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Mycophenolate Mofetil and Enteric-Coated Mycophenolate Sodium with the Concomitant Use of Proton Pump Inhibitors in Patients who Received Kidney Transplant

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ABSTRACT

Objective: This study aims to describe and compare the transplant outcomes of kidney transplant patients who received either mycophenolate mofetil or enteric-coated mycophenolate sodium with the concomitant use of proton pump inhibitors.

Methods: This was a 9-year retrospective observational study conducted between January 1, 2011, and December 31, 2019 at Ibni Sina Hospital, Nephrology Department, Ankara University Faculty of Medicine.

Results: Among 349 kidney transplant patients, 290 were eligible for the study aged [median (interquartile range)] 41 (33-50) years in the mycophenolate mofetil group and 41 (31-50) years in the enteric-coated mycophenolate sodium group. More than half of them were male (54% in mycophenolate mofetil vs. 60% in enteric-coated mycophenolate sodium groups) and the majority received a living transplant (79% in both). There was no statistically significant difference in transplant outcomes including protein/creatinine ratio [(median (interquartile range)): 150 (2-308) vs. 153 (58-397), P = .742], creatinine doubling (8% vs. 10%, P = .589), change in medications (46% vs. 48%, P = .775), delayed graft function (8% vs. 14%, P = .153), biopsy-proven acute rejection (14% vs. 18%, P = .327), graft loss (7% vs. 10%, P = .351), and overall mortality (4% vs. 6%, P = .337) among the patient groups who received either mycophenolate mofetil or enteric-coated mycophenolate sodium, respectively.

Conclusion: The transplant outcomes including graft survival, biopsy-proven acute rejection, graft loss, or delayed graft function of the kidney transplant patients who received mycophenolate mofetil or enteric-coated mycophenolate sodium with proton pump inhibitors were similar. Therefore, proton pump inhibitors and mycophenolate mofetil or enteric-coated mycophenolate sodium can be prescribed together safely with appropriate follow-up intervals.

Key words: Drug–drug interactions, enteric-coated mycophenolate sodium, kidney transplant, mycophenolate mofetil, proton pump inhibitors

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INTRODUCTION

End-stage kidney disease (ESKD) is an important public health concern worldwide due to its increasing prevalence, requiring costly treatments, and high morbidity and mortality rates.[1,2] Hemodialysis, peritoneal dialysis, and kidney transplant (KTx) are kidney replacement therapies and possible treatments for ESKD.[1,2] Kidney transplant is the treatment of choice for most patients with ESKD because of its superior morbidity, mortality, and cost outcomes compared to that of the other treatment options.[2] Immunosuppressive therapy is prescribed for patients who have received a KTx to prevent graft rejection and increase graft survival.[3-5] The most commonly used maintenance immunosuppressive

therapy consists of calcineurin inhibitors (cyclosporine or tacrolimus), glucocorticoids (prednisolone or methylprednisolone), and antiproliferative agents (mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS), or azathioprine).[3-5] Mycophenolate is currently prioritized among the antiproliferative agents due to better maintenance of the kidney response to the treatment compared to that achieved with azathioprine.[6]

Gastrointestinal side effects have been commonly reported after treatment with MMF in patients who have received a KTx.[7] Dose reduction, division of the dose, or discontinuation of the drug to manage these side effects cause graft loss and acute rejection.[8] Enteric-coated mycophenolate sodium, which enables drug release in the small intestine, has been developed to reduce gastrointestinal side effects.[7] Mycophenolate mofetil and EC-MPS were found to have an equivalent effect on the release of mycophenolic acid (MPA), which is an active drug[9-11] Although no difference was found in terms of the effect and tolerance of these 2 drugs, it was emphasized that economic factors could be effective in drug selection.[12]

One of the most common complications seen in KTx patients is peptic ulcer disease, which may lead to mortality and morbidity.[13] Proton pump inhibitors (PPIs) are added for long-term treatment or prophylaxis to prevent complications.[13] Although the use of MMF or EC-MPS with PPIs causes drug–drug interactions (DDIs), the effect of the interaction on the active blood levels of the drug is controversial. Therefore, DDI checkers provided by drug databases recommend a close follow-up of patients who are treated with mycophenolate combined with PPIs.[14,15]

While there are studies that have investigated the effect of drug interaction with PPIs, there are no comparative studies that have reported the effects of the interaction on long-term clinical outcomes such as graft loss, graft survival, or mortality. The current comparative studies on drug effects involved very few individuals, and the studies were of short duration[16,17] Therefore, the aim of this study was to describe and compare the clinical transplant outcomes of KTx patients who received either MMF or EC-MPS with the concomitant use of PPIs.

