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Mycophenolate mofetil vs Enteric-coated mycophenolate sodium in de-novo kidney transplant recipients (summary of the side effects within first three months): single center experience

Micofenolato mofetilo vs Micofenolato de sodio con cubierta entérica en receptores de trasplante renal de novo (resumen de efectos secundarios en los primeros 3 meses): experiencia de un solo centro

Mustafa Hakan Sozen[1], Aydin Dalgic[1], Ramazan Kozan[2], Ahmet Ziya Anadol[2]

RESUMEN

Objetivo: Este estudio compara y evalúa los efectos secundarios gastrointestinales, de la médula ósea y hepatotóxicos de MMF y EC-MPS en los primeros 3 meses después de un trasplante renal de novo. **Material y Métodos:** Retrospectivamente, se analizaron datos de 100 receptores de trasplante renal, entre enero de 2016 y diciembre de 2021, en el Centro de Trasplantes de la Universidad de Gazi. Los pacientes se dividieron en dos grupos: MMF (grupo A, n=68) y EC-MPS (grupo B, n=32). Se evaluaron los efectos secundarios dentro de los primeros tres meses después del trasplante, incluyendo efectos secundarios gastrointestinales (dispepsia, distensión abdominal, diarrea), complicaciones de la médula ósea y hepatotoxicidad. El análisis estadístico se realizó utilizando el software SPSS. **Resultados**: En el grupo A, no se observaron efectos secundarios de MMF en el 38% de los receptores durante los primeros 3 meses postoperatorios. El 62% de los receptores tuvieron los siguientes efectos secundarios: gastrointestinal en el 22%, médula ósea en el 24% y hepatotoxicidad en el 16%. En el grupo B, no se observaron efectos secundarios de EC-MPS en el 43% de los receptores durante los primeros 3 meses postoperatorios. El 57% de los receptores experimentaron los siguientes efectos secundarios: médula ósea en el 28%, gastrointestinal en el 25%, y hepatotoxicidad en el 4%. El manejo implicó ajustes en la medicación, con la cesación de los efectos secundarios en la mayoría de los casos. **Conclusiones**: En conclusión, este estudio resalta los perfiles de seguridad favorables en general de MMF y EC-MPS en el período post-trasplante temprano. Sin embargo, subraya la ventaja potencial de EC-MPS sobre MMF en términos de hepatotoxicidad, con EC-MPS demostrando una incidencia más baja de hepatotoxicidad en comparación con MMF.

Palabras Clave: trasplante renal; micofenolato mofetilo; micofenolato sódico con recubrimiento entérico; inmunosupresión; efectos secundarios

ABSTRACT

Aim: This study assesses and compares GI, bone marrow (BM), and hepatotoxicity side effects of MMF and EC-MPS in the first 3 months after de-novo kidney transplantation. **Material and Methods:** Retrospective data from

Correspondencia:
Ramazan Kozan
ORCID:
0000-0002-3835-8759
dr.kozan@hotmail.com

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1) Department of General Surgery, Gazi University Faculty of Medicine, Ankara, Türkiye. Transplantation Center, Gazi University, Ankara, Türkiye.
2) Department of General Surgery, Gazi University Faculty of Medicine, Ankara, Türkiye.

100 kidney transplant recipients were analyzed between January 2016 and December 2021 at Gazi University Transplantation Center. Patients were divided into two groups: MMF (group A, n=68) and EC-MPS (group B, n=32). Side effects within the first three months post-transplantation were assessed, including gastrointestinal side effects (dyspepsia, bloating, diarrhea), bone marrow complications, and hepatotoxicity. Statistical analysis was performed using SPSS software. **Results:** In group A, we have not seen any side effects of MMF in 38% of recipients during the postoperative first three months. Sixty-two percent of recipients had the following side effects: gastrointestinal 22%, bone marrow 24%, and hepatotoxicity 16%. In group B, we have not seen any side effects of EC-MPS in 43% of recipients during the postoperative first three months. Fifty-seven percent of recipients experienced the following side effects: BM in 28%, GI in 25%, and hepatotoxicity in 4%. Management involved medication adjustments, with side effects ceasing in most cases. **Conclusions**: In conclusion, this study highlights the overall favorable safety profiles of MMF and EC-MPS in the early post-transplant period. However, it underscores the potential advantage of EC-MPS over MMF in hepatotoxicity, with EC-MPS demonstrating a lower incidence of hepatotoxicity than MMF.

