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Clinical Features and Outcomes of Mycophenolate Mofetil-induced Diarrhea: A Systematic Review

Prajwal Dhakal[1], Rakesh K. Gami[2*], Adams Kusi Appiah[3], Smith Giri[4], Harlan Sayles[3] and Vijaya R. Bhatt[3]

[1]Michigan State University, East Lansing, MI, USA.
[2]All Saints University, Kingstown, Saint Vincent and the Grenadines.
[3]University of Nebraska Medical Center, Omaha, NE, USA.
[4]The Yale New Haven Hospital, New Haven, CT, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Authors PD and VRB designed the study. Authors PD, VRB, RKG and SG performed the literature search. Authors AKA and HS performed the statistical analysis. All authors participated in data interpretation. Author PD wrote the first draft of the manuscript. All authors critically reviewed and edited the manuscript. All authors approved the final manuscript.

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ABSTRACT

Mycophenolate Mofetil (MMF) is an immunosuppressive drug frequently used for prevention of graft rejection in solid-organ and hematopoietic stem cell transplants. MMF-induced diarrhea is a known complication, however, details regarding its clinical manifestations, treatment options, and outcomes are less clear. Differentiating MMF-induced diarrhea from other causes of diarrhea in an immunocompromised host on the basis of histology may be difficult, hence deeper clinical understanding of MMF-induced diarrhea can be valuable. Our objective was to determine the clinical manifestations and outcomes of MMF-induced diarrhea. Major databases were searched to include 44 articles that provided data on 560 episodes of diarrhea induced by MMF or its derivatives.

**Corresponding author: E-mail: gamirakesh@gmail.com;*

Results depicted the median age of 45 years (range 8-70); 29% were females. The latency between use of MMF and onset of diarrhea was 990 days (range 12- 5760). Watery diarrhea was the presenting symptom in 98%. MMF was discontinued or dose reduced in 56%, switched to enteric coated mycophenolate mofetil sodium in 12%, and continued in 14%. Eighty-five percent of cases who were managed with discontinuation/dose reduction of MMF and 81% of cases who switched from MMF to enteric coated mycophenolate mofetil sodium responded. The median time to response for either change to enteric coated mycophenolate sodium or discontinuation/dose reduction of MMF was 20 days (range 1-120 days).
Thus, MMF-induced diarrhea generally presents with watery diarrhea, and a majority of patients respond to discontinuation or dose reduction of MMF within a few weeks. Where continuation of MMF is important, a different drug formulation may be an option.

Keywords: Mycophenolate mofetil; mycophenolic acid; diarrhea; mycophenolate mofetil induced diarrhea.

ABBREVIATIONS

EC-MPS : Enteric-coated Mycophenolate sodium
GVHD : Graft versus Host Disease
IBD : Inflammatory Bowel Disease
MMF : Mycophenolate Mofetil
MPA : Mycophenolic Acid

1. INTRODUCTION

Mycophenolate mofetil (MMF) is an immunosuppressive drug frequently used for prevention of graft rejection in solid-organ transplant and prophylaxis against graft-versus-host disease (GVHD) after hematopoietic cell transplant [1]. MMF is converted to its active metabolite mycophenolic acid (MPA) which inhibits inosine monophosphate dehydrogenase, leading to blockade of the de novo pathway of purine synthesis and ultimately, selective inhibition of lymphocyte proliferation [2]. Since its approval in 1995, MMF use has increased steadily in both solid organ and hematopoietic stem cell transplants. MMF is currently the most common immunosuppressive drug with about 80-90% of solid organ transplants being treated with MMF [3,4]. Additionally, MMF has also been used off-label in other non-transplant cases including lupus nephritis, autoimmune hepatitis, psoriasis, and myasthenia gravis [5-8].

