)
African American	41 (67.2%)	30 (73.2%)	11 (55.0%)
Caucasian	18 (29.5%)	10 (24.4%)	8 (40.0%)
Other	2 (3.3%)	1 (2.4%)	1 (5.0%)
Causes of End-Stage Renal Failure			
Diabetes Mellitus	29 (47.5%)	21 (51.2%)	8 (40.0%)
Hypertension	42 (68.9%)	25 (61.0%)	17 (85.0%)
Glomerular Disease	10 (16.4%)	9 (22.0%)	1 (5.0%)
Polycystic Disease	4 (6.6%)	4 (9.8%)	0 (0%)
Other/Unknown	6 (9.8%)	4 (9.8%)	2 (10.0%)
Average Time Post Transplant to Conversion to myfortic (months)	33 (1–97)	34 (1–97)	34 (1–94)
Time from Conversion to Enrollment in MPACT (months)	11 (4–19)	12 (6–19)	10 (4–17)
Daily myfortic dose at Conversion (mg)	1121 (360–2160)	992 (360–2160)	1385 (720–2160)

[a]Data are n(%) or mean(range).

*All patients regiments included daily prednisone use.

as their own control by evaluation of quality of life and Gl symptoms before and after Gl co-medication reduction or discontinuation.

2.2. Gl co-medication. At baseline, patients taking Gl co-medication once daily (QD) were asked to reduce the dose to as needed (PRN). Patients taking GI co-medication twice daily (BID) were asked to reduce their dose to QD. Additional doses were permitted if necessary. Patients were given diaries to document any additional doses.

At day 30, patients remaining on QD dosing were reduced to PRN. Patients were evaluated for increased Gl toxicity signs and symptoms at day 30 and 90. Study diaries were reviewed at each visit to assess Gl co-medication requirements.

2.3. Patient-reported outcomes. At each study visit, patients were asked to complete three questionnaires: I) The Gastrointestinal Symptom Rating Scale (GSRS), which evaluates the burden of Gl symptoms; 2) The Gastrointestinal Quality of Life Index (GIQLI) which assesses the impact of Gl complaints on daily life; and 3) The Psychological General Well-Being Index (PGWBI) which assesses overall quality-of-life [3] (Table 1).

2.4. Study endpoints. The primary endpoint was the change in overall GSRS scores from baseline to month 3 as patients reduced or discontinued their GI co-medications. The secondary endpoints were maintenance or an increase in quality of life (QoL) by evaluating the impact of Gl symptoms on patient's perceptions of symptom severity, Gl specific health related QoL, general health-related QoL using the 3 questionnaires described above and cost savings for patients.

2.5. Cost savings. The monthly cost of taking a proton pump inhibitor (PPI) or a H2 receptor antagonist (H2RA) was calculated based on the 2006 average wholesale price of the commonly used drugs, both generic and name brand, in each class [9]. Omeprazole, esomeprazole and lansoprazole were used to calculate a comparable price index for PPIs. Ranitidine HCL and famotidine were used to calculate the comparable price index for H2RAs. The average price was calculated for both PPIs and H2RAs. Using the calculated average price for both types of Gl medications, the annual savings were then determined based on QD and BID dosing (Table 2).

2.6. Twelve month follow up. Approximately 12 months after the 90-day study visit, patients were assessed for GI symptoms and use of GI co-medications. Current Gl co-medication use and Gl symptoms were compared to the 90-day visit.

2.7. Statistics. The percent of patients discontinuing or reducing GI co-medication was determined by comparing each patient's baseline Gl co-medication dose regimen to their 30-day and 90-day GI co-medication dose regimens. Severity of GI complications was calculated for the 3 month treatment period at baseline, 1-month and 3-month. Changes in the overall GSRS, GIQLI, PGWBI scores from baseline for all patients were tested using a paired t test at the 0.05 level of significance.