MAIN POINTS

- The transplant outcomes of the patients who received either mycophenolate mofetil or enteric-coated mycophenolate sodium with concomitant use of proton pump inhibitors (PPIs) were similar.
- This study provides evidence-based data on the safe use of PPIs in combination with mycophenolate derivatives.
- Drug interaction databases could reconsider lowering the current risk for the drug–drug interactions between mycophenolate and PPIs.

METHODS

Study Design and Population

This was a 9-year retrospective observational study conducted between January 1, 2011, and December 31, 2019 at the Ibni Sina Hospital, Nephrology Department, Ankara University Faculty of Medicine. Ibni Sina Hospital is a 1,000-bed, government-run tertiary university hospital in Türkiye. It is one of the largest university hospitals, including almost all specialty clinics. The KTx clinic accepts patients mainly from the Ankara Province; however, a considerable number of patients are from other cities in Türkiye. Therefore, follow-up was not applicable for all patients transplanted in the clinic due to patients' preferences to visit a physician from their city instead of traveling to Ankara.

Patients who have received a KTx, aged $\geq$ 18 years, and who received MMF or EC-MPS with PPIs in maintenance therapy were enrolled. Patients who had no history of regular follow-up and graft loss within 3 months after the transplant were excluded. Patient medical and medication records were collected by using an electronic database at the hospital.

The Ethics Committee for Human Research of Ankara University Faculty of Medicine approved the study (Date: March 26, 2020; Decision No: I2-138-20).

Patient Characteristics and Outcome Measures

Patient characteristics, including sex, age, medication history, weight, height, body mass index (BMI), and donor age, were collected. The relationship between the recipient and donor, ABO incompatibility, transplant type, human leukocyte antigen (HLA) mismatch, anti-thymocyte globulin (ATG) induction, and time from transplant to data collection year were also recorded to consider their effects on the transplant outcomes.

Drug–drug interactions were detected using the Lexicomp® database.[14] Patients were determined to have interacting drugs in their medication regimen when there was at least 1 medication interacting with mycophenolate.

Graft function was estimated in terms of glomerular filtration rate (eGFR) calculated with the Modification of Diet in Kidney Disease (MDRD) 4-variable equation.[18,19] Modification of Diet in Kidney Disease provides better diagnostic performance and is recommended for use in KTx patients.[20]

The transplant outcomes consisted of the latest protein/creatinine ratio, creatinine doubling, change in medication, delayed graft function, adverse events (cytomegalovirus (CMV) and BK virus infections), biopsy-proven acute rejection (BPAR) within the first year of Tx, graft survival, and overall mortality. Except for BPAR, patients were followed up from transplant to data collection day. Creatinine doubling reflects the sustained decrease in eGFR and is a commonly

used composite endpoint in nephrology trials.[21] Changes in immunosuppressive therapy, including the mechanistic target of rapamycin inhibitors, glucocorticoids, calcineurin inhibitors, antimetabolites, and PPIs, were followed throughout the study. The alteration in the medication regimen was assumed to be due to patients not achieving the expected outcomes with the initial regimen.

Comparisons were made between patients who received either MMF or EC-MPS. Patients were divided based on the generic name of the PPIs that they were treated with to eliminate the effect of different PPIs on the comparisons. Kidney Disease Improving Global Outcomes guidelines were used to estimate the reference range of tacrolimus.[22]

Statistical Analysis

The patients' characteristics and outcomes were evaluated descriptively. The chi-square test was used for nominal categorical values, which were described in percentages, and the Mann–Whitney *U* test was used for non-parametric continuous variables, which were described as median and interquartile range (IQR). The normality was assessed. For the chi-square test, a 2-sided significance level of 5% was applied. If the *P*-value was <.05, it was considered a statistically significant difference. Statistical Package for the Social Sciences version 21.0 (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp., Armonk, NY, USA) and Microsoft Excel for Windows version 2016 were used for the descriptive analysis.