MMF has a low risk profile for nephrotoxicity, cardiotoxicity, and diabetogenic potential. Gastrointestinal side effects such as nausea, vomiting, and diarrhea secondary to MMF-induced diarrhea, are known complications and have been ascribed to local as well as systemic effects of MMF [9,10]. However, details regarding its clinical manifestations, treatment options, and outcomes are less clear. Differentiating MMF-induced diarrhea from other causes of diarrhea in an immunocompromised host, or from gut GVHD may be difficult [11-14], hence deeper clinical understanding of MMF-induced diarrhea can be valuable. Here we analyze the reported cases of diarrhea secondary to MMF to provide summative data regarding clinical features and outcomes of MMF-induced diarrhea.

2. METHODS

This is a retrospective review of all cases of MMF-induced diarrhea (Fig. 1). Using various search terms such as mycophenolate mofetil, mycophenolic acid, mycophenolate sodium, colitis, diarrhea (see Supplementary File for details), all cases indexed in PubMed, EMBASE, Cochrane, and Scopus from inception to July 2016 were reviewed. The bibliography of each relevant article was searched for additional reports. Inclusion criteria included prospective or retrospective clinical studies and case series, reported in the English language, and providing data on clinical manifestations, treatment options, and outcomes of diarrhea induced by MMF or its derivatives (such as mycophenolic acid, and enteric coated mycophenolate sodium). Cases were included irrespective of the indication of MMF. Non-human studies and diarrhea attributed to other etiologies such as infection, GVHD or inflammatory bowel disease were among the 124 articles that were excluded.

Although each study used their own definition, in some cases similar to the DIDACT study [15], diagnosis of MMF-induced diarrhea was based on the exclusion of any other etiology for the gastrointestinal symptoms, by resolution of the diarrhea with no intervention other than substituting another agent for MMF, and typical histologic findings.