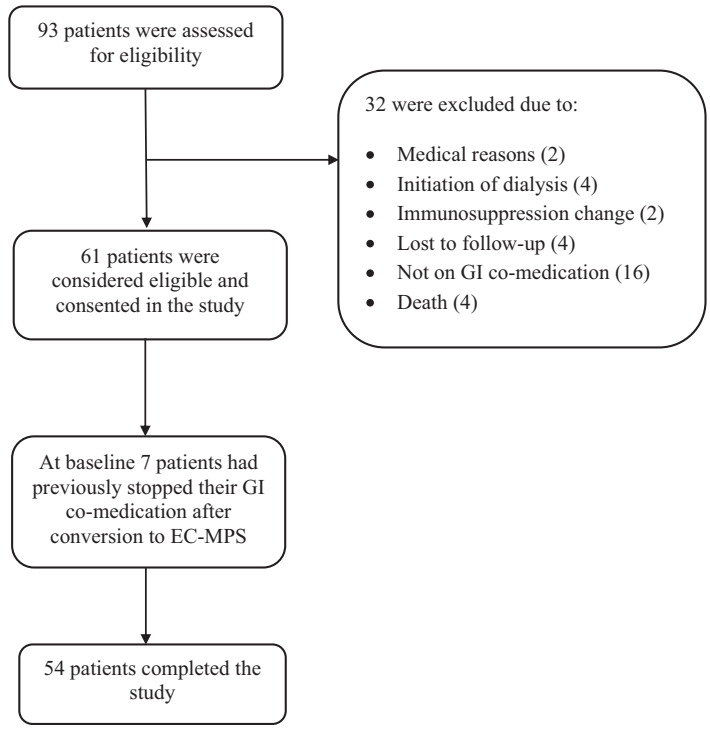

Figure 1: Patient population.

3. Results

3.1. Patient population. Patients were between 34 and 69 years of age with an average time of 33 months (range 1-97 months) post-transplant to conversion to EC-MPS (Table3). The patients' initial EC-MPS dose was maintained throughout the study period. Patients were taking EC-MPS, tacrolimus (TAC, Prograf, Astellas Pharma US, Northbrook, IL) or cyclosporine modified (CsA, Neoral, Novartis, East Hanover, NJ), a steroid and at least one GI co-medication. At baseline, 44% of patients were taking a PPI and 56% were taking a H2RA. All immunosuppressive regimens included prednisone at 5 mg daily throughout the study period.

Recruitment extended from March to October 2006. Thirty-two patients were ineligible for the study due to 1) no GI co-medication, 2) medical need for GI co-medication, 3) initiation of dialysis, 4) immunosuppression change, 5) lost to follow up, and 6) death. Sixty-one patients

were consented, seven of which discontinued their GI co-medication prior to visit one (Figure 1).

Successful discontinuation or reduction of GI co-medication was achieved in 42 (78%) patients after 30 days and was sustained through day 90. There was no significant change in PRO assessments at baseline, day 30 or day 90 despite discontinuation or reduction in GI co-medication.

3.2. Patient- reported outcomes. GSRS scores improved in patients who discontinued their GI co-medication (Figure 2). GSRS scores remained stable for patients who reduced or maintained their GI co-medication. Overall, 60% of patients had a stable total GSRS score throughout this study despite decreasing GI co-medication. Patient scores for the GIQLI questionnaire remained stable throughout this study. Additionally, the PGWBI scores remained constant throughout the study period suggesting that discontinuing Gl co-medication did not have a negative impact on the psychological well-being of patients.

3.3. Cost savings. Projected annual savings ranged from an average of $740.16 to $3,281.92 per patient (Table 2). Projected savings were greatest for patients taking a PPI BID ($3,821.92), and smallest for patients taking a H2RA QD ($740.16). However, the perceived cost savings from Gl medications may be neutralized or at worse offset by the higher cost of EC-MPS compared to the generic MMF. Ultimately, as generic versions of EC-MPS emerge on the market, the perceived cost saving will become more apparent between EC-MPS and MMF since EC-MPS may not require additional medications for GI irritability.

3.4. Twelve-month follow up. Patients were contacted by telephone 12 months after the 90 day visit for an interview to investigate the long-term outcomes of reducing or discontinuing GI co-medication. Thirty-eight patients (90%) reported either further reduction or no change in GI co-medication. Two patients reported an increase in GI co-medication and two returned to dialysis.