RESULTS

Patient and Donor Characteristics

Among 349 of the patients who had received a KTx, a total of 290 (83%) patients were eligible for the study. The rest were excluded because of death before discharge (n = 1), lack of use of PPIs (n = 1), lack of use of MMF or EC-MPS (n = 3), use of azathioprine (n = 16), or lack of follow-up after the transplantation (n = 38) (Figure 1). Totally, 59% of the patients were prescribed MMF, and 41% of the patients were prescribed EC-MPS. Almost all of the KTx patients received methylprednisolone and tacrolimus in their immunosuppressive therapy (99%). The percentage of patients who were prescribed cyclosporine and prednisolone was 1%. Patients were either prescribed lansoprazole or pantoprazole in their PPI regimen. The median (IQR) for PPI use was 6 (4-9) years in both groups.

More than half of the KTx patients were male (54% in MMF vs. 60% in EC-MPS groups). The majority were younger than 65 years (94% in MMF vs. 96% in EC-MPS groups) and had received a living transplant (79% in both groups). ABO incompatibility was present in only 2 patients (1%). Nearly half of the patients had used at least 1 chronic medication that interacts with mycophenolate (46% in MMF vs. 48% in EC-MPS groups) over time. Anti-thymocyte globulin induction was present in 22% of the patients, and 16% of the patients received MMF and EC-MPS. In the MMF group, the median (IQR) BMI (kg/m^2), donor age, HLA mismatch, years since transplantation, and eGFR (mL/min/1.73 m^2) were 24 (21-27), 48 (40-56), 3 (2-4), 6 (4-9), and 52 (37-68), respectively. In the EC-MPS group, the median (IQR) BMI (kg/m^2), donor age, HLA mismatch, years since transplantation, and eGFR (mL/min/1.73 m^2) were 23 (21-30), 51 (41-57), 3 (2-4), 6 (4-9), and 54 (35-72), respectively. There was no statistically significant difference in terms of the characteristics among the patients who received MMF or EC-MPS (Table 1).

The majority of the patients had hypertension in both groups (77% in MMF vs. 76% in EC-MPS, $P = .585$). Less than a quarter of the patients had diabetes mellitus (29% in MMF vs. 19% in EC-MPS, $P = .056$).

Patients who were prescribed lansoprazole were more likely to be followed up for longer than the follow-up time of those who were prescribed pantoprazole in both the MMF and EC-MPS groups ($P < .001$ vs. $P < .001$) (Table 1).

The doses (mean (standard deviation (SD)) at baseline, 6th, and 12th months were 1910.9 (215.51), 1875.0 (2422.75), and 1530.7 (467.88) mg in the MMF group and 1440.7 (321.32), 1249.4 (224.74), and 1247.4 (426.78)mg in the EC-MPS group,

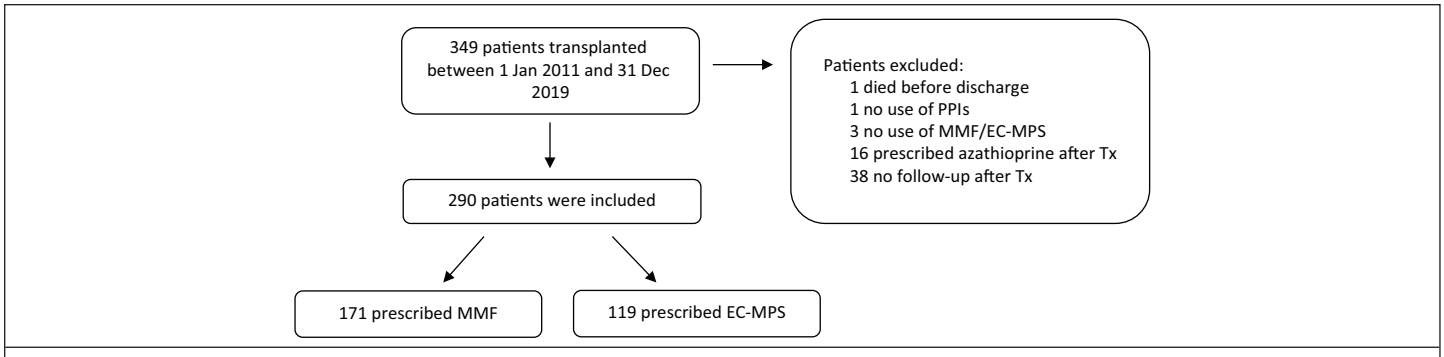

Figure 1. Flow diagram of the patient selection process. EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; PPIs, proton pump inhibitors; Tx, transplant.