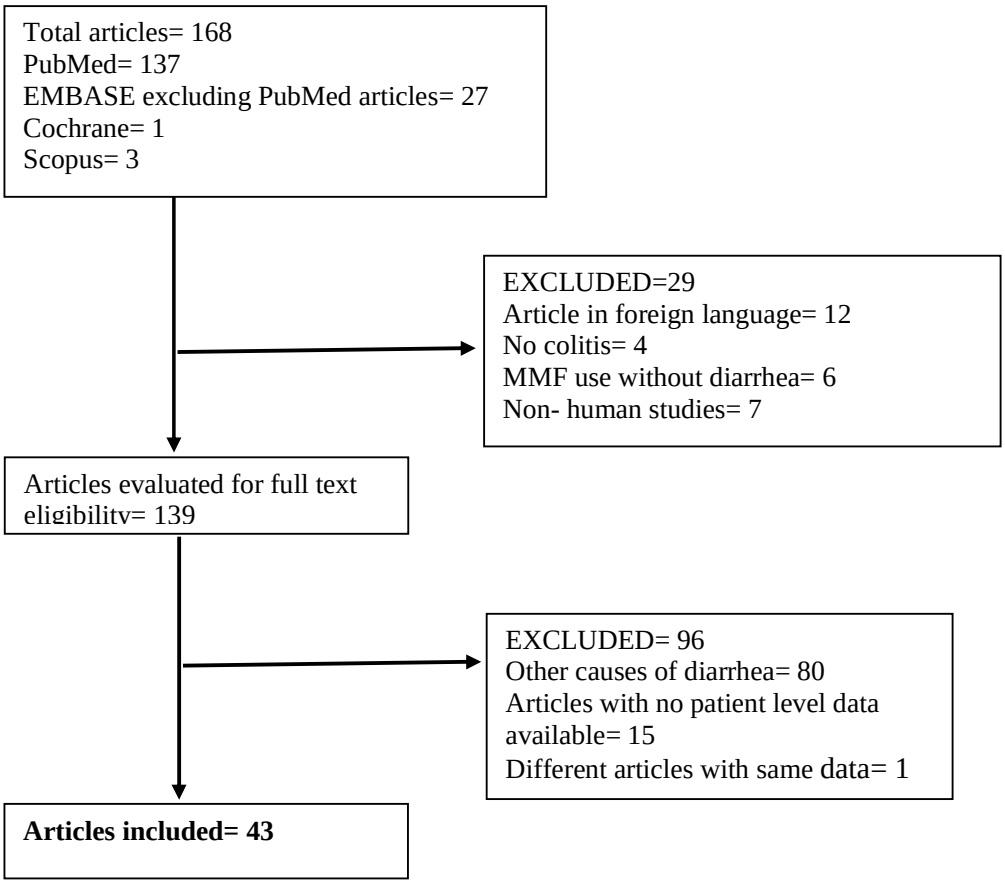

Fig. 1. Flow diagram for selection of article

Statistical analyses included the computation of medians, ranges, frequencies, and proportions. The non-parametric Wilcoxon rank sum test was used to compare latency to diarrhea following first MMF use by whether a subject responded to discontinuation or dose reduction. A Pearson correlation coefficient was used to evaluate a possible linear association between latency to diarrhea following first MMF use and time to response after holding MMF for those patients who responded following MMF discontinuation or decreased in dose. Analyses were completed using the SAS statistical software version 9.4 (The SAS Institute, Cary, NC).

3. RESULTS

Forty-three articles with a total of 544 patients and 560 episodes of suspected or confirmed MMF-induced diarrhea were included [1,11-14, 16-53]. The median age was 45 years (range 8-75), and 29% were females. In 98% of cases, MMF was used for solid organ transplant, including kidney (n=423), liver (n=56), heart (n=12), kidney and pancreas (n=5), and heart/pancreas (n=5). Bone marrow transplant was the indication in only one case [39]. The non-transplant indications included psoriasis (n=19) [42], systematic lupus erythematosus (n=1) [16,48], autoimmune autonomic dysfunction (n=1), scleroderma (n=1) [30], and chronic active hepatitis (n=1) [26].

The median latency between the use of MMF and onset of diarrhea was 990 days (range 12-5760). Watery diarrhea, as frequent as every 20 minutes in one case [24], and large volumes at times, was the presenting symptom in 98% of cases. Other less common presentations included bloody diarrhea (n=4) [11,37,44], abdominal pain (n=1) [48], steatorrhea (n=1) [47], anemia (n=1) [1], weight loss (n=1) [48], and abdominal pain as well as weight loss (n=1) [34]. In 7% (n=36) of cases, colonoscopy was done to study the effect of MMF in the gastrointestinal tract even if the patient was asymptomatic.

For management of diarrhea, MMF was discontinued or dose reduced in 56% (n=311) [1,11-14,16-19,21,22,24,25,27,29-38,40-47,49-52], switched to enteric coated mycophenolate mofetil sodium (EC-MPS) in 12% (n=67) [20,23,46,49,53] and continued in 14% of cases (n=77) [13,21,32,36,46,52] (Fig. 1). The information was missing in other cases. While 85% of cases managed with discontinuation or dose reduction of MMF responded to the treatment, 2% (n=6) [40,41,43] continued to have diarrhea. The latency from initiation of MMF to onset of diarrhea did not differ by whether a patient responded to discontinuation or dose reduction (Wilcoxon rank-sum p-value = 0.58). About 81% of cases who switched from MMF to EC-MPS responded and 7% (n=5) [20,46] did not. Among the patients who continued MMF, diarrhea was persistent in 13% (n=13) [13] while it resolved spontaneously in 60%. The information was lacking in the rest of the cases.

Table 1. Clinical features and outcomes of mycophenolate mofetil-induced diarrhea

Variable	Level	Count	Percentage	Total analyzed
Age (median [Min, Max](years)		45[8, 75]		68
Time to response after holding MMF (median [Min, Max] (days)		20[1, 120]		28
Latency (median [Min, Max](days)		990[12, 5760]		59
Gender	Female	47	29.2	161
	Male	98	60.9	
	NM	16	9.9	
Immunosuppressant initially	MMF	526	97.6	539
	EC-MPS	13	2.4	
Indication for use				
Transplant Indication	Kidney	423	77.8	544
	Liver	56	10.3	
	Heart	12	2.2	
	Bone marrow transplant	1	0.2	
	Other	26	4.7	
Non-transplant Indication	Psoriasis	19	3.5	
	Others	5	1.0	
	NM	2	0.4	
Presenting symptom	Diarrhea	499	98.2	508
	Hematochezia	4	0.8	
	Others	5	1.0	
MMF discontinued/decreased in dose	Discontinuation/Dose reduction	311	56	555
	Continued	105	19	
	Switched to EC-MPS	67	12.1	
	NM	72	13	
Response to discontinuation or dose reduction	Yes	452	85	532
	No	11	2.1	
	NM	69	12.9	
Outcome	Improved	441	81.4	539
	No improvement	32	6.0	
	NM	68	12.6	
Complications	Graft rejection	11	57.8	19
	Dehydration	6	31.6	
	Toxic colitis	1	5.3	
	Weight loss	1	5.3	