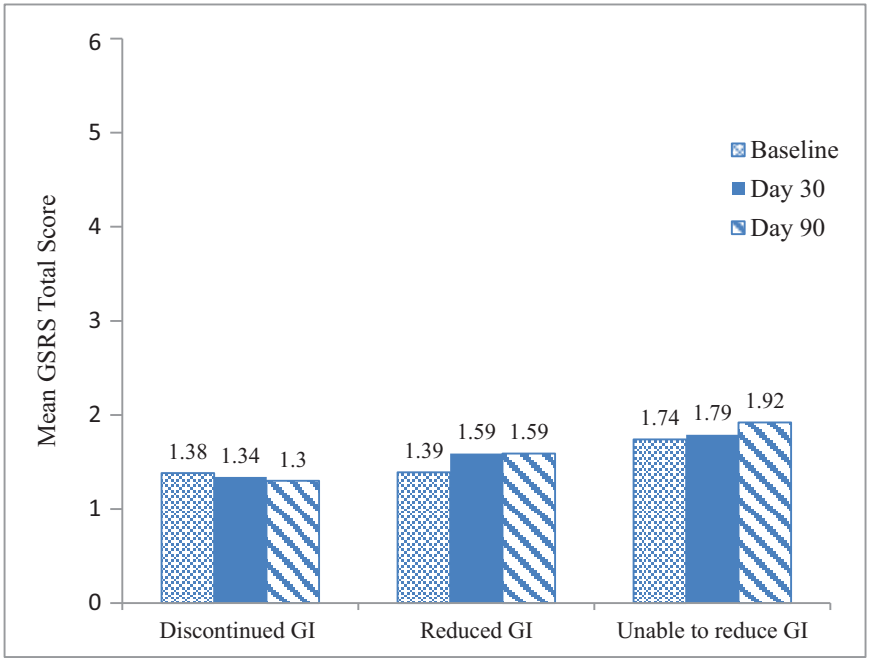

Figure 2: Patient-reported results: mean total GSRS score at baseline (while receiving GI co-medication) and at day 30 and 90 after reducing or discontinuing GI co-medication. Patients were divided into 3 groups: patients who discontinued their GI co-medication, patients who reduced their GI co-medication and patients who were unable to reduce their GI co-medication.

4. Discussion

This study demonstrates that patients converted to EC-MPS from MMF due to GI toxicity can reduce or eliminate their GI co-medication (78%) without a significant impact on GI symptoms or psychological well-being as assessed by multiple PRO measures. This success was found even though patients' medications included a daily steroid dose, which has also been associated with GI complications [10]. Additionally, cost savings reported by the patients as a result of discontinuing or reducing their GI co-medications are significant.

The potential economic benefit of up to $3,000/year per patient from discontinuing or reducing GI co-medication represents a significant savings, even when considering the cost of ongoing immunosuppression. Moreover, minimizing the use of GI co-medication avoids potential complications associated with PPI/H2RA. Utilizing immunosuppressive regimens with less GI toxicity could minimize the need for GI co-medications with their attendant risk and effects on cost savings. The introduction of generic MMF offers potential cost savings on immunosuppression although the conversion from MMF to EC-MPS is clinically indicated in those patients with GI intolerance to MMF.

The GSRS questionnaire revealed the overall symptom burden from discontinuing GI co-medication remained unchanged. These results were similar for patients on either tacrolimus or cyclosporine. Similar results suggest that Gl quality of life and psychological well-being remains stable following withdrawal of a Gl co-medication regardless of calcineurin inhibitor.

The results further illustrate the relevance of our data in many ways. First, decreasing exposure to GI co-medication in this study may increase mycophenolic acid (MPA) levels without increasing GI symptoms in our patients taking EC-MPS [11]. Second, the reduction in MPA area under the curve (AUC) with GI co-medications illustrates the importance of reducing GI co-medications because of their effect on MPA absorption. A recent study by Kofler and colleagues demonstrated a 25% reduction in MPA-AUC when administered with GI co medications in heart transplant recipients [12]. Additionally, the reduction in MPA-AUC with PPIs was further associated with a 42% increase in activity of inosine mono phosphate dehydrogenase, the targeted enzyme of MPA, in a study of lupus nephritis [13]. Fourth, if patients require GI co-medications despite conversion to EC-MPS, the impact of GI co medication on MPA exposure is eliminated [14, 15].

The subjects in the current observational study were from a single center population who had been successfully converted from MMF to EC-MPS due to GI toxicity in the multicenter, randomized-controlled myTime trial. This population was further studied to determine if GI co-medication could be reduced or discontinued. Immunosuppression regimens of all subjects included CNI and prednisone. Reduction or discontinuation of GI co-medication was possible in the majority of the subjects. Consideration should be given to GI

co-medication minimization due to the clinical significance and potential cost savings for transplant recipients.

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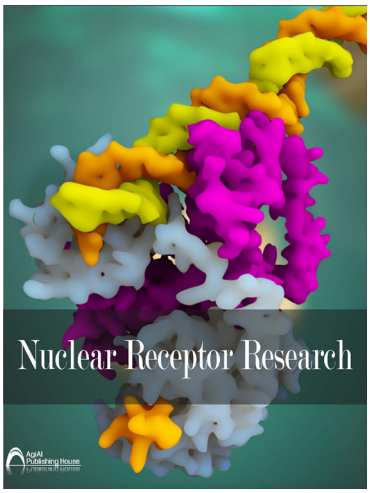

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