Keywords: kidney transplantation; mycophenolate mofetil; enteric-coated mycophenolate sodium; immunosuppression; side effects.

INTRODUCTION

The success of organ transplantation is due, in part, to the availability of potent and more selective immunosuppression agents. More than 80% of kidney transplant recipients are discharged on a maintenance immunosuppression regimen that includes a mycophenolic acid (MPA)--based compound. Two formulations of MPA are currently available in the United States. Mycophenolate mofetil (MMF; CellCept, Roche Laboratories, Inc., Nutley, NJ), a morpholino ester prodrug of MPA, was approved to prevent acute allograft rejection in kidney transplant patients in 1995. The use of MMF is associated with improved graft and patient survival and reduced early and late acute allograft rejection [1]. Enteric-coated mycophenolate sodium (EC-MPS; Myfortic; Novartis Pharmaceuticals Corp., East Hanover, NJ) is a delayed-release formulation of MPA approved in the United States in 2004 [2].

The Mycophenolate (MPA) formulations are the most frequently used immunosuppressive drugs in solid organ transplantation. Enteric-coated mycophenolate sodium (EC-MPS) is a new formulation of mycophenolic acid that delivers the active moiety MPA, the same active moiety delivered by mycophenolate mofetil (MMF).

Similar safety and efficacy outcomes were observed in two pivotal phase III trials comparing EC-MPS and MMF: one in de novo renal transplant patients and one in stable maintenance renal transplant patients [3]. However, dose-dependent adverse gastrointestinal effects (GI) are common with MPA-based therapy. Reducing or interrupting MMF dosing for GI side effects has been associated with increased risk of graft loss and healthcare costs [3,4].

Here, we retrospectively analyzed data from patient charts at Gazi University Transplantation Center to assess and compare the GI, bone marrow (BM), and hepatotoxicity side effects of MMF and EC-MPS in the first three months after de novo kidney transplantation.

MATERIAL AND METHODS

Data were retrospectively collected from patients' charts who received their first kidney transplantation at Gazi University Transplantation Center between January 2016 and December 2021. A total of 103 kidney transplant operations were performed, with 21 out of 103 recipients being pediatric and 82 out of 103 recipients being adults, enrolling one hundred of 103 recipients for this study. There were 68 de novo MMF (group A) and 32 EC-MPS (group B) patients in each group. In group A, the mean age was 32,4 ±14,6 years old. Twenty-nine of the recipients were female, and 39 were male. Transplantations were performed with kidneys from 34 deceased donors and 34 with living donors. In group B, the mean age was 29,1 ±13,5 years old. Fourteen of the recipients were female, and 18 were male. Transplantations were performed with kidneys from 18 deceased donors and with 14 living donors.

The immunosuppressive protocol consisted of a calcineurin-based triple regimen and

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Basiliximab induction (only for deceased donors, second or more transplantation, and high PRA). All recipients received a single preoperative dose of either MMF 1000 mg or EC-MPS 720 mg in living transplantation. After transplantation from D0, all patients received either MMF 1000 mg BID or EC-MPS 720 mg BID.

All procedures carried out in this study complied with the ethical standards of the institutional and/or national research committee and the principles outlined in the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical standards. This study was approved by the Local Ethical Committee of Gazi University (reference No. 2024-294).