EC-MPS: Enteric coated-Mycophenolate sodium; MTCD: Mixed connective tissue disease
MMF: Mycophenolate mofetil; NM: Not mentioned; SLE: Systemic Lupus Erythematosus

The median time to response to either change to EC-MPS or dose reduction/ discontinuation of treatment was 20 days (range 1-120). There was no correlation between latency of onset of diarrhea (time in days from the first use to onset of diarrhea) and time to response after dose reduction /discontinuation of MMF (in days) (Pearson correlation coefficient= 0.04, p-value=0.84).

Complications related to the diarrhea and/or its subsequent management developed in 4% (n=19) of cases including graft rejection in solid-organ transplant (n=11) [1,41,46,52] after discontinuation or dose reduction of MMF, acute dehydration (n=6) [17], toxic colitis (n=1) [42], and severe weight loss of >60 pounds (n=1) [24].

All of the graft rejection cases were kidney transplants, thus, leading to hemodialysis [1,41,46,52]. Al-Absi et al. [1] described graft rejection in 3 cases- 2, 3, and 6 months following MMF discontinuation. The data for the duration for graft rejection was lacking in rest of the cases (n=8) [41,46,52].

Other management options, in addition to discontinuation or dose reduction of MMF or switching MMF to EC-MPS, were tried to prevent complications of withdrawal of immunosuppressants, or to treat diarrhea. Such additional therapies included mizoribine (n=22) [46,52], azathioprine (n=14) [1,11,16,17,19,29, 31,34,38,45,50], sirolimus (n=10) [1,17,34], antibiotics (n=2) [41], tacrolimus (n=2) [11,27], octreotide (n=1) [43], infliximab (n=1) [22], and right hemicolectomy (n=1) [34].

4. DISCUSSION

The gastrointestinal toxicity has been ascribed to the local as well as systemic effects of MMF [9,10]. Gastrointestinal side effects have been reported to occur in as many as 45% of cases taking MMF [12,17]. However, the incidence of MMF-induced diarrhea remains unknown.

In this large review of 560 episodes of MMF-induced diarrhea, watery diarrhea was the most common presenting symptom. Other presentations such as bloody diarrhea, abdominal pain, steatorrhea, and weight loss were uncommon and could raise concerns for certain infectious or other causes of diarrhea.

Since the latency between MMF use and diarrhea ranged widely from early as 3 days to more than 10 years, the latency may not help in diagnosis. The exact cause for this wide variation in latency of symptoms is unknown. Since the diarrhea as a side effect of MMF typically develops within days or weeks of initiating the drug, this may relate to a bias in the literature or alternatively it may be that MMF is an innocent bystander in the development of diarrhea.

The median time to response after discontinuation or dose reduction of MMF was 20 days with a range of 1-45 days, thus the response may not necessarily be rapid and could take a few weeks. Time to response did not depend on the latency to diarrhea following initiation of MMF.

Although our review focused on clinical findings, histopathological changes have been described in some of the studies reported here. In some cases, colonoscopies and eventually, biopsies were done to study the effect of MMF in the gastrointestinal tract even in asymptomatic patients. Colonic biopsies in patients using MMF have been shown to have various changes similar to inflammatory bowel disease (IBD), acute graft versus host disease or duodenal villous atrophy [12,13,26,39,48]. Calmet et al. [12] grouped histological findings into acute colitis-like findings (50%) and IBD-like characteristics (36%), GVHD-like features (8%), and ischemia-like findings (6%). Selbst et al. [13] described the changes similar to IBD (28%), GVHD (19%), acute colitis (16%), and ischemia (3%). Since these changes are not restricted to MMF-diarrhea, a distinct diagnosis based purely on histology might not be possible, and clinical correlation is frequently required.