Table 1. Characteristics of the Patients

	MMF				EC-MPS				*P*
PPI Type, n (%)	Lansoprazole (94, 55%)	Pantoprazole (77, 45%)	Total (171, 100%)	*P*	Lansoprazole (61, 51%)	Pantoprazole (58, 49%)	Total (119, 100%)	*P*	.533
Age, median (IQR) ≥65 years, n (%)	41 (32-50) 3 (3)	43 (35-51) 3 (3)	41 (33-50) 6 (4%)	.404 1.000	40 (30-48) 0 (0)	42 (31-50) 1 (1)	41 (31-50) 1 (1)	.342 .487	.600 .246
Male, n (%)	51 (30)	42 (25)	93 (54)	.970	31 (26)	40 (34)	71 (60)	.044	.372
BMI (kg/m^2), median (IQR)	24 (21-26)	25 (22-28)	24 (21-27)	.098	23 (21-26)	24 (21-27)	23 (21-30)	.722	.228
Donor age, median (IQR)	48 (37-44)	51 (44-58)	48 (40-56)	.502	52 (41-58)	54 (41-58)	51 (41-57)	.700	.243
Transplant type, n (%) Living (spouse, first, second, third, or fourth degree relatives) Cadaveric	73 (43) 21 (12%)	62 (36) 15 (9%)	135 (79) 36 (21%)	.648	48 (40) 13 (11%)	46 (39) 12 (10%)	94 (79) 25 (21%)	.934	.993
HLA mismatch, median (IQR)	3 (2-5)	3 (2-4)	3 (2-4)	.009	3 (3-5)	3 (2-4)	3 (2-4)	.096	.610
ATG induction, n (%)	17 (10)	21 (12)	38 (22)	.150	6 (5)	13 (11)	19 (16)	.061	.187
Time since Tx, years, median (IQR)	8 (7-10)	4 (3-5)	6 (4-9)	<.001	9 (8-10)	4 (3-5)	6 (4-9)	<.001	.949
Use of medication interacts with mycophenolate*, n (%)	54 (32)	29 (17)	83 (49)	.010	36 (30)	24 (20)	60 (50)	.054	.752
eGFR (mL/min/1.73 m^2), median (IQR)	52 (37-74)	53 (37-64)	52 (37-68)	.622	46 (26-64)	60 (45-81)	54 (35-72)	.002	.804

*Includes number of patients whose chronic medications such as aspirin, basiliximab, hydrochlorothiazide, levonorgestrel, and leflunomide interact with mycophenolate.
ATG, antithymocyte globulin; BMI, body mass index; EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigens; IQR, interquartile range; MMF, mycophenolate mofetil; PPI, proton pump inhibitor; Tx, transplantation.

respectively (Table 2). The baseline ($P < .001$) and 12th month ($P = .020$) doses were statistically different between drug groups due to the dosing of equimolar MPA.

The GFR values (mean (SD)) at baseline, 6th, and 12th months were 57.1 (24.80), 65.5 (20.33), and 67.7 (18.77) mL/min/1.73 m^2 in the MMF group and 60.8 (24.75), 72.8 (15.30), and 75.1 (15.41) mL/min/1.73 m^2 in the EC-MPS group, respectively (Table 2). The 6th ($P = .022$) and 12th month ($P = .010$) GFR values were statistically different between drug groups.

The tacrolimus levels (mean (SD)) at baseline, 6, and 12 months were 8.8 (3.34), 6.7 (2.58), and 6.3 (1.73)ng/mL in the MMF group and 8.4 (3.51), 6.3 (1.50), and 6.3 (2.17) ng/mL in the EC-MPS group, respectively (Table 2). Therefore, during the first 12 months after the transplant, patients' tacrolimus levels were within the reference range. There were statistically different tacrolimus levels between drug groups.

Transplant Outcomes

A few of the KTx patients who received either MMF or EC-MPS had negative transplant outcomes, including chronic rejection (0% in both groups) and CMV infections (4% in MMF vs. 6% in EC-MPS groups), and the overall mortality rate was 4% (in MMF) vs. 7% (in EC-MPS). In the comparison between the MMF and EC-MPS patient groups, creatinine doubling, changes in medication, delayed graft function, BK virus infection, BPAR, and graft loss were 8% vs. 10%, 46% vs. 48%, 8% vs. 14%, 18% vs. 20%, 14% vs. 18%, and 7% vs. 10% in the MMF versus EC-MPS groups, respectively. The protein/creatinine ratios (median (IQR)) in patients who received MMF and EC-MPS were 150 mg/g (2-308) and 152 mg/g (58-397), respectively. There was no statistically significant difference in terms of transplant outcomes among the patients who received MMF or EC-MPS (Table 3).