All data retrospectively were analyzed from patient charts at Gazi University Transplantation Center to assess and compare common gastrointestinal (diarrhea, dyspepsia, and floating), bone marrow (pancytopenia, leukopenia, anemia), and hepatic side effects (at least a two-fold elevation of aspartate aminotransferase (AST) and alanin aminotransferase (ALT) levels) of MMF and EC-MPS in the first three months after de-novo kidney transplantation.

All the statistical analysis was performed with SPSS software, version 20 (SPSS Inc., Chicago, IL, USA). Data were expressed as median and range. Relevant variables were analyzed using descriptive statistics.

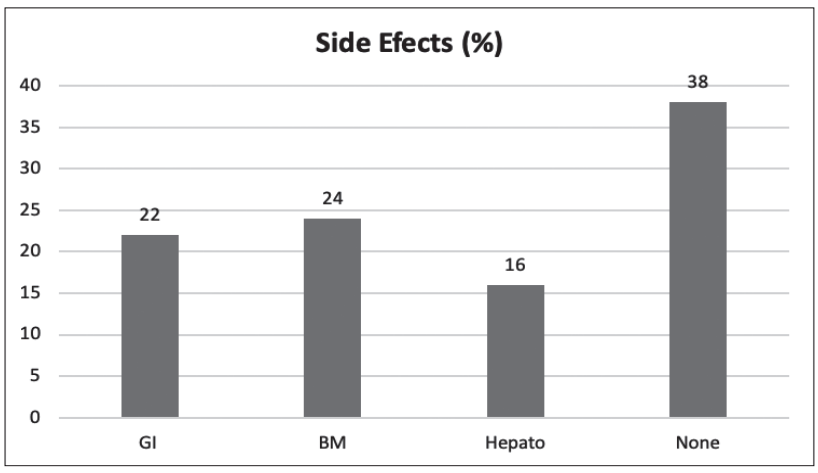
RESULTS

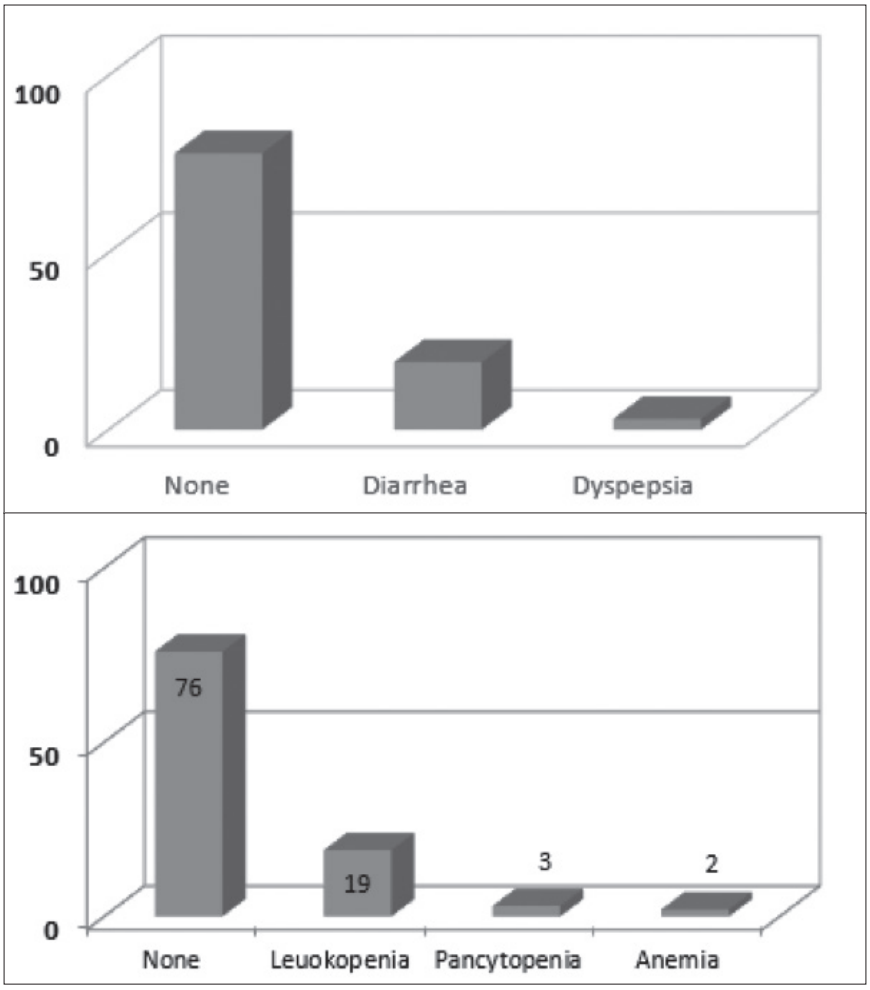
In group A, we have not seen any side effects of MMF in 38% (n=26) recipients during the postoperative first three months. Sixty-two percent of recipients had the following side effects: gastrointestinal 22%, bone marrow 24%, and hepatotoxicity 16%. Most GI side effects are diarrhea (n=13), and dyspepsia (n=2). The majority of BM side effects are leukopenia (n=13), pancytopenia (n=2), and anemia (n=1) (**Figure 1**) (**Table 1**). Side effects have ceased by stopping MMF in 13 patients, reducing the drug in 13 patients, and converting them in 9 patients.

Table 1: MMF vs EC-MPS comparison of side effects [n (%)]

Toxicity	MMF (n=68)	EC-MPS (n=32)
Gastrointestinal:	**15 (22%)**	**9 (28%)**
Diarrhea	13	6
Dyspepsia	2	2
Bloating	-	1
Bone Marrow:	**16 (24%)**	**8 (25%)**
Leukopenia	13	7
Anemia	2	-
Pancytopenia	1	1
Hepato	**11 (16%)**	**1 (4%)**
None-Overall	**26 (38%)**	**14 (43%)**

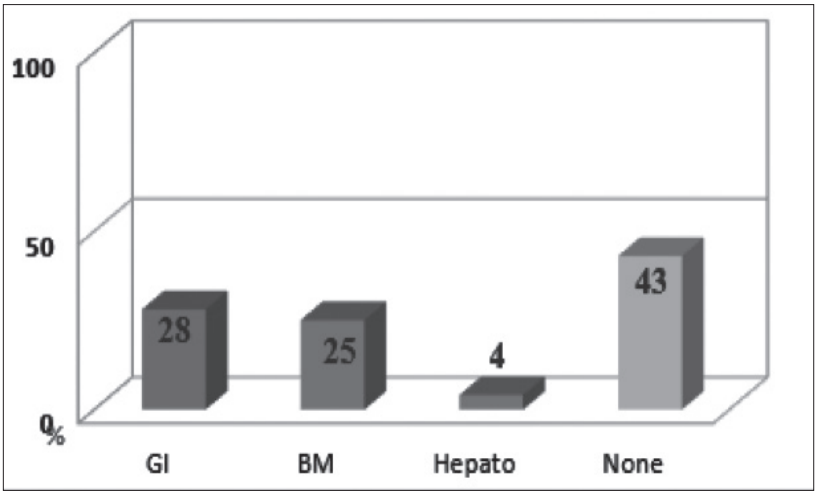
Figure 1: Group A: Overall, GI and BM side effects (%)





In group B, we have not seen any side effects of EC-MPS in 43% (n=14) of recipients in the first three postoperative months. Fifty-seven percent of recipients experienced the following side effects: BM in 28%, GI in 25%, and hepatotoxicity in 4% (**Table 1**). Among the GI side effects, there were cases of diarrhea (n=6), dyspepsia (n=2), and floating (n=1). For bone marrow, leukopenia was observed in seven cases, while pancytopenia was observed in one case (**Figure 2**).

Figure 2: Group B: Overall, GI and BM side effects (%)



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The side effects stopped after stopping EC-MPS in 5 patients, reducing the dose in 8 patients, and converting them in 5 patients.