Dose reduction or discontinuation of MMF, when feasible, have been the mainstay of therapy and are associated with a 98% response rate. However, there were some reports of graft rejection in solid organ transplants after dose reduction or especially discontinuation of MMF. When there is a risk of graft rejection, alternative immunosuppressants should be considered. In this review, MMF was changed to EC-MPS in 14% of the total cases, and 93% of these patients responded. Decreased gastrointestinal side effects of EC-MPS in comparison to MMF, was the basis of EC-MPS use in these cases [46,54]. A randomized, multicenter, open-labeled study on renal transplant cases showed that the recipients' gastrointestinal quality of life index was significantly better in EC-MPS patients versus MMF patients. Some studies, however,

have failed to show any statistical difference in gastrointestinal side effects between EC-MPS and MMF although both were effective in preventing transplant rejection [55,56]. This may be explained to an extent by the fact that gastrointestinal effects observed with MMF are the result of both local as well as systemic effects. While local effects are less with EC-MPS, the systemic effects may be similar [10,57].

Additionally, Zhao et al. and Qin et al. have described switches from MMF to mizoribine leading to resolution of cases of severe diarrhea [46,52]. In some cases, azathioprine [1,11,16, 17,19,29,31,34,38,45,50], sirolimus [1,17,34] and tacrolimus [11,27] were the immunosuppressants used after discontinuation or dose reduction of MMF. In Maes et al. [41] in addition to reduction in MMF dose, empirical antibiotics, cholestyramine, probiotic, and loperamide were used in selected cases.

In the remaining 21% of the total cases, MMF or EC-MPS was continued and diarrhea persisted in 13% of them while 87% had spontaneous resolution. Although the exact cause is not known, resolution of symptoms even with continuation of MMF may indicate tolerance to the drug effects and needs further study. However, the reason for persistent diarrhea even after discontinuation or dose reduction in the remaining 2% of cases was not discussed in the studies and it is difficult to speculate the cause.

The outcome of MMF-induced diarrhea was generally good including cases of spontaneous resolution. However, if left untreated, MMF-induced diarrhea may result mainly in dehydration, and rarely in toxic colitis or profound weight loss. The rate of death due to MMF-induced diarrhea has not been reported.

There are several limitations of our review. No definite guidelines exist for diagnosis of MMF-induced diarrhea and the articles in our review used their own criteria, which is a limitation of the retrospective nature of the study. In addition, the definitive diagnosis of any drug induced adverse effect with recurrence of symptoms upon re-challenge with the drug was not done or not reported in these studies. Additionally, in some cases, use of other therapies such as antibiotic therapy may have contributed to improvement of symptoms along with dose reduction or discontinuation of MMF or switching to EC-MPS.

In this context, our systematic review provides valuable information regarding the clinical manifestations of MMF-induced diarrhea. This study is hoped to lay the foundation for developing diagnostic criteria for MMF-induced diarrhea and may provide baseline epidemiologic information for comparative studies in the future.

5. CONCLUSION

MMF-induced diarrhea generally presents with watery diarrhea; the presence of bloody stool should raise concerns for other possibilities. The latency period can range from months to years, hence a long latency period does not exclude the possibility of MMF-induced diarrhea. A vast majority of patients respond to cessation of MMF or dose reduction within a few weeks, however, cessation of MMF may result in graft rejection. In cases where continuation of immunosuppressive therapy is considered important to prevent graft rejection, alternate management option for management of MMF-induced diarrhea could include switching to a different drug formulation, or initiation of a different immunosuppressant.

SUPPORTING INFORMATION

The supplemental information describes the search strategies used in different databases to identify the eligible articles for our study. The additional supplemental information may be found in the online version of this article.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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