Patients who were prescribed lansoprazole were more likely to have changes in maintenance immunosuppressive therapy than those who were prescribed pantoprazole in both the MMF and EC-MPS groups ($P < .001$ vs. $P = .013$) (Table 3).

DISCUSSION

This study described and compared the transplant outcomes of KTx patients who received either MMF or EC-MPS with the concomitant use of PPIs. This study was conducted with a

Table 2. Mean (SD) of Baseline, 6th Month, and 12th Month Doses, GFR Values, and Tacrolimus Levels

	MMF	EC-MPS	P
Doses (mg)*			
Baseline, mean (SD)	1910.9 (215.51)	1440.7 (321.32)	<.001
6th month, mean (SD)	1875.0 (2422.75)	1249.4 (224.74)	.053
12th month, mean (SD)	1530.7 (467.88)	1247.4 (426.78)	.020
GFR values (mL/min/1.73 m^2)			
Baseline, mean (SD)	57.1 (24.80)	60.8 (24.75)	.405
6th month, mean (SD)	65.5 (20.33)	72.8 (15.30)	.022
12th month, mean (SD)	67.7 (18.77)	75.1 (15.41)	.010
Tacrolimus levels (ng/mL)			
Baseline, mean (SD)	8.8 (3.34)	8.4 (3.51)	.313
6th month, mean (SD)	6.7 (2.58)	6.3 (1.50)	.086
12th month, mean (SD)	6.3 (1.73)	6.3 (2.17)	.948

*MMF 1000 mg and EC-MPS 720 mg contain near equimolar MPA.
EC-MPS, enteric-coated mycophenolate sodium; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; SD, standard derivation.

larger number of patients who have received a KTx and a longer patient follow-up period than the number of patients and follow-up times reported in previously published studies.[16,23,24] The results of the present study showed that there was no difference in transplant outcomes among patients who had received a KTx and used either MMF or EC-MPC with concomitant PPI use. Although there could be differences in the pharm acokinetic/pharmacodynamic profiles of MMF and EC-MPS with concomitant PPI use, the transplant outcomes were less likely to be changed.

The findings are consistent with other studies conducted among KTx patients and healthy volunteers. A study that evaluated the pharmacokinetic profile of MMF and EC-MPS in combination with pantoprazole concluded that although the pharmacokinetics of MMF and EC-MPS were affected by PPI exposure, there was no effect on the pharmacodynamics of MPA among 17 KTx patients.[16] Therefore, the immunosuppressive effects of MMF and EC-MPSs are similar.[16] Another study reported that combinations with omeprazole and MMF or EC-MPS showed similar MPA concentrations among 100 KTx patients who received MMF or EC-MPS.[25] In a study involving 12 healthy volunteers, the use of MMF or EC-MPS with omeprazole significantly reduced the absorption of MMF but did not affect the absorption of EC-MPS.[22] In a study that compared MMF and EC-MPS with concomitant use of omeprazole, the clinical effect on the transplant outcome (BPAR) was the same within the first week after Tx in 88 patients, while the clinical effect with EC-MPS was better than MMF because of higher MPA exposure.[24] However, BPAR can occur up to 3 months after KTx.

In our study, patients' transplant outcomes were followed up for up to 9 years. There was no difference in the transplant

Table 3. Outcomes of the Patients After Transplant

	MMF				EC-MPS				P
PPI Type, n (%)	Lansoprazole (94, 55%)	Pantoprazole (77, 45%)	Total (171, 100%)	P	Lansoprazole (61, 51%)	Pantoprazole (58, 49%)	Total (119, 100%)	P	.533
Protein/creatinine ratio, median (IQR)	102 (1-273)	182 (95-335)	150 (2-308)	.008	135 (3-419)	167 (84-264)	152 (58-397)	.749	.742
Creatinine doubling, n (%)	10 (6)	4 (2)	14 (8)	.196	9 (8)	3 (3)	12 (10)	.083	.589
Change in medication use, n (%)	57 (33)	22 (13)	79 (46)	<.001	36 (30)	21 (18)	57 (48)	.013	.775
Delayed graft function, n (%)	10 (0.6)	4 (2)	14 (8)	.189	7 (6)	9 (8)	16 (14)	.518	.153
Adverse events:	6 (4)	1 (1)	7 (4)	.130	2 (2)	5 (4)	7 (6)	.264	.485
infections, n (%)	21 (12)	9 (5)	30 (18)	.068	13 (11)	11 (9)	24 (20)	.750	.572
Cytomegalovirus									
BK virus									
Biopsy-proven acute rejection in the first year, n (%)	14 (8)	9 (5)	23 (14)	.541	13 (11)	8 (7)	21 (18)	.282	.327
Graft loss, n (%)	9 (5)	3 (2)	12 (7)	.148	9 (8)	3 (3)	12 (10)	.083	.351
Overall mortality, n (%)	3 (2)	3 (2)	6 (4)	1.000	2 (2)	5 (4)	7 (6)	.440	.337

EC-MPS, enteric-coated mycophenolate sodium; IQR, interquartile range; MMF, mycophenolate mofetil; PPI, proton pump inhibitor.

outcomes in KTx patients who received MMF or EC-MPS with PPIs and tacrolimus levels were not substantially altered. Mycophenolic acid concentrations/exposure correlates with the incidence of transplant outcomes, including BPAR, in KTx patients,[26] and the interaction between MMF and PPIs in our study population seemed clinically insignificant. The mechanism of interaction was due to the higher gastric pH caused by PPIs.[16] Since the gastric pH was increased, the dissolution and hydrolysis of MMF were altered, causing lower bioavailability of the drug.[16] Moreover, PPIs such as lansoprazole and pantoprazole did not cause statistically significant differences in transplant outcomes in this study. Therefore, pantoprazole and lansoprazole might have the same mechanism of interaction, in contrast to the study that suggested that rabeprazole was less likely to affect MPA concentrations.[13]

The difference in changes in maintenance immunosuppressive therapy between patients treated with lansoprazole and pantoprazole in both the MMF and EC-MPS groups might have resulted from the fact that the patients who received a transplant earlier were more likely to be prescribed lansoprazole than pantoprazole (median: 8-9 years vs. 4 years) due to the prescribing trend in early years. Thus, they were observed for a longer time, providing more time to detect the changes.

Patients with chronic kidney disease have a high burden of comorbidities such as hypertension, heart failure, and coronary disease that affect their clinical outcomes.[27] These patients are prescribed many chronic medications to manage these comorbidities. In this study, nearly half of the patients who received a KTx used a chronic medication that interacts with MPA from high to low severity. These chronic medications were aspirin, hydrochlorothiazide, and indapamide, which are used for the management of cardiovascular diseases. Therefore, after KTx, a medication review is required immediately after the Tx or when patients have been prescribed a new medication. Some chronic medications used before Tx can interact with the drugs used for immunosuppressive therapy, including MPA, or vice versa. There is a need for enhanced collaboration between physicians across different specialties while prescribing medications to avoid these interactions.

Although there was no statistically significant difference among the transplant outcomes of the KTx patients, the percentage of patients who experienced these outcomes such as creatinine doubling and BPAR was higher in KTx patients who received EC-MPS than in those who received MMF. Further studies with a larger sample size are needed to investigate the possible reasons for the higher occurrence of these outcomes in patients who received a KTx. and were prescribed EC-MPS.

There were several limitations in this study. There could be other risk factors such as cold ischemia that might affect the occurrence of BPAR. Mycophenolic acid concentrations were not measured in the transplant clinic and its concentrations could not be obtained as this was a non-invasive retrospective study. The results of this study cannot be generalized for all KTx patients because it was a single-center study, and transplant outcomes might be affected by the provision of care, which can vary among institutions. Finally, there is a known variable in DDI between MMF and PPI among patients, and it is known that Black patients are at higher risk for undesirable clinical outcomes than those of other races; however, Black patients were not included in this study.[28]

CONCLUSION

Although there was a DDI between PPIs and MMF, our findings showed that this interaction did not affect the transplant outcomes and was unlikely to be clinically significant. Therefore, PPIs and MMF or EC-MPS can be prescribed together safely with appropriate follow-up intervals.

Ethics Committee Approval: The Ethics Committee for Human Research of Ankara University Faculty of Medicine approved the study (Date: March 26, 2020, Decision No: I2-138-20).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.P., A.T.O.; Design – A.P., A.S., Ş.E.; Supervision – A.T.O., Ş.Ş.; Data Collection and/or Processing – A.P., A.S., Ş.E.; Analysis and/or Interpretation – A.P., A.S., Ş.E.; Literature Review – A.P., A.S., Ş.E.; Writing – A.S., Ş.Ş.; Critical Review – A.T.O., Ş.Ş.

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