We have not seen any statistical differences between the two groups concerning side effects (p> 0,5) (**Figure 3**).

Also, we have not seen any graft loss due to biopsy-proven acute rejection who received MMF or EC-MPS within three months after de-novo kidney transplantation.

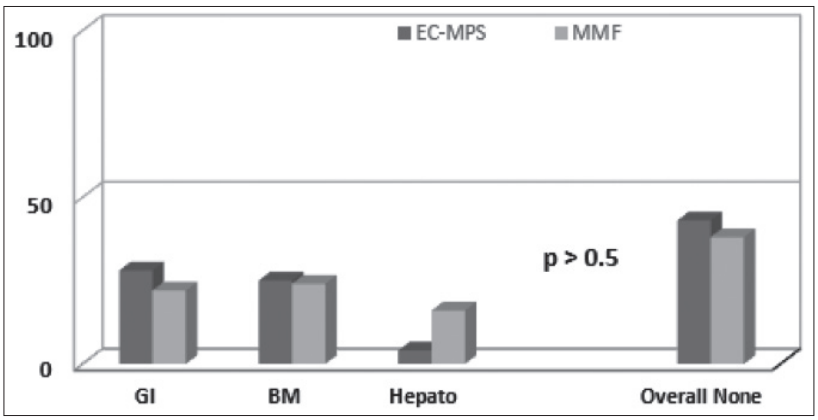

Figure 3: MMF vs EC-MPS comparison of side effects (%)

DISCUSSION

The presented study offers valuable insights into the short-term side effects of MMF and EC-MPS in kidney transplant recipients during the initial three months post-transplantation. The findings contribute to the existing literature on immunosuppressive strategies and shed light on the safety profiles of these two commonly used medications [1-5].

In the study, most patients in both groups did not experience any side effects, highlighting the overall tolerability of MMF and EC-MPS. These results are positive, as minimizing adverse events is crucial for patient well-being and adherence to immunosuppressive regimens, which are essential for graft survival [3].

The observed side effects, when present, varied between the two groups. In the MMF group (group A), gastrointestinal disturbances, such as diarrhea and dyspepsia, were notable, along with bone marrow and hepatotoxicity issues. On the other hand, the EC-MPS group (group B) exhibited a more balanced distribution of side effects, with bone marrow complications, particularly leukopenia, being prominent.

The side effects management involved discontinuation, dose reduction, or conversion of medications, highlighting the importance of close monitoring and tailored interventions (34.6%). Those issues underscore the dynamic nature of immunosuppressive therapy, requiring ongoing assessment and adjustment to optimize patient outcomes [4,5].

Notably, there were no statistically significant differences in side effects between the two groups within the first three months after de novo kidney transplantation. This similarity suggests that, in the short term, both MMF and EC-MPS are equally well-tolerated by kidney transplant recipients. Such information is valuable for clinicians when choosing immunosuppressive agents based on individual patient characteristics.

However, it is essential to acknowledge the limitations of this study. Firstly, the relatively short follow-up period of three months may not capture long-term side effects or the impact on graft survival [3-5]. A more extended follow-up would provide a more comprehensive understanding of MMF and EC-MPS safety profiles. Secondly, while reasonable, the study's sample size might limit the generalizability of the findings to broader populations. More extensive multicenter studies could validate and extend these results. Additionally, the study did not delve into patient-specific factors that might influence the likelihood of side effects, such as pre-existing comorbidities or genetic variations.

In conclusion, this study highlights the overall favorable safety profiles of MMF and EC-MPS in the early post-transplant period. However, it

underscores the potential advantage of EC-MPS over MMF in hepatotoxicity, with EC-MPS demonstrating a lower incidence of hepatotoxicity than MMF. These findings contribute valuable insights into selecting immunosuppressive regimens in kidney transplantation, particularly in minimizing adverse effects and optimizing patient outcomes.

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