



Adverse effects of mycophenolic acid in renal transplant recipients: gender differences

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Abstract

Background Mycophenolic acid is widely used immunosuppressive drug, associated with adverse effects which increase patient morbidity and decrease medication adherence. **Objective** To evaluate the adverse effects in renal transplant recipients under mycophenolate treatment with respect to gender. **Setting** University Clinical Centre of Nis, Clinic of Nephrology, Serbia. **Method** This research included 96 renal transplant recipients, who received immunosuppressive regimen, based on tacrolimus or cyclosporin A, prednisone and mycophenolic acid. The high-performance liquid chromatography method combined with protein precipitation was used for the analysis of mycophenolate concentration in human plasma. Drug concentration and dose-adjusted concentration were determined with respect to the patients' gender. An adverse effect scoring system developed by nephrologists within the University of Buffalo Nephrology/Transplant Program was used to monitor adverse effects of therapy. **Main outcome measure** Individual and scores of adverse effects in relation to the dosing regimen and gender. **Results** Results showed statistically lower dose and concentrations in men compared to the women in our investigation group. Also, female patients demonstrated higher mean scores (cumulative and subscores) within the same dosing regimens of mycophenolic acid. The gastrointestinal score was significantly higher in women who received a dose greater than 720 mg compared to men (0.20 ± 0.12 vs 0.12 ± 0.12). Women demonstrated higher individual adverse effects such as diarrhea and skin changes (41.7 vs 17.0; $p=0.038$ and 62.5 vs 30.2; $p=0.037$, respectively). **Conclusions** The results of our research showed that recipients' gender may play an important role in pharmacokinetic profile of mycophenolic acid, suggesting that women had higher concentration of mycophenolic acid and more serious side effects.

Keywords Adverse effects · Gender · Mycophenolic acid · Renal transplantation

Impacts on practice

- For mycophenolic acid, which is not routinely monitored, gender differences in drug pharmacokinetic could be accounted for by adjusting doses and therapy management.

- It is important to choose the best therapy option for each individual patient and to minimize the adverse effects in order to improve graft outcomes and immunosuppressive adherence post-transplant.

Introduction

A renal transplantation is the chosen treatment option for patients with end-stage kidney failure. Throughout the world, the most prescribed immunosuppressive protocol contains calcineurin inhibitors (CNI)—tacrolimus or cyclosporin A, antimetabolite drug (mycophenolic acid or mycophenolate mofetil) and corticosteroid. Mycophenolic acid (MPA) is available either as an ester prodrug (mycophenolate mofetil, MMF) or as a sodium salt (mycophenolate sodium, EC-MPS). Following oral administration, MMF

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undergoes rapid and extensive presystemic elimination by deesterification, creating its active metabolite—MPA. Previous studies and clinical experience showed that pharmacotherapy protocol including MMF or EC-MPS along with corticosteroids and CNI have significantly decreased the incidence of acute rejection and improved patient and renal allograft survival [1, 2]. MPA is primarily glucuronidated to a pharmacologically inactive glucuronide metabolite (MPAG) by UDP-glucuronosyltransferases (UGT) in the intestine and liver, which is in turn transported into the bile by the multidrug resistance-associated protein 2 (MRP2) and possibly other efflux transporters that have yet to be elucidated [3].

Immunosuppressive drugs are associated with significant adverse effects which increase patient morbidity and decrease medication adherence [4–6]. Frequent mild to moderate adverse effects, as a result of overexposure to MPA, lead to increased patient non-adherence and therefore affect patients' quality of life. On the other hand, underexposure to MPA may be associated with the risk of graft rejection and long-term allograft survival post-transplant [7, 8].

Previous studies suggested different target therapeutic ranges of MPA concentration with respect to chosen CNI, tacrolimus (TAC) or cyclosporin A [9, 10]. Miura et al. [11, 12] reported that monitoring of the trough level is insufficient for therapeutic drug monitoring because there is wide inter-patient and intra-patient variability in MPA pharmacokinetics. It was shown that renal and hepatic impairment, dialysis, gender, food, ethnicity, co-morbidities, time after transplantation, hyperbilirubinaemia, hypoalbuminaemia, pharmacogenetics and drug–drug interactions seemed to have an influence on the variability of MPA pharmacokinetics [13, 14].

Authors reported that recipients' gender may be a significant factor in MPA exposure variability and adverse effects following MMF/MPA therapy [15, 16]. Meaningful gender-based differences in drug disposition pathways could result in corresponding differences in dosage requirements between men and women. Sex influences were observed in glucuronidation with more rapid MPA clearance, body mass index normalized clearance and lower dose normalized MPA area under the concentration versus time curve (AUC) in males compared to females [15, 17]. These clinical findings were confirmed by experimental evidence in rats and in vitro studies, in which gender differences in UGT activity were reported [18, 19].

Previous studies have suggested that implementation of MPA monitoring in clinical practice may provide more adjusted dosage regimens and optimal drug exposure, which can lead to overall improvement of clinical outcomes [20, 21].

This article is a result of our continuous work within a field of pharmacokinetic variability of immunosuppressive

drugs. This research proposes a new approach into clinical pharmacology of mycophenolic acid and indicates the importance of the gender on the adverse effects during its treatment.

Aim of the study

The aim of this study was the evaluation of adverse events within renal transplant recipients under MPA treatment with respect to gender.

Ethics approval

Patients gave written informed consent and all investigations were approved by the Ethical committee (Faculty of Medicine, University of Nis).

Method

This research was performed in 96 Serbian renal transplant recipients. The patients were routinely monitored and treated in the Clinic of Nephrology (University Clinical Centre of Nis, Serbia) during 2017. All patients enrolled in this cross-sectional study were in the late post-transplant period (> 12 months), median 69.5 months (interquartile range 41–105 months). Data were collected during 12 months.

Renal transplant recipients received oral MMF (Cellcept®, Roche) or enteric-coated MPA (Myfortic®, Novartis Pharma) as a part of a triple immunosuppressive regimen, which also included prednisone (PRE) and tacrolimus (Tac) or cyclosporin A (CyA). The dose of MPA and MMF varied from 0.72 to 1.44 g/day and from 1.00 to 2.00 g/day, respectively. It was administered in two divided doses, every 12 h. In order to make comparable doses of MMF and MPA blood levels in both groups, doses of MMF and MPA were converted to the equivalent of MPA by multiplying the MMF dose by 0.72. The choice of MMF or the MPA was driven according to the physicians' habits. During the follow-up period, there was no switch from MMF to MPA (or MPA to MMF). There was an initial unique dose for each patient (1440 mg, expressed as MPA dose), then adjusted overtime according to BMI and already present leucopenia. Based on clinical experience, in stable renal recipients, the dose was reduced to half after 12 months.

In order to avoid gastrointestinal adverse effects of immunosuppressive treatment and to provide a satisfactory patient's adherence, proton pump inhibitor (PPI) in 20 mg daily dose was administered to 80.52% patients, whereas other patients (19.48%) received ranitidine. The PPI is preferred for treating gastrointestinal adverse effects in renal transplant recipients, but 19.48% received ranitidine because of other drugs in therapy and their interactions with PPI.

Renal transplant recipients had stabilized graft function and received the same immunosuppressive regimen (CyA or Tac based immunosuppressive protocol) with the unchanged dose of MPA for at least 3 months prior the research. Patients with acute rejection episodes, or who were switched to another immunosuppressive regimen (CyA to Tac) during the follow-up period or those with creatinine clearance lower than 15 mL/min were excluded from the study.

Gender, age, time after transplantation, the presence of diabetes mellitus, organ source (living or deceased donor) and immunosuppressive co-medication were recorded for all patients.

Hematological and routine biochemical parameters, such as number of erythrocyte (RBC), leucocytes (WBC) and platelets (PLT), level of hemoglobin (HGB), haematocrit (%), serum albumin (ALB), urea (URE), creatinine (CRE) levels were measured in Clinical Chemistry Laboratory in the Clinic of Nephrology using automated random access clinical chemistry analyzer (ERBA XL-600, ERBA Diagnostics Mannheim GmbH, Mannheim, Germany). The estimated glomerular filtration rate (e-GFR) was calculated using the 4-factor MDRD equation [22].

A fasting blood sample was taken from each patient during routine control at the Clinic at 8.00 h, before the next dose of the drug administration. The MPA trough concentration in human plasma was determined by validated high-performance liquid chromatography (HPLC) method [23].

Adverse effect scoring system

Patients' gender may be a significant factor in MPA exposure variability and may be associated with adverse effects following MPA therapy. Previous findings suggest gender should be considered during MPA immunosuppression [15]. In order to monitor adverse effects of therapy, we used an adverse effect scoring system developed by nephrologists within the University of Buffalo Nephrology/Transplant Program [24].

The scoring system focused on 18 common non-renal adverse effects associated with immunosuppressive regimens. Patients were asked to estimate the severity of any adverse effect (i.e. 0 → no adverse effect; 1+ → mild to 3+ → severe manifestations). Adverse effect scores [gastrointestinal (GIT), central nervous system (CNS), aesthetic] were formed to estimate the organ system specific adverse effects. The cumulative score was calculated as the quotient of each patient's total score divided by the maximum score of all possible symptoms. This cumulative score showed the number of adverse effects with a appropriate severity rating [24]. All patients filled out the questionnaire at least 6 months after transplantation.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS software version 20. Clinical and biochemical data were compared using the *t* test for normally distributed data (expressed as mean ± SD) and Mann–Whitney *U* test for data that were not normally distributed. One way analysis of variances (ANOVA) test and Kruskal–Wallis test for not normally distributed data was used for comparison with three or more groups. Chi square test was performed for categorical variables. The difference in the compared data was considered statistically significant when the *p* value was less than 5% ($p < 0.05$).

Results

The conducted research included 96 patients who underwent renal transplantation: 60 (62.57%) men and 36 (37.5%) women, with an average age of about 44.33 ± 11.45 years. The mean post-transplantation time was 79.31 ± 53.49 months. Seventy-one (74.0%) patients received living donor and 25 (26.0%) deceased donor grafts. The demographic characteristics of patients, their biochemical and haematological parameters are shown in Table 1. The median value of MPA and prednisone daily dose was 884.57 mg and 8.03 mg, respectively. Nineteen patients did not have any form of MPA in therapy.

The results showed that gender was a statistically significant determinant of pharmacokinetic variability. The obtained data showed that women had a statistically higher dose of MPA and plasma trough concentration of MPA compared to men with a transplanted kidney ($p < 0.05$), while there was no difference in dose-adjusted plasma trough concentration of MPA (Table 2).

All analyzed scores did not show a statistically significant difference as to whether patients receive MPA: GIT score ($Z = 0.914$; $p = 0.361$), aesthetic score ($Z = 0.113$; $p = 0.910$), CNS score ($Z = 0.714$; $p = 0.475$) and cumulative score ($Z = 1.163$; $p = 0.245$) (Table 3).

In addition, female patients demonstrated higher mean scores (cumulative and subscores) within the same MPA dosing regimens. The results of the conducted study showed that the GIT score is significantly lower in men who received a dose greater than 720 mg compared to women. Men who received a lower dose had a greater aesthetic, CNS, and cumulative score compared to men who received a higher dose of MPA (Table 4).

Table 5 shows the distribution and overall frequency of individual immunosuppressive adverse effects based on patients' gender. Women demonstrated a higher total score than men and this was particularly evident for the occurrence

Table 1 Characteristics of the patients

	Male (n = 60)	Female (n = 36)	<i>p</i>
Age (years)	45.05 ± 10.59	43.61 ± 12.79	NS
Time post-transplant (months)	81.97 ± 53.33	76.67 ± 54.06	NS
Donor type			
Living	42 (70.0%)	29 (80.6%)	NS
Deceased	18 (30.0%)	7 (19.4%)	
Number of drugs in therapy			
< 5	6 (10.0%)	4 (11.1%)	NS
≥ 5	54 (90.0%)	32 (88.9%)	
MPA dose			
Without MPA	7 (11.7%)	12 (33.3%)	0.010*
720 mg	37 (61.7%)	12 (33.3%)	
> 720 mg	16 (26.7%)	12 (33.3%)	
Prednisone dose			
< 10 mg	42 (70.0%)	24 (66.7%)	NS
≥ 10 mg	18 (30.0%)	12 (33.3%)	
CNI			
Tacrolimus	51 (85.0%)	30 (83.3%)	NS
Cyclosporine	9 (15.0%)	6 (16.7%)	
Hematocrit			
Low level	15 (25.0%)	14 (38.9%)	NS
Normal level	45 (75.0%)	20 (55.6%)	
High level	0 (0.0%)	2 (5.6%)	
Albumin (g/L)	41.75 ± 0.25	41.95 ± 0.27	NS
WBC (cells/mm ³)	8.3 ± 1.67	7.0 ± 1.88	NS
Serum creatinine (μmol/L)	132.55 ± 19.35	126.78 ± 23.69	NS
eGFR (mL/min/1.73 m ²)	55.09 ± 11.37	49.95 ± 10.45	NS

MPA mycophenolic acid, CNI calcineurin inhibitors, WBC leucocytes, eGFR estimated glomerular filtration rate, NS non significant, Normal level of hematocrit for male: 42–54%, for female: 38–46%

**p* < 0.05

Table 2 Dose, concentration and dose-adjusted concentration of MPA in relation to gender

	Gender of the patients		<i>Z</i>	<i>p</i>
	Male (n = 53)	Female (n = 24)		
Dose of MPA (mg) ^a	849.06 ± 212.91	990 ± 304.92	−2.014	0.044*
	720 (720–1440)	900 (720–1440)		
Concentration of MPA (μg mL ^{−1})	2.71 ± 2.26	4.31 ± 3.19	−2.082	0.037*
	2.10 (0.08–12.33)	3.05 (1.36–11.21)		
Dose-adjusted concentration of MPA (μg mL ^{−1} /mg)	0.0032 ± 0.0025	0.0046 ± 0.004	−1.454	0.146
	0.0027 (0.0–0.11)	0.0034 (0.001–0.016)		

Data are shown as mean ± standard deviation and median (range)

Z Mann–Whitney *U* test

**p* < 0.05

^aMMF dose was calculated as MPA equivalent

of diarrhea and skin changes (41.7 vs 17.0; *p* = 0.038 and 62.5 vs 30.2; *p* = 0.037, respectively).

The frequency of individual side effects in both genders with different dose regimens of MPA is shown in Fig. 1. Female patients demonstrated higher individual adverse effects within the same MPA dosing regimens. There was a significant difference in myopathy between men and women who received an MPA dose of 720 mg. Results suggested that skin changes were statistically more common in women compared to men who received a higher dose of MPA.

Discussion

Mycophenolic acid is a part of the most prescribed immunosuppressive protocols in the world. Although, it does not have as narrow therapeutic index as TAC, its adverse effects may still complicate post-transplantation period in renal transplant recipients. The previous researches showed large intra- and inter-individual variability in plasma concentration and exposure of MPA after renal transplantation [25, 26].

It has been shown so far that gender and drug–drug interactions may influence the pharmacokinetics of tacrolimus and others CNI, and also MPA [27–29]. The obtained results showed that women had higher plasma trough concentration of MPA compared to men. This finding is in accordance with previous research, which showed that females have slower MPA clearance [15]. The same study showed race-dependent pharmacokinetics of MPA. Our research did not analyze the influence of race, due to all of the patients enrolled in this study had the Caucasian origin. Conversely, Pescovitz et al. [30] did not find any association between gender and pharmacokinetic parameters of MPA. Show et al. [31] demonstrated that ethnicity and gender do not significantly affect the primary pharmacokinetic parameters of MPA. In contrast to our study, this research was conducted in the early post-transplantation period. This suggests that gender may

Table 3 Scores of adverse effects, depending on the therapy of MPA

	Without MPA (n = 19)	With MPA (n = 77)	Z	p
Gastrointestinal	0.13 ± 0.09	0.17 ± 0.14	0.914	0.361
Aesthetic	0.12 ± 0.11	0.13 ± 0.13	0.113	0.910
CNS	0.18 ± 0.18	0.21 ± 0.18	0.714	0.475
Cumulative	0.22 ± 0.16	0.18 ± 0.17	1.163	0.245

MPA mycophenolic acid, CNS central nervous system, Z Mann–Whitney U test

influence MPA pharmacokinetics in the late period after transplantation, contributing to its variability and long-term adverse effects associated with MPA exposure.

This study has shown that 57% of stable renal transplant recipients experienced gastrointestinal symptoms, even when they received a proton pump inhibitor (PPI) or histamine 2 (H2) receptor antagonist—ranitidine. Similar results have been reported in other studies [16, 32], although reported frequencies of gastrointestinal adverse effects were generally

Table 4 Scores of adverse effects in relation to the MPA dosing regimen in both genders

Scores of adverse effects	Dose of MPA			
	720 mg		> 720 mg	
	Male (n = 37)	Female (n = 12)	Male (n = 16)	Female (n = 12)
Concentration of MPA ($\mu\text{g mL}^{-1}$)	2.37 ± 1.65	4.12 ± 3.63	3.51 ± 3.24	4.17 ± 2.83
Gastrointestinal	0.17 ± 0.15	0.21 ± 0.17	0.12 ± 0.12 ^c	0.20 ± 0.12
Aesthetic	0.16 ± 0.15 ^a	0.20 ± 0.10	0.06 ± 0.11	0.10 ± 0.11
CNS	0.23 ± 0.17 ^b	0.30 ± 0.18	0.12 ± 0.15	0.18 ± 0.19
Cumulative	0.19 ± 0.12 ^a	0.24 ± 0.12	0.10 ± 0.07	0.16 ± 0.11

MPA mycophenolic acid, CNS central nervous system

^aMale (720 mg) versus Male (> 720 mg), $p < 0.01$

^bMale (720 mg) versus Male (> 720 mg), $p < 0.05$

^cMale (> 720 mg) versus Female (> 720 mg), $p < 0.05$

Table 5 The frequency of severity scores for immunosuppressive adverse effects

Adverse effects	0	1+	2+	3+	Overall frequency (%)	p
	M/F	M/F	M/F	M/F		
Vomiting	48/21	5/3	0/0	NA	9.4/12.5	NS
Diarrhea	44/14	9/9	0/1	NA	17.0/41.7	0.038
Dyspepsia	44/16	6/6	2/1	1/1	17.0/33.3	NS
Acid suppressive therapy	10/5	39/18	4/1	NA	81.1/79.2	NS
Acne	37/19	6/4	8/1	2/0	30.2/20.8	NS
Skin changes	37/9	12/10	4/4	0/1	30.2/62.5	0.037
Hirsutism	47/23	4/1	2/0	0/0	11.3/4.2	NS
Moon facies	31/12	18/8	3/4	1/0	41.5/50.0	NS
Gingival hyperplasia	37/16	13/4	3/4	NA	30.2/33.3	NS
Buffalo hump	50/24	3/0	NA	NA	5.7/0.0	NS
Tremor	31/10	17/11	4/2	1/1	41.5/58.3	NS
Headache	38/16	15/8	NA	NA	28.3/33.3	NS
Insomnia	31/13	16/8	5/3	1/0	41.5/45.8	NS
Myopathy	31/13	17/5	5/6	0/0	41.5/45.8	NS
Ophthalmic changes	49/23	4/1	NA	NA	7.5/4.2	NS
Mania/excitable behavior	29/11	19/12	5/1	NA	45.3/54.2	NS
Depression	35/14	17/9	1/1	0/0	34.0/41.7	NS
Post-transplant diabetes mellitus	44/21	9/3	NA	NA	17.0/12.5	NS

M/F male/female, NA not applicable, NS non significant

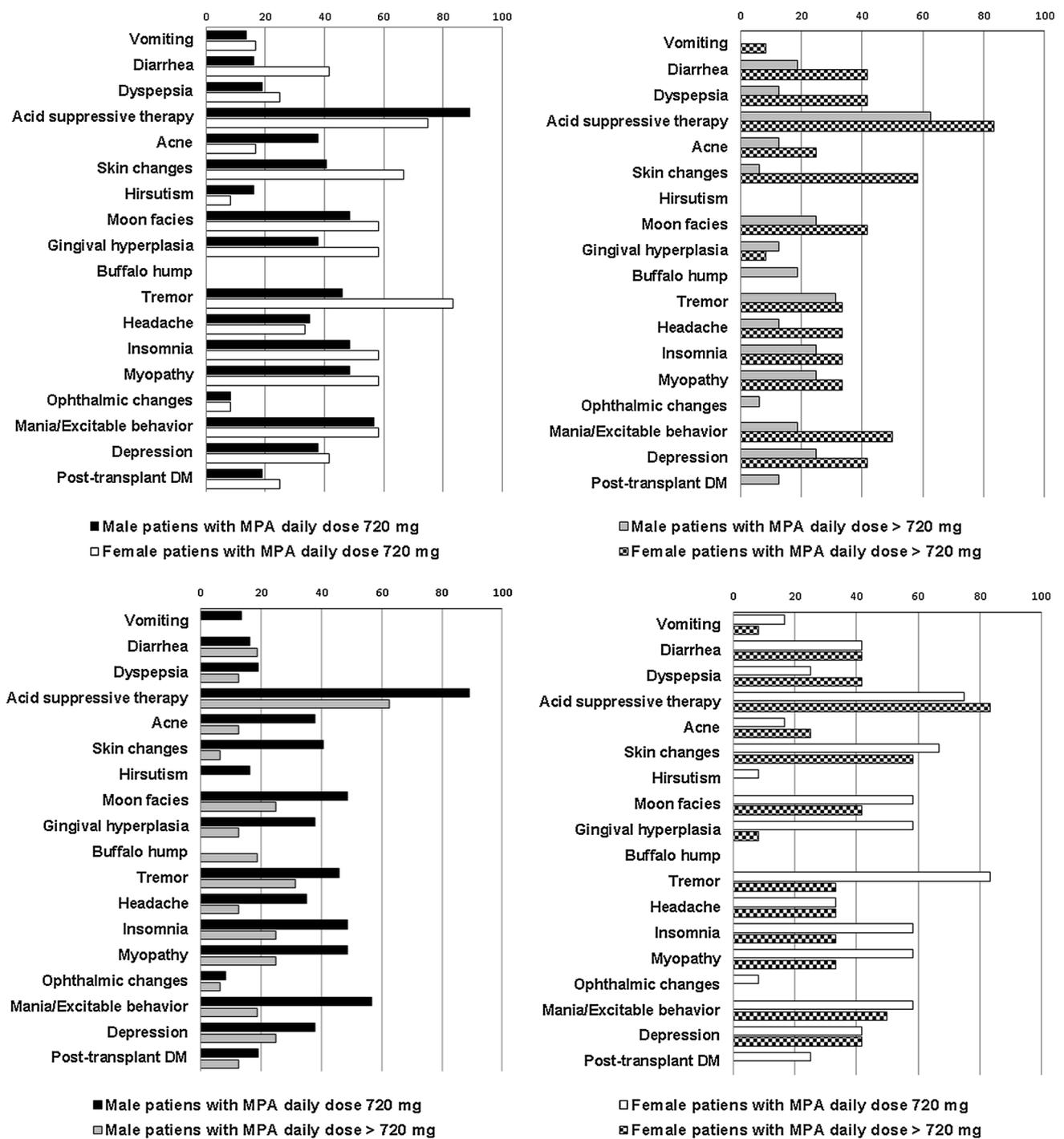


Fig. 1 Individual adverse effects in relation to the MPA dosing regimen and gender

higher. This variation may be related to the methodology used for the estimation of gastrointestinal symptoms in different researches, because such symptoms are often underestimated by both patients and physicians. In addition, our patients received PPI (usually pantoprazole) or ranitidine in order to reduce the gastrointestinal side effects that are common under immunosuppressive therapy with mycophenolate.

Pantoprazole is a frequently prescribed PPI against gastrointestinal side effects in renal transplant patients, such as heartburn and nausea [33].

Female recipients demonstrated more severe symptoms, particularly evident in the occurrence of diarrhea. Additionally, they had a statistically higher dose of MPA and plasma trough concentration of MPA compared to men.

This is consistent with findings from other studies [34–36]. The potential mechanism through which MMF causes the intestinal symptoms is the inhibition of cell division and the induction of apoptosis at the level of the colonic crypts through an immune-mediated mechanism, as well as the loss of villous, normal structure of duodenum [37]. Following our findings, women demonstrated a higher gastrointestinal score than men, with statistical significance in the group that received a dose greater than 720 mg compared to men with the same dose of MPA. Morissette et al. [38] studied gender differences in MMF pharmacokinetics in 100 renal transplant patients using the MPAG/MPA concentration ratio as a measure of overall glucuronidation. The nearly two-fold difference in the rate and extent of UGT-mediated glucuronidation, indicated that males have increased glucuronidation as compared to females ($p < 0.0001$), thus impacting mycophenolate dosing [38].

Although females demonstrated higher mean subscores (GIT, aesthetic, CNS) and cumulative score compared with male patients, these differences were not statistically significant. All of the analyzed scores were higher in patients who received a 720 mg MPA dose compared to a higher dose of MPA. Vanhove et al. [34] found that gastrointestinal side effects and hematologic toxicity were the main reason for the dose reduction of MMF in the first post-transplant year. Bunnapradist et al. [39] confirmed that gastrointestinal side effects are dose dependent in patients treated with MPA. On the other hand, Zhang et al. [40] investigated the efficacy and safety of intensified EC-MPS protocol in renal transplant recipients. This regimen did not increase the incidence of adverse effects, including diarrhea and leucopenia. The discrepancy between the MPA dose and frequency of side effects is probably due to the fact that the average time post-transplant was 6.7 years in the group who received an MPA dose of 720 mg compared to patients who received a higher dose of MPA where the average time post-transplant was 5.5 years. In addition, MPA dose of 720 mg was received by older patients (46.7 vs 41.7 years old) with multiple comorbidities.

Individual aesthetic adverse effects such as skin changes were more frequent in women ($p < 0.05$). Skin changes were statistically more common in women who received an MPA dose greater than 720 mg compared to men with the same MPA dose. Acne is reported in 30.2% of male and 20.8% of female transplant recipients treated with MPA. Acne was mainly located on the face and trunk, which is in accordance with other findings [41]. The male predominance of this skin problem suggests that this adverse effect is hormone-dependent [42]. In our study post-transplant diabetes occurred in 17% of men and 12.5% of female renal transplant recipients. The incidence of diabetes reported here is similar to that noted in other studies [43, 44].

Potential limitations of this study are related to concomitant medications with overlapping adverse effects profiles and inability to distinguish causative relationships to individual medications. In addition, the patients filled out the questionnaire for renal transplant recipients which didn't include doctor verification. Consequently, objective immunosuppressive monitoring can be limited with routine clinical application of these patient rating scales.

In conclusion, women had statistically higher MPA dose and concentrations compared to the men and demonstrated higher mean scores (cumulative and subscores) within the same MPA dosing regimens. The GIT score was significantly higher in women who received a dose greater than 720 mg compared to men. Women demonstrated higher individual adverse effects such as diarrhea and skin changes. For MPA, which is not routinely monitored, gender differences in drug pharmacokinetic could be accounted for by adjusting doses and therapy management. Therefore, it is important to choose the best therapy option for each individual patient and to minimize the adverse effects in order to improve graft outcomes and immunosuppressive adherence post-transplant.

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Conflicts of interest The authors report no conflicts of interest